NHS England

Evidence review: Total Pancreatectomy with Islet Autotransplantation for Chronic Pancreatitis

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Contents

1 Introduction

Indication and epidemiology

- Chronic pancreatitis (CP) is characterised by irreversible morphological and functional abnormalities due to longstanding inflammation and fibrosis of the pancreatic parenchyma[a] (Bramis et al 2012). The exocrine tissue of the pancreas produces pancreatic enzymes for digestion and the endocrine cells form the islets that produce and secrete hormones such as insulin and glucagon into the bloodstream. Destruction of exocrine and endocrine cells of the pancreas can result in malabsorption and diabetes respectively (Vallance 2015).

- Recurrent abdominal pain is experienced by 95% of individuals with CP, which is in turn associated with poor quality of life and depression (Vallance 2015).

- Cases of CP appear to be increasing and although the exact prevalence is unknown, in Western Europe there are estimated to be around 26 cases per 100,000 population (Vallance et al 2015).

- Although there is significant aetiological variation worldwide, the most common predisposing factor in the UK is alcohol excess (Jupp, Fine and Johnson 2010). Less common causes include biliary disease, hyperlipidaemia and hyperparathyroidism. CP can also be autoimmune or hereditary. Hereditary CP is a very rare form of early onset CP. With the exception of the young age at diagnosis and a slower progression, its clinical course and treatment does not differ from those of patients with CP of other causes (Rosendahl et al 2007).

- The most debilitating aspect of the disease is the chronic, intractable pain that is typically very difficult to manage and is multifactorial in origin. The primary goal of managing CP is to achieve long-term pain relief while reducing associated complications. An ideal intervention would not only relieve pain but also reduce chronic opioid use, maximise endocrine and exocrine function, improve quality of life and reduce complications such as pancreatic cancer, pseudocyst[b] and duodenal stenosis[c] (Vallance et al 2015).

- Treatment often occurs in a stepwise progression; initially with dietary modification, pancreatic enzyme supplementation and non-narcotic analgesia. This usually progresses to narcotic analgesia often requiring the guidance of a pain specialist. Refractory pain results in the need for more aggressive procedures such as endoscopic pancreatic decompression[d] and coeliac plexus nerve blocks[e], both of which have been met with varying success (Radomski and Zureikat 2017).

- In some patients, total pancreatectomy (TP) is carried out to alleviate pain however this leaves individuals liable to the complication of brittle diabetes[f]. For this reason, TP with islet cell autotransplantation (IAT) has gained popularity (Vallance et al 2015).

The intervention

- Total pancreatectomy with islet cell autotransplantation (TP/IAT) can relieve the severe pain associated with CP whilst preventing or minimising the occurrence of brittle diabetes (Bramis et al 2012). TP/IAT is usually performed in a single operation.

[a] Parenchyma: the functional part of an organ
[b] Pseudocyst: a contained pocket of fluid in or around the pancreas
[c] Duodenal stenosis: narrowing of the first part of the small intestine
[d] Decompressive surgery: surgery to facilitate drainage of the biliary system
[e] Coeliac plexus block: a block of the function of an abdominal nerve transmitting pain from the pancreas
[f] Brittle diabetes: very unstable blood sugar levels due to complete lack of insulin

- The procedure involves the infusion of islet cells from the patient's own pancreas into their liver. Following removal of the pancreas, the islet cells are isolated and prepared for transplantation. 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).

Existing national policies and guidance

In September 2008, NICE issued interventional procedures guidance on autologous pancreatic islet cell transplantation for improved glycaemic control after pancreatectomy (NICE 2008). NICE made a number of recommendations including the following:

1. *The current evidence on autologous pancreatic islet cell transplantation for improved glycaemic control after pancreatectomy shows some short term efficacy, although most patients require insulin therapy in the long term. The reported complications result mainly from the major surgery involved in pancreatectomy (rather than from the islet cell transplantation). The procedure may be used with normal arrangements for clinical governance in units with facilities for islet cell isolation.*

2. *During consent, clinicians should ensure that patients understand that they may require insulin therapy in the long term. They should provide them with clear written information. In addition, the use of the NICE's information for patients ('Understanding NICE guidance') is recommended.*

3. *Patient selection for this procedure should involve a multidisciplinary team with experience in the management of benign complex chronic pancreatic disease. The procedure should be carried out by surgeons with experience in complex pancreatic surgery and clinicians with experience in islet cell isolation and transplantation.*

4. *Further audit and research should address the long-term efficacy of the procedure; quality of life, insulin independence and the management of patients' diabetes.*

2 Summary of results

Clinical effectiveness

- The literature search for this rapid evidence review found 15 studies; three systematic reviews (Wu et al 2015, Bramis et al 2012, Dong et al 2011), four uncontrolled studies of TP/IAT (Fazlalizadeh et al 2016, Morgan et al 2015, Chinnakotla et al 2014a, Wilson et al 2014), one comparative study (Bhayani et al 2014) and five uncontrolled studies conducted in paediatric patients only (Bellin et al 2017, Chinnakotla et al 2014b, Wilson et al 2013, Bellin et al 2011, Bellin et al 2008). The paediatric studies are used as a proxy for CP of genetic/hereditary aetiology. We also found one cost study of TP/IAT based on a small comparative study. We excluded studies with less than 100 patients apart from paediatric only studies used as a proxy for CP of genetic/hereditary aetiology as agreed with NHS England.
- There were no randomised studies of TP/IAT, one observational study and one cost study compared TP/IAT to TP without IAT (Bhayani et al 2014). No other studies compared TP/IAT to other treatments.
- Studies included in the systematic reviews have not been discussed separately in this rapid evidence review.

- The most common outcomes of effectiveness reported by the studies identified were metabolic measures (C-peptide[g] and glycated haemoglobin A1c (HbA1c)[h] levels), pain relief measured by reduction in narcotic use, quality of life and insulin independence (not a critical outcome).

What is the clinical effectiveness and cost effectiveness of TP/IAT in the management of uncontrolled pain caused by small duct chronic pancreatitis and resistant to other forms of treatment in patients of all ages?

- One systematic review (Bramis et al 2012) included two studies which report post-operative reduction of 116mg and 55mg daily respectively in the use of morphine. One case series reported narcotic independence rate of 55% at one year and 73% at five years (Wilson 2014).
- Two systematic reviews (Dong et al 2011, Wu et al 2015) and one other study (Wilson et al 2014) reported on metabolic outcomes. Mean HbA1c values of between 6.4% and 7.5% were reported at up to five years follow-up. These studies also reported median C-peptide levels within the normal range of 0.8 to 3.1ng/mL at between one-year and over five years follow-up.
- Two systematic reviews and four other studies reported on mortality or survival outcomes. The two systematic reviews report 30-day mortality rates of 2.1% (95% CI: 1.2-3.8%) and 5% (95% CI: 2 to 10%) respectively. They also report long-term and last follow-up mortality rate of 1·38 per 100 person-years[i] (95% CI: 0·66-2·11) and 1.09 per 100 person-years (95% CI: 0.21-1.97) respectively (Wu et al 2015, Dong et al 2011). One study reported mortality rates of 0% (Fazlalizadeh et al 2016). One study reported a five year survival of 94.6% (Wilson et al 2014) and another reported a 10-year survival of 84% (Chinnakotla et al 2014).
- One retrospective study reported a 90-day morbidity rate of 64% however; no details were provided (Morgan et al 2015). Another study reported that hypoinsulinaemia occurred in 42.3% of patients; renal failure in 12% and that 8.4% of patients had wound infections immediately after TP/IAT. These results were obtained from a hospital database. However, the exact time period was not specified (Fazlalizadeh et al 2016). One study reported a 41% 30-day major morbidity[j] rate in patients with TP/IAT compared with 29% in patients who had TP alone (p=0.02) (Bhayani et al 2013).
- Two systematic reviews which carried out meta-analyses reported pooled insulin independence rates of 27% (95% CI: 21-33%) and 28.4% (95% CI: 15.7-46.0) at one year and 21% (95% CI: 16-27%) and 19.7% (95% CI: 5.1-52.6%) at two years respectively (Dong et al 2011, Wu et al 2015).
- We did not identify any cost-effectiveness studies relevant to the NHS in England; however we found one cost study that concluded that TP/IAT is cost-neutral when compared with no TP/IAT (non-surgical or other surgical therapy) (Garcea 2013).
- Garcea et al conducted a study which assessed the effectiveness of TP in 97 patients with CP; 60 underwent TP + IAT and 37 underwent TP alone. The authors reported that TP/IAT surgery resulted in significant reduction in opiate use (p<0.001) compared with TP without IAT. They also reported longer survival (16.6 vs. 12.9 years p=0.011)) and higher rate of insulin independence (21.6% no other details given) with TP/IAT compared with TP without IAT. The cost of TP/IAT with attendant admission and analgesia costs over the 16-year survival period was reported as £110,445 compared with £101,608 estimated 16-year costs if no TP/IAT (other surgery or no surgery) was undertaken.

[g] C-peptide is produced in equal amounts to insulin and is the best measure of endogenous insulin secretion (that is insulin produced by the body) in patients with diabetes. Levels are therefore suppressed in type 1 diabetes or in instances where insulin secretion is minimal.
[h] Glycated haemoglobin is a form of haemoglobin that is measured primarily to identify the three-month average plasma glucose concentration. The recommended HbA1c range for most with diabetes is to keep the value under 48 mmols/mol (<6.5%). People at risk of hypoglycaemia, or for whom such tight blood glucose regulation is not advised, may be advised to keep their HbA1c below 59 mmols/mol (<7.5%).
[i] 1.38 cases would be expected for 100 persons observed for 1 year or 20 persons observed for 5 years.
[j] Major morbidity was defined as re-intubation, prolonged intubation, pneumonia, cardiac arrest, myocardial infarction, renal failure requiring dialysis, deep or organ space infection, pulmonary embolus, transfusion requirement, sepsis, shock, stroke or coma.

What is the effectiveness and cost effectiveness of TP/IAT in the management of small duct chronic pancreatitis due to genetic disorders resistant to other forms of treatment?

Paediatric studies were used as a proxy for CP of genetic/hereditary aetiology (HGP).

- In terms of pain control, five studies of paediatric patients only reported narcotic independence rates of between 37% and 100% at one year to 2.5 years follow-up.
- One retrospective study reported that metabolic measures were poorer in patients with HGP; Fasting glucose was higher in HGP ($p<0.001$) and HbA1c levels poorer (higher) in HGP ($p=0.004$) however, no details were reported (Chinnakotla et al 2014a). Two studies of paediatric patients only reported mean HbA1c values of 5.9% and 5.8% at two years follow-up (Bellin et al 2017,Chinnakotla et al 2014b). The latter study also reported mean C-peptide levels of 2.85±0.07ng/mL (normal range = 0.8 to 3.1ng/mL) at five years follow-up (Chinnakotla et al 2014b).
- No paediatric only studies reported on mortality or survival rates.
- One case series found a 20% post-operative surgical complication rate in children aged five to eight years of age; no other details were given (Chinnakotla et al 2014b).
- One study reported a difference in insulin independence between the groups; HGP 16/80 (20%) vs. non-hereditary/genetic (NHGP) 133/404 (32.9%) $p=0.022$ (Chinnakotla et al 2014a). Four studies of paediatric patients only (Bellin et al 2017, Chinnakotla 2014b, Wilson et al 2013, Bellin et al 2013) reported slightly higher rates of insulin independence of between 29% and 64% at last follow-up (nine months to 11 years).
- We did not identify any cost/cost-effectiveness studies relating specifically to TP/IAT in patients with HGP.

Does IAT confer benefit, specifically in improving diabetic control after TP? What is the duration of benefit?

- One study reported a higher rate of insulin independence (21.6%) with TP/IAT compared with TP without IAT however, no other details were provided. The authors also stated that patients requiring insulin had reduced requirements when compared to TP without IAT group; 22 versus 35IU ($p=0.002$). The authors did not find a difference in HbA1c between the two groups. No results on C-peptide levels were reported (Garcea et al 2013).

Evidence for improvement of QoL

- One study reported significant improvements in PhysQoL[k] relative to baseline at one, two, and three years post-surgery of 7.1, 5.8, and 7.8 and in PsychQoL[l] relative to baseline at one year, two years, and three years post-surgery of 3.9, 4.9, and 6.6 ($p < 0.001$ for all) (Morgan et al 2015). Another study reported MCS[m] and PCS[n] scale scores statistically improved over time ($p<0.001$) however, no details were reported (Chinnakotla et al 2014a). In one study, 92% of patients reported overall improvement in their health at one year and 85% at 5 years follow-up (Wilson et al 2014). One study of paediatric patients only also reported scores of 70.3 for both physical health and mental health using the Short Form 36-Item Health Survey however no baseline scores were provided (Wilson 2013).

[k] PhysQoL - physical quality of life score
[l] PsychQoL- psychological QoL score
[m] MCS- mental component summary of the SF-36 survey
[n] PCS- physical component summary of the SF-36 survey

3 Methodology

- A description of the relevant Population, Intervention, Comparison and Outcomes (PICO) to be included in this review was prepared by NHS England's Policy Working Group for the topic (see section 9 for PICO).
- The PICO was used to search for relevant publications in the following sources: PubMed, Embase, Cochrane Library, TRIP and NICE Evidence (see section 10 for search strategy).
- The search dates for publications were between 1st January 2005 and 24th March 2017.
- The titles and abstracts of the results from the literature searches were assessed using the criteria from the PICO.
- Full text versions of papers which appeared potentially useful were obtained and reviewed to determine whether they were appropriate for inclusion. Papers which matched the PICO were selected for inclusion in this review.
- Evidence from all papers included was extracted and recorded in evidence summary tables, critically appraised and their quality assessed using National Service Framework for Long Term Conditions (NSF-LTC) evidence assessment framework (see section 7 below).
- The body of evidence for individual outcomes identified in the papers was graded and recorded in grade of evidence tables (see section 8 below).
- Conference abstracts, commentaries, letters, editorials and case reports were excluded.

4 Results

A total of 14 papers matching the PICO were identified; three systematic reviews (Wu et al 2015, Bramis et al 2012, Dong et al 2011), four uncontrolled studies of TP/IAT (Fazlalizadeh et al 2016, Morgan et al 2015, Chinnakotla et al 2014a, Wilson et al 2014) one comparative study (Bhayani et al 2014) and five uncontrolled studies conducted in paediatric patients only (Bellin et al 2017, Chinnakotla et al 2014b, Wilson et al 2013, Bellin et al 2011, Bellin et al 2008). We also found one cost study of TP/IAT based on a small comparative study. We excluded studies with less than 100 patients apart from paediatric only studies used as a proxy for CP of genetic/hereditary aetiology as agreed with NHS England. Studies included in the systematic reviews have not been discussed separately in this rapid evidence review.

What is the clinical effectiveness and cost effectiveness of TP/IAT in the management of uncontrolled pain caused by small duct chronic pancreatitis and resistant to other forms of treatment in patients of all ages?

Pain reduction

One systematic review included two studies which reported that mean morphine use decreased postoperatively (by 116mg and 55mg) compared with baseline (Bramis et al 2012).

One case series which assessed long-term outcomes after TP/IAT reported narcotic independence of 55% at one year and 73% at five years ($p<0.05$) (Wilson et al 2014).

One study reported that surgery resulted in significant reduction in opiate use, and visual analogue scale scores for pain but the authors did not find a difference between TP/IAT and TP without IAT (Garcea et al 2013).

Metabolic measures

C-peptide levels were reported in two systematic reviews and one case series. The review by Wu et

al (2015) reported C-peptide levels[o] from two included studies at 6 months of 1.7ng/ml (SD 0.57ng/ml) and 1.4ng/ml (SD 0.36ng/ml) respectively. Another of the studies included by Wu et al reported C-peptide at 3 years; 90% of patients had levels >0.6ng/ml. Another included study reported median C-peptide levels of 0.4ng/ml (IQR[p] 0.27 to 1.00) at last follow-up, median follow-up of 12 months (6.75 to 24 months).
The systematic review by Dong et al (2011) reported that one study measured C-peptide[q] at one year; 433pmol/l (SD 100pmol/l) [1.307ng/ml (SD 0.30ng/ml)]. The case series by Wilson et al (2014) reported a mean C-peptide of 1.08ng/ml (range 0.1 to 5.3ng/ml) after over five years.

HbA1c levels were reported in two systematic reviews and one case series. The review by Wu et al (2015) reported mean HbA1c[r] levels from three studies at six months follow-up: 7.5%, 7.1% and 6.7% respectively. Another systematic review found three studies that reported HbA1c at one year with mean or median of 7%, 6.9% and 6.4% respectively (Dong et al 2011). The case series by Wilson et al (2014) reported a mean HbA1c of 6.9% (range 4.6% to 11.8%) after over five years.

Two systematic reviews carried out meta-analyses and reported pooled insulin independence rates of 27% (95% CI: 21-33%) and 28.4% (95% CI: 15.7-46.0) at one year and 21% (95% CI: 16-27%) and 19.7% (95% CI: 5.1-52.6%) at two years respectively (Dong et al 2011, Wu et al 2015). Another systematic review found that insulin independence varied according to follow-up: One trial reported a rate of 33% insulin independence at follow-up up to 25 months. One trial reported a rate of 18% at mean follow-up of 1.5 years. In two studies, insulin independence ranged from 46% to 64% at a mean follow-up of five years. In two studies, insulin independence was 10% at a mean follow-up of eight years and 28% at a mean follow-up of 10 years (Bramis et al 2012). The case series by Wilson et al (2014) reported an insulin independence rate of 38% at one year and 27% at five years.

One study reported a higher rate of insulin independence (21.6%) with TP/IAT compared with TP alone however, no other details were provided. The authors also stated that patients requiring insulin had reduced requirements when compared to the TP without IAT group; 22 versus 35IU (p=0.002) (Garcea et al 2013).

Post-operative complications/morbidity

One retrospective study reported a 90-day morbidity rate of 64% but no details were provided (Morgan et al 2015); another study reported an overall morbidity of 57.8% (Fazlalizadeh et al 2016). The latter reported that hypoinsulinaemia occurred in 42.3% of patients; renal failure in 12% and that 8.4% of patients had wound infections (Fazlalizadeh et al 2016). One study reported a 41% major morbidity[s] rate in patients with TP/IAT compared with 29% in patients who had TP alone (p=0.02) (Bhayani et al 2013). One study found a 7.4% post-operative surgical complication rate in children aged five to eight years of age. (Chinnakotla et al 2014b).

Survival/mortality rates

Two meta-analyses and four other studies reported on mortality or survival outcomes. The meta-analyses (11 and 10 studies respectively) report 30-day mortality rates of 2.1% (95% CI: 1.2-3.8%) and 5% (95% CI: 2 to 10%) respectively. They also report long-term and last follow-up mortality rate of 1·38 per 100 person-years[t] (95% CI: 0·66-2·11) and 1.09 per 100 person-years (95% CI: 0.21-1.97) respectively (Wu et al 2015, Dong et al 2011).

[o] The reference range of C-peptide is 0.8-3.1 ng/mL; C-peptide levels are suppressed in type 1 diabetes mellitus
[p] the interquartile range (IQR), is a measure of statistical dispersion, being equal to the difference between 75th and 25th percentiles
[q] The reference range of C-peptide is 0.8-3.1 ng/ml; C-peptide levels are suppressed in type 1 diabetes mellitus
[r] Glycated haemoglobin is a form of haemoglobin that is measured primarily to identify the three-month average plasma glucose concentration. The recommended HbA1c range for most with diabetes is to keep the value < 48 mmols/mol (< 6.5%). People at risk of hypoglycaemia, or for whom such tight blood glucose regulation is not advised, may be advised to keep their HbA1c < 59 mmols/mol (< 7.5%).
[s] Major morbidity was defined as re-intubation, prolonged intubation, pneumonia, cardiac arrest, myocardial infarction, renal failure requiring dialysis, deep or organ space infection, pulmonary embolus, transfusion requirement, sepsis, shock, stroke or coma.
[t] 1.38 cases would be expected for 100 persons observed for 1 year

In one systematic review cumulative mortality at one year (10 studies; n=321) was reported as 4.9% (95% CI: 2.6% to 7.3%) and 6.2% (95% CI: 3.3% to 9.2%) at two years (five studies; n=254) (Dong et al 2011). One study reported mortality rates of 0% (Fazlalizadeh et al 2016). One study reported a five year survival of 94.6% (Wilson et al 2014) and another reported a 10-year survival of 84% (Chinnakotla et al 2014a).

One study reported longer survival in patients who had TP/IAT compared with those who had TP without IAT (16.6 vs. 12.9 years) (Garcea et al 2013).

Cost-effectiveness

We did not identify any cost-effectiveness studies relevant to the NHS in England; however we found one cost study that concluded that TP/IAT is cost-neutral when compared with no TP/IAT (non-surgical or other surgical therapy) (Garcea et al 2013).

Garcea et al conducted a study which assessed the effectiveness of TP in 103 patients with CP; 66 underwent TP + IAT and 37 underwent TP alone. The study cohorts were identified from a prospectively maintained Leicester database of all patients undergoing TP + IAT. TP patients not undergoing IAT were identified from theatre records, case notes were also requested to obtain necessary information. All patients from 1990 to 2012 were included in the study (Garcea et al 2013).

The cost of TP/IAT with attendant admission and analgesia costs over the 16-year survival period was reported as £110,445 compared with £101,608 estimated 16-year costs if no TP/IAT (other surgery or no surgery) was undertaken (Garcea et al 2013).

What is the clinical effectiveness and cost effectiveness of TP/IAT in the management of uncontrolled pain caused by small duct chronic pancreatitis due to genetic disorders and resistant to other forms of treatment?

Chinnakotla et al 2014a studied patients with hereditary/genetic pancreatitis. Five observational studies in paediatric patients only (Bellin et al 2017, Chinnakotla et al 2014, Wilson et al 2013, Bellin et al 2011, Bellin et al 2008) were used as a proxy for CP of genetic/hereditary aetiology.

Pain reduction

One study reported that pain improved significantly after TP/IAT ($p<0.001$) with no difference between hereditary/genetic pancreatitis (HGP) and non-HGP aetiologies ($p=0.227$). They found that over 10 years, narcotic use reduced from 70% to less than 20% ($p<0.001$) with no difference between HGP and non-HGP aetiologies (Chinnakotla et al 2014a).

One study reported that all had pain relief after TP/IAT with all the patients off narcotics at one year follow-up (Bellin et al 2017). One study reported that pancreatitis pain and the severity of pain statistically improved in 80% to 90% of patients after TP/IAT ($p =<0.001$) and that the relief from narcotics was sustained (Chinnakotla et al 2014b).

One study reported that preoperatively, patients required on average 32.7 morphine equivalent mg per day (MEQ), which improved to 13.9 MEQ at most recent follow-up. Eleven patients (79%) were narcotic independent. Median follow-up was 9 months (range =1 to 78) (Wilson et al 2013). One study reported outcomes on 18 of the 24 patients whose medical records were reviewed. They found that 11/18 (61%) were narcotic independent; mean follow-up was 2.5 years (Bellin et al 2008).

Metabolic measures

In one study metabolic measures were found to be poorer in patients with HGP compared to patients with non-HGP aetiologies; Fasting glucose was higher in HGP ($p<0.001$) and HbA1c levels poorer (higher) in HGP ($p=0.004$); no details were reported (Chinnakotla et al 2014a).

One study found median post-TP/IAT HbA1c was 5.9% (5.6% to 6.3%), and within patient post-TP/IAT mean HbA1c was ≤6.5% for all but two patients at last follow-up (last follow-up ranged between two and 11 years) (Bellin et al 2017).

One study reported a difference in insulin independence between the groups; HGP 16/80 (20%) vs. NHGP 133/404 (32.9%) p=0.022 (Chinnakotla et al 2014a). Another study found an insulin independence rate of 82% (Bellin et al 2017). One study reported that 75 patients undergoing TP/IAT, 31 (41.3%) achieved insulin independence (Chinnakotla et al 2014b).
One study reported all of the patients were discharged after TP/IAT with scheduled insulin requirements (mean, 17 U/d). This requirement decreased to a mean of 10.1 U/d at most recent follow-up visits. Four patients (29%) progressed to insulin independence (Wilson et al 2013).
One study reported outcomes on 18 of the 24 patients whose medical records were reviewed. They found that 10/18 (56%) were insulin independent (Bellin et al 2008).

Does IAT confer benefit, specifically in improving diabetic control after TP? What is the duration of benefit?

One study reported a higher rate of insulin independence (21.6%) with TP/IAT compared with TP without IAT however, no other details were provided. The authors also stated that patients requiring insulin had reduced requirements when compared to TP without IAT group; 22 versus 35IU (p=0.002). The authors did not find a difference in HbA1c between the two groups. No results on C-peptide levels were reported (Garcea et al 2013).

Evidence for improvement of QoL

One study reported significant improvements in PhysQoL[u] relative to baseline at one, two, and three years post-surgery of 7.1, 5.8, and 7.8 respectively ($p < 0.001$ for all). The percentage of patients with ≥ 3-point improvement was 65%, 60% & 61% at one, two, and three years respectively. The authors also reported significant improvements in PsychQoL[v] relative to baseline at one year, two years, and three years post-surgery of 3.9, 4.9, and 6.6 ($p < 0.001$ for all). Percentage of patients with ≥ 3-point improvement was 49%, 58% & 66% at one, two, and three years respectively (Morgan et al 2015).

One study's assessment of health-related quality of life at five years using the RAND version of the SF-36 found that the mental component summary (MCS) and physical component summary (PCS) both improved over time ($p<0.001$) and that there was no significant difference between HGP and NHGP (p=0.428 and 0.287 respectively), no details were reported (Chinnakotla et al 2014a).

One study reported that the responses to the SF-36 Health Survey among those 12 years of age and older show a statistical improvement in physical and mental health following TP-IAT using mixed model methods. The Physical Component Summary Scale (PCS) score improved with time (p value = 0.007) changing from pre transplant by nearly two standard deviations (17.2 points). The Mental Component Summary Scale (MCS) also improved by a similar margin (p value = 0.024), an improvement of over two standard deviations (22.2 points) (Chinnakotla et al 2014b).

One study reported that before TP/IAT, patients had below average health-related quality of life, based on data from the SF-36; they had a mean physical component summary (PCS) score of 30 and mental component summary (MCS) score of 34 (2 and 1.5 standard deviations, respectively, below the mean for the U.S. population). By one year after surgery, PCS and MCS scores improved to 50 and 46 respectively (PCS $p<0.001$, MCS p=0.06). Mean scores improved for all eight component subscales. (Bellin et al 2011).

[u] PhysQoL - physical quality of life score
[v] PsychQoL- psychological QoL score

5 Discussion

The studies included in this rapid evidence review are mostly uncontrolled, single centre observational studies mainly case series; therefore of low quality. We included one unrandomised retrospective comparative study which only reported on safety outcomes. We also included one cost study which was based on a small unrandomised study; the comparator group for this study were not matched as they were identified from theatre records.

Evidence from several of the uncontrolled single centre studies and one unrandomised comparative study suggests that TP/IAT is associated with significant pain relief in patients with chronic pancreatitis. The comparative study reported that all patients experienced pain reduction (patients who had TP/IAT and those who had TP without IAT) however daily morphine requirements after TP/IAT was significantly less than after TP without IAT. These findings need to be interpreted with caution because no baseline data was presented and there was a wide variation in the daily use of morphine within both groups so it is unclear how individual patients benefit.

Evidence from meta-analyses of observational studies suggests that after two years around 80% of patients who undergo TP/IAT would require insulin. This implies that the benefits of TP/IAT in terms of insulin requirements are relatively small. However the goal of TP/IAT is to avoid brittle diabetes, which is more reliably measured by C-peptide levels. Published studies indicate that diabetic control measured by HbA1c and C-peptide levels is impressive initially but, for C-peptide levels, there appears to be a downward trend with time. The duration of the benefit of TP/IAT over TP alone in terms of metabolic outcomes is therefore unclear.

TP/IAT appears to be associated with more adverse effects than TP alone probably because of the complexity of the procedure. However, evidence on survival and mortality rates from two non-randomised retrospective studies is conflicting so it is unclear whether TP/IAT has any survival benefits over TP without IAT.

One cost study concluded that TP/IAT is cost-neutral when compared with non-surgical therapy. However the study had a number of limitations; the evidence supporting TP/IAT as a treatment option for chronic pancreatitis is from uncontrolled, single centre studies mostly case series. These studies are subject to significant bias and therefore more reliable evidence is required to inform treatment policies.

There does not appear to a difference in response to TP/IAT in terms of improvement in pain and quality of life between patients with CP of genetic aetiology and those with CP of non-genetic aetiology. However one study reported higher HbA1c levels in patients with CP of genetic aetiology but no details were provided; it is therefore not possible to know how reliable this finding is. We did not identify any cost/cost-effectiveness studies relating specifically to TP/IAT in patients with CP of genetic aetiology.

It is unclear from the published literature what benefits TP/IAT has over TP without IAT in terms of diabetic control in the long term, therefore more robust comparative studies with longer term outcomes would help to inform treatment decisions.

Evidence from several of the uncontrolled single centre studies suggests that TP/IAT is associated with significant improvements in quality of life in patients with chronic pancreatitis irrespective of aetiology. However without a control arm it is unclear whether TP/IAT confers any benefits in terms of these outcomes over TP without IAT or any other interventions.

6 Conclusion

The evidence for the clinical and cost-effectiveness of TP/IAT is limited to uncontrolled, single centre studies mostly case series and two unrandomised comparative studies which are not generalisable or reliable. The majority of the studies were carried out in Minnesota, USA.

Although the evidence from the studies suggests the TP/IAT is controlling pain and improving quality of life, there were no randomised studies allowing for direct comparison with TP without IAT or other treatments. It is therefore not clear whether these effects can be solely attributed to the intervention. In addition it is unclear whether the initial effect on brittle diabetes is maintained in the long term particularly when graft function starts to decline.

In summary, while TP/IAT may be useful in controlling pain, improving quality of life and reducing brittle diabetes in the short-term in patients with chronic pancreatitis, there is insufficient good quality evidence to make clear recommendations particularly in comparison to alternative treatments and with respect to longer term.

7 Evidence Summary Table

Studies of TP/IAT with no comparators									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Wu et al 2015	S1 - Systematic review and meta-analysis 12 studies – single-centre case series N=677	Patients with chronic pancreatitis undergoing islet autotransplantation after total pancreatectomy	TP/IAT				8/10	Direct	Wu et al concluded that IAT is a safe modality for patients with CP who need to undergo TP. The review addressed clear questions. The included studies were of poor quality; they were all single-centre case series. The studies were small, so bias could not be ruled out. In addition, the studies were not comparative and so it is not clear how these compare with TP alone or alternative interventions. Given a very limited and poor quality evidence base, the authors' conclusions should be treated with caution.
				Primary Clinical effectiveness	Metabolic Outcomes	**Three studies reported mean HbA1c at six months;** 7,5%, 7.1% and 6.7% respectively 7.7% at one year (1 study) 8.5% at two years 91 study).			
						Two studies reported C-peptide levels[w] at 6 months 1.7ng/ml (SD 0.57ng/ml) and 1.4ng/ml (SD 0.36ng/ml) respectively One study reported C-peptide at 3 years; 90% had levels >0.6ng/ml One study reported median C-peptide levels of 0.4ng/ml (IQR[x] 0.27 to 1.00) at last follow-up. median follow-up of 12 months (6.75 to 24 months)			
				Primary Clinical effectiveness	Insulin independence	**Rate of insulin independence** At last follow-up = 3.72 /100 person-years (95% CI: 1.00-6.44) (11 studies).The			

[w] The reference range of C-peptide is 0.8-3.1 ng/mL; C-peptide levels are suppressed in type 1 diabetes mellitus
[x] the interquartile range (IQR), is a measure of statistical dispersion, being equal to the difference between 75th and 25th percentiles

						follow-up ranged from 1 to 210 months. At 1 year follow-up = 28.4% (95% CI:15.7-46.0) of 362 patients (5 studies) At 2 year follow-up =19.7% (95% CI: 5.1-52.6%) of 297 patients (3 studies)			
				Primary Safety	Mortality	**11 studies** **30-day mortality** =2.1% (95% CI: 1.2 to 3.8%). **Mortality at last follow-up** = 1.09 per 100 person-years (95% CI: 0.21-1.97). The follow-up ranged from 1 to 210 months.			
Bramis et al 2012	R1 - Systematic review Five studies - 4 case series and 1 retrospective cohort study published between 1983 and 2009 included (N=296)	Patients with chronic pancreatitis undergoing pancreatectomy	Total, sub-total or completion pancreatectomy followed by islet autotransplantation	Primary Clinical effectiveness	Post-op morphine use	One study (n=45) reported a post-op mean reduction in morphine use of 116mg/day Another study (n=50) reported a post-op mean reduction in morphine use of 55mg. The study does not explicitly state whether the reduction is per day or other time period.	8/10	Direct	Bramis et al concluded that TP/IAT had favourable outcomes with regard to pain reduction. The review addressed clear questions, Relevant sources were searched but no specific attempts were made to find unpublished studies, so publication bias could not be excluded. It appeared that included studies were not assessed for quality; the studies were observational and had small sample sizes, so bias could not be ruled out. Synthesis of studies in narrative format was appropriate, given the variation in the included studies. Given a very limited and poor quality evidence base, the authors' conclusions should be treated with caution particularly as the studies had no control arms.
				Primary Clinical effectiveness	Insulin independence	**Rate of insulin independence** 33% at 1 to 25 months (1 study 18% at 1.5 years mean follow-up (1 study**)** 46% of patients at 5 years mean follow-up (1 study) 64% at 5 years (1 study) 10% at 8 years mean follow-up (1 study) 28% at 10 years (1 study)			
				Quality of life	Not stated	One study reported a 79% improvement in QoL			
Dong et al 2011	S1 - Systematic	Patients undergoing pancreatectomy	TP/IAT	Primary	Metabolic outcomes	HbA1c at one year = 7%, 6.9% & 6.4% (three studies)	8/10	Direct	Dong et al concluded that IAT post pancreatectomy offers some patients a

	review and meta-analysis 15 observational studies included	11 studies of TP; two of PP & two included both 13 studies included CP & two included patients with benign pancreatic tumours Sample size ranged from 3 to 173	N=354	Clinical effectiveness		One study measured C-peptide[y] at one year; 433pmol/l (SD 100pmol/l) [1.307ng/ml (SD 0.30ng/ml]			chance for insulin independence. The review addressed clear questions. Although this review included studies of PP/IAT, the results were reported separately. The included studies were of poor quality; they were all single-centre case series. The studies were small, so bias could not be ruled out. Without a control arm it is not clear how the intervention compares with alternative treatments. Given a very limited and poor quality evidence base and lack of control group, the authors' conclusions should be treated with caution.
				Primary Clinical effectiveness	Insulin independence	**Rate of insulin independence** The pooled rate at 1 year (5 studies; n=221) = 27% (95% CI: 21-33%) and at 2 years (3 studies; n=201) = 21% (95% CI: 16-27%). At last follow-up (14 studies) = 4.62 per 100 person years (95% CI: 1.53 to 7.72). Follow-up ranged from 1 and 100 months Transient insulin independence rate[z] = 8.34 per 100 person-years (95% CI: 3.32 to 13.37). Duration =15.57 months (95% CI: 10.35 to 20.79).			
				Safety	Mortality	**30-day mortality** =5% (95% CI: 2 to 10%) (11 studies) Cumulative mortality at 1 year (10 studies) = 4.9% (95% CI: 2.6 to 7.3%) and 6.2% (95% CI: 3.3% to 9.2%) at two years (five studies; n=254) Long term mortality = 1·38 per 100 person-years (95% CI: 0·66-2·11) (12 studies) Follow-up ranged from 1 and 100 months			
Fazlalizadeh et al 2016 USA	Retrospective cohort study n=754 (86% had CP)	Patient who underwent TP/IAT identified from a national inpatient	TP/IAT	Primary Safety	Mortality	Mortality =0% during hospitalisation post-op as the database was for inpatients only	7/10	Indirect	Study was retrospective and uncontrolled and therefore all the patients may not have been identified due to entry error.

[y] The reference range of C-peptide is 0.8-3.1 ng/mL; C-peptide levels are suppressed in type 1 diabetes mellitus
[z] Patients were independent of insulin for a short period of time

	Between 2002 & 2012	sample (NIS) database		Primary Safety	Post-op complications	**Overall morbidity =57.8%** including wound infections =8.4%; post-surgical hypoinsulinaemia = 42.3%; renal failure = 12%			Key or long-term outcomes including quality of life or narcotic independence could not be measured as it is a hospital database. There was no comparator group so it is unclear how these results compare with TP alone or other treatments. This makes it difficult to make treatment recommendations.
Morgan et al 2015 USA	Retrospective cohort study Review of a database of patients undergoing TP/IAT between March 2009 to May 2014 n=127	Patients with CP or recurrent acute pancreatitis undergoing TP/IAT	TP/IAT (n=97) or completion pancreatectomy [aa] with IAT (n=30)	Primary Quality of life	SF-12 PhysQoL	Mean improvements in PhysQoL relative to baseline at one, two, and three years post-surgery were 7.1, 5.8, and 7.8 respectively $p < 0.001$ for all. Percentage of patients with ≥ 3-point improvement was 65%, 60% & 61% at one, two, and three years respectively.	6/10	Indirect	Study was retrospective and uncontrolled and therefore all the patients may not have been identified due to entry error. The study reports significant improvements in quality of life scores for up to three years after TP/IAT. However the results should be interpreted with caution (Morgan et al 2015). There was no comparator group so it is unclear how these results compare with TP alone or other treatments. This makes it difficult to make treatment recommendations.
					SF-12 PsychQoL	Mean improvements in PsychQoL relative to baseline at 1 year, 2 years, and 3 years post-surgery were 3.9, 4.9, and 6.6 $p < 0.001$ for all. Percentage of patients with ≥ 3-point improvement was 49%, 58% & 66% at one, two, and three years respectively.			
				Secondary Safety	90-day morbidity rate	90-day morbidity rate = 64% No details reported			
Wilson et al 2014 USA	Case series n=112	Patients with CP undergoing TP/IAT	TP/IAT	Primary Clinical effectiveness	Narcotic requirements	narcotic independence rate = 55% at one year; 73% at five years	7/10	Direct	Study was retrospective and uncontrolled and therefore all the patients may not have been identified due to entry error. There was no comparator group so it is unclear how these results compare with TP alone or other treatments. This makes it difficult to make treatment
				Primary Clinical effectiveness	Glycaemic control	Insulin independence rate =38% at one year; 27% at five years			
				Primary	Metabolic	At ≥5 years (range=60 to			

[aa] Completion pancreatectomy (CP) is a re-operative procedure to excise remnant pancreatic tissue after a prior pancreatic resection

				Clinical effectiveness	measures	151 months) – Mean(SEM) HbA1c (n=40) =6.9±0.3 (range=4.6 to 11.8) C-peptide (n=21) = 1.08±0.3 (range=0.1 to 5.3) There was a lot of missing data for metabolic outcomes at 5 years			recommendations. In addition, there was a lot of missing data for metabolic outcomes at 5 years follow-up which make results difficult to interpret.
				Primary Safety	Survival	5-year survival = 94.6%			
				Primary Quality of life	SF-36	**Baseline vs. 1 yr. vs.5 yrs** **PCS** 38.1±7.6 vs.75.2±4.5 vs. 83.2±3.6 (p<0.001 compared with baseline) **MCS** 39.6±5.1 vs.75.3±3.5 vs.76.8±3.1 (p<0.001 compared with baseline) 92% reported overall improvement in health at one year and 85% at five years.			
Studies of TP/IAT with no comparators, in patients with chronic pancreatitis of genetic aetiology (including paediatric studies used as a proxy)									
Chinnakotla et al 2014a USA	Retrospective cohort study n=484	Patients with (n=80; mean age 22years) or without hereditary/genetic (n=404; mean age 38 years) chronic pancreatitis undergoing TP/IAT	TP/IAT	Primary Clinical effectiveness Pain relief	**10-year follow-up** Improvement in pain for all patients p<001	**HCP[bb] vs. NHCP[cc]** p= 0.227(NS) No details were reported	6/10	Direct	Study was retrospective and uncontrolled (although results were sometimes highlighted for patients with CP of genetic aetiology) and therefore all the patients may not have been identified due to entry error. A lot of details were missing from these results which make it difficult to interpret. All patients received TP/IAT so it is unclear how these results compare with TP alone or other treatments. This makes it difficult to make treatment recommendations.
				Primary Clinical effectiveness	Narcotic use	**10-year follow-up** **HCP** Narcotic use reduced from 70% to <20% (p<0.001) **HCP vs. NHCP** P= 0.110 (NS) No details were reported			
				Primary Clinical	Glycaemic control; Insulin independence,	**Insulin independence – HCP vs. NHCP** 16/80 (20%) vs. 133/404			

[bb] Chronic pancreatitis of hereditary aetiology
[cc] Chronic pancreatitis of non-hereditary aetiology

				effectiveness		(32.9%) p=0.022			
				Primary Clinical effectiveness	Metabolic measures; fasting glucose levels & HbA1c levels	**Fasting glucose – HCP vs. NHCP** Higher in HCP p<0.001) no details reported. **HbA1c levels – HCP vs. NHCP** Poorer (higher) in HCP p=0.004 no details reported.			
				Primary Safety	Survival	10-year survival overall = 84% **HCP vs. NHCP** 5-year survival = 90.3% (n=80) vs. 89.7%; (n=404) The difference was NS			
				Primary Quality of life	Health-related quality of life using the RAND version of the SF-36 (see appendix 1)	**MCS** Improved over time (p<0.001) no details reported There was no difference between HCP and NHCP (p=0.428) **PCS** Improved over time (p<0.001) no details reported There was no difference between HCP and NHCP (p=0. 287)			
Bellin et al 2017 Minnesota, USA	Observational study n=17	Children < 8years old undergoing TP/IAT for CP 14/17 had genetic risk factors	TP/IAT	Primary Clinical effectiveness	Pain (narcotic independence)	17/17 had pain relief. 17/17 were independent of narcotic therapy No details given	6/10	Direct	This observational study concluded that young children with severe refractory CP may be good candidates for TP/IAT, with high rates of pain relief and insulin independence, and excellent glycaemic control in the majority. However the authors' conclusions should be interpreted with caution. There was no comparator group so it is unclear how these results compare with TP alone or other treatments. This makes it difficult to make treatment recommendations.
				Primary Clinical effectiveness	Insulin independence	14/17 (82%) had any period of insulin independence. 11/17 (64%) were insulin independent at last follow-up			
				Primary Clinical effectiveness	Glycaemic control	At last follow-up (2 to 11 yrs) HBA1c was available for 16/17 patients. Median value was 5.9%. All but two patients had values of ≤6.5% no other details reported.			

				Secondary Safety	Hospitalisation rates	Data available for 15/17 patients. 5.0 hospitalisations per person-year pre-transplant vs. 0.35 hospitalisations per person-year post-transplant p<0.001			
Chinnakotla et al 2014b Minnesota, USA	Case series n=75	Children (<19 years old) undergoing TP/IAT for CP who had failed medical, endoscopic and surgical treatment between 1989 and 2012	TP/IAT	Primary Clinical effectiveness	Pain (narcotic independence)	Pancreatic pain reduced by about 80% to 90%. No details reported.	7/10	Direct	This case series concludes that TP/IAT provides sustained pain relief and improved quality of life. However the authors' conclusions should be interpreted with caution. There was no comparator group so it is unclear how these results compare with TP alone or other treatments. This makes it difficult to make treatment recommendations.
				Primary Clinical effectiveness	Metabolic measures	**Mean ± SEM of HbA1c** 6.88±2.4% at one year; 5.8±0.55% at two years; 5.7±0.52% at three years **Mean ± SEM C-peptide** 2.21±1.43ng/ml at one year; 3.38±1.89ng/ml at three years; 2.85±0.07ng/ml at five years (The reference range of C-peptide is 0.8-3.1 ng/mL) C-peptide levels are suppressed in type 1 diabetes mellitus			
				Primary Clinical effectiveness	Insulin independence	41.3% achieved insulin independence within 12 months. No other details reported.			
				Primary Safety	Surgical complications	Surgical complications occurred in 15/75 (20%) of patients. No other details reported.			
				Primary Quality of life	Quality of life SF-36	92 surveys completed by 30 recipients PCS improved compared with baseline with time by 17.2 points (~2SD) p=0.007 MCS improved compared with baseline with time by 22.2 points (>2SD) p=0.024 3.86 Years (Range - 0.6 years to 23.49 years)			

Wilson et al 2013 USA	Retrospective study n=14 Median follow-up was 9 months (range =1 to 78)	Paediatric patients (≤18 years old) undergoing TP/IAT over a 10-year period (December 2002–June 2012)	TP/IAT	Primary Clinical effectiveness	Pain (narcotic independence)	11/14 (79%) were narcotic independent post-op Median MEQ[dd] was 32.7pre-op vs. 13.9 post-op	7/10	Direct	Study was retrospective and uncontrolled and therefore all the patients may not have been identified due to entry error. There was no comparator group so it is unclear how these results compare with TP alone or other treatments. This makes it difficult to make treatment recommendations.
				Primary Clinical effectiveness	Insulin independence	4/14 (29%) progressed to insulin independence post-op			
				Primary Quality of life	Quality of life – SF-36	Median follow-up – 9 months MCS and PCS both 70.3 No baseline scores reported Median follow-up was 9 months (range =1 to 78)			
Bellin et al 2011 Minnesota, USA	Case series n=19	Consecutive children (ages 5–18 years) undergoing TP/IAT from December 2006 to December 2009	TP/IAT	Primary Quality of life	Health-related quality of life based on SF-36 PCS and MCS	At 12 months, PCS – 30 before TP/IAT vs. 50 after TP/IAT p<0.001 At 12 months, MCS – 34 before TP/IAT vs. 46 after TP/IAT p=0.06	7/10	Direct	This case series by Bellin et al concluded that quality of life significantly improve after TP/IAT in subsets of paediatric patients with severe chronic pancreatitis and that minimal or no insulin was required for most patients. However these conclusions should be interpreted with caution. No details of their findings or p-values were reported. In addition, there was no comparator group so it is unclear how these results compare with TP alone or other treatments. This makes it difficult to make treatment recommendations.
				Secondary Clinical effectiveness	Metabolic measures	19/19 had HbA1c ≤6.5% ranging from 5.8 to 12.1% C-peptide values between 0.4 & 3.1ng/ml No details were reported			
				Secondary Clinical effectiveness	Pain (narcotic independence)	**At 18 ± 8 months follow-up** 14/19 discontinued narcotics altogether 2/19 reported rare use (a few times a year).			
				Secondary Clinical effectiveness	Insulin independence (II)	**At 18 ± 8 months follow-up** 7/19 had complete insulin independence; 4/19 had very little requirements.			
Bellin et al 2008 Minnesota, USA	Retrospective medical notes review n=24 6 were lost to follow-up	Patients with CP ≤18 years old who underwent P-IAT from July 1989 to June 2006.	P-IAT 23 TP/IAT and 1 PP/IAT	Primary Clinical effectiveness	Narcotic independence	Median follow-up = 2.5 years 11/18 (61%) were narcotic independent	7/10	Indirect	Study was retrospective and uncontrolled therefore all the patients may not have identified due to entry error. There was no comparator group so it is unclear how these results compare with TP alone or other treatments. This makes it difficult to make treatment recommendations.
				Primary Clinical effectiveness	Insulin independence	One year follow-up 8/14 (56%) were insulin independent			

CI- confidence interval; HbA1c- Glycated haemoglobin; HCP – hereditary/genetic chronic pancreatitis; II – insulin independence; MEQ - morphine equivalent mg per day; MCS- mental component summary; NHCP- non-hereditary/genetic chronic pancreatitis; NS – not significant; PCS- physical component summary; PhysQoL - physical quality of life score; P-IAT –

[dd] MEQ – morphine equivalent mg per day

Pancreatectomy with islet autotransplantation; PP- partial pancreatectomy; PsychQoL- psychological QoL score; SEM - standard error of the mean SF-12 – Short form-12 Quality of Life Survey; SF-36 - The 36 Item Short Form (36) Medical Outcomes Survey; TP– total pancreatectomy; TP/IAT – total pancreatectomy with islet autotransplantation

Studies of TP/IAT compared with TP without IAT									
Bhayani et al 2013 USA	Unrandomised retrospective comparative study n= 317	Patients with CP (77%) or benign neoplasms	TP (n=126) vs. TP/IAT (191)	Primary Safety	Short-term major morbidity[ee] Minor morbidity[ff] Transfusions Longer hospitalisation Mortality	Major morbidity occurred more frequently in the TP+IAT group (41% - 79/191) vs. TP alone group (29% - 36)/126 p=0.02 No difference in minor morbidity p=0.950 Transfusions were significantly more frequent after TP+IAT (20% - 39/191) vs. TP alone group (7% - 9/126) p=0.01 There was no difference in mortality [3% (TP/IAT) vs. 1% (TP alone) p=0.06]	7/10	Indirect	This was a comparative multicentre study however there was no randomisation or blinding. Due to the retrospective design of the study, selection bias is highly likely. In addition the lack of randomisation or blinding may have introduced bias and therefore the results need to be interpreted with caution.
Garcea et al 2013 Leicester, UK	Cost study n=103	Patients with CP who underwent TP ± IAT identified from a database. All patients from 1990 to 2012 were included Median follow-up for TP without IAT is 11.5 years and 13.0 years for TP/IAT	TP/IAT and TP alone	Primary Clinical effectiveness	Insulin independence	TP/IAT vs.TP alone Higher rate of insulin independence (21.6%) however figure for comparator was not reported Insulin requirement TP/IAT vs. TP alone 22 versus 35IU (p=0.002) No difference in HbA1c- details not reported	6/10	Direct	This study reported that the cost of TP/IAT with attendant admission and analgesia costs over the 16-year survival period was £110,445 compared with £101,608 estimated 16-year costs if no TP/IAT (including no surgery) was undertaken. These results should be interpreted with caution because it was not based on any randomised trial data. Sustained benefits beyond that studied were assumed. Costs were computed based on broad and generalised

[ee] Major morbidity was defined as re-intubation, prolonged intubation, pneumonia, cardiac arrest, myocardial infarction, renal failure requiring dialysis, deep or organ space infection, pulmonary embolus, transfusion requirement, sepsis, shock, stroke or coma.
[ff] Minor morbidity was defined as urinary tract or superficial wound infection, deep vein thrombosis, or creatinine elevated by >2 mg/dl above baseline without the need for dialysis.

				Primary Clinical effectiveness	Median morphine usage per 24 hours	TP/IAT vs.TP alone 10mg (range 0 to 920) vs. 60mg (range 0 to 460) p<0.001			assumptions but no sensitivity analyses were carried out to see how much these assumptions could have affected the results. The baseline outcome and costs data were based on extrapolation of retrospectively collected three year pre-operative data. This makes the assumptions on improved outcomes less reliable.
				Primary Safety	Median survival	TP/IAT vs.TP alone 16.6 vs. 12.9 years p=0.011			
				Primary Costs	Costs over 16 years	TP/IAT vs. assumed no surgery- no TP/IAT or other surgery £110,445 vs. £101,608			

Grade of evidence table

Total pancreatectomy with islet autotransplantation with no comparators					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Metabolic measures	Bellin 2017 Wu et al 2015 Chinnakotla 2014a Chinnakotla 2014b Wilson 2014 Dong et al 2011	6/10 8/10 6/10 7/10 7/10 8/10	Direct Direct Direct Direct Direct Direct	A	Metabolic measures refer to C-peptide and glycated haemoglobin A1c (HbA1c) levels in the studies included. C-peptide is produced in equal amounts to insulin and is the best measure of endogenous insulin secretion (that is insulin produced by the body) in patients with diabetes. Levels are therefore suppressed in type 1 diabetes or in instances where insulin secretion is minimal. HbA1c is a form of haemoglobin that is measured primarily to identify the three-month average plasma glucose concentration. It is usually a reliable indicator of diabetic control. The studies provide an estimate of the mean HbA1c and C-peptide levels after TP/IAT. Wu et al reported mean C-peptide levels at six months for two studies (1.7ng/mL and 1.4ng/mL) the usual range is 0.8 to 3.1ng/mL. One study reported that 90% of patients had levels greater than 0.6ng/mL at three years and another reported 0.4ng/mL at last follow-up. Wu et al, (systematic review and meta-analysis) could not combine the results but reported mean HbA1c levels at 6 months for three studies (7.5%, 7.1% and 6.7%). One of the studies reported levels at one year (7.7%) and at two years (8.5%). The recommended HbA1c range for most people with diabetes is to keep the value <48 mmols/mol (< 6.5%). People at risk of hypoglycaemia, or for whom such tight blood glucose regulation is not advised, may be advised to keep their HbA1c <59 mmols/mol (< 7.5%). The HbA1c levels suggest borderline to uncontrolled diabetes. While the C-peptide levels reported seem to be within the normal range initially but there might be a downward trend with time. The results seem to suggest that metabolic outcomes decline with time. The duration of benefit in the longer term in terms of metabolic outcomes of TP/IAT compared to TP alone is therefore unclear as the review did not include any comparative studies. In addition, the studies were small single centre case

					series hence prone to bias. This means that the benefits may have been exaggerated.
Insulin independence	Bellin 2017 Wu et al 2015 Chinnakotla 2014a Chinnakotla 2014b Wilson 2014 Wilson 2013 Bramis et al 2012 Dong et al 2011 Bellin 2011 Bellin 2008	6/10 8/10 6/10 7/10 7/10 7/10 8/10 8/10 7/10 7/10	Direct Direct Direct Direct Direct Direct Direct Direct Direct Indirect	A	Insulin independence refers to when a patient achieves the required fasting blood glucose and HbA1c levels without the use of exogenous insulin. This is not a critical outcome. The studies provide an estimate of the proportion of patients who are independent of insulin after TP/IAT. Dong et al and Wu et al carried out meta-analyses and reported pooled insulin independence rates of 27% (95% CI: 21-33%) and 28.4% (95% CI: 15.7-46.0) at one year and 21% (95% CI: 16-27%) and 19.7% (95% CI: 5.1-52.6%) at two years respectively (Dong et al 2011, Wu et al 2015). The studies of paediatric patients only report higher rates of insulin independence. These results suggest that just over a quarter of patients would be insulin independent one year after TP/IAT and this goes down to about one fifth of patients after two years. This means that after two years around 80% of patients who undergo TP/IAT would require insulin. This suggests that the benefits of TP/IAT in terms of insulin requirements are relatively small. Although these results are from meta-analyses, they should still be interpreted with caution because the results are based on results from small single centre case series (not comparative studies) therefore prone to bias. This means that the benefits may have been exaggerated. Additionally, insulin independence is not a critical outcome. The ability to control blood sugar levels, whether using exogenous insulin or not, is considered more important.

Pain reduction (Measured by post-op morphine/opioid/narcotic use)	Bellin 2017 Chinnakotla 2014a Chinnakotla 2014b Wilson 2014 Wilson 2013 Bramis et al 2012 Bellin 2011 Bellin 2008	6/10 6/10 7/10 7/10 7/10 8/10 7/10 7/10	Direct Direct Direct Direct Direct Direct Direct Indirect	A	Pain reduction refers to any pain relief associated with chronic pancreatitis that patients get after TP/IAT surgery. This is measured by the reduction in the use of narcotic analgesia typically morphine in the studies included. The studies provide an estimate of the reduction in narcotic use (morphine) after TP/IAT. The systematic review by Bramis et al found two studies that reported on reduction in the use of morphine in patients who had undergone TP/IAT. The authors reported that mean morphine use had decreased postoperatively [by 116mg (n=45) and 55mg (n=50)] compared with baseline. These results suggest favourable pain relief after TP/IAT. However these results should be interpreted with caution because the included studies were of poor quality; they were mainly single centre case series. In addition it is unclear how these results compare to TP alone or other interventions.
Post-op complications/morbidity	Fazlalizadeh 2016 Morgan et al 2015 Chinnakotla 2014b	7/10 6/10 7/10	Indirect Indirect Direct	A	Post-operative complications or morbidity refers to any adverse effects that occurred as a result of TP/IAT. The results provide an estimate of the complication and morbidity rates after TP/IAT. Fazlalizadeh et al 2016 reported that hypoinsulinaemia occurred in 42.3% of patients; renal failure in 12% and that 8.4% of patients had wound infections. This study suggests that hypoinsulinaemia is very common after TP/IAT Without a control arm it is unclear how these results compare to TP without IAT, therefore the results of this study should be interpreted with caution.
Survival/Mortality rates	Fazlalizadeh 2016 Wu et al 2015 Chinnakotla 2014a Wilson 2014 Dong et al 2011	7/10 8/10 6/10 7/10 8/10	Indirect Direct Direct Direct Direct	A	Mortality rates refer to a measure of deaths after TP/IAT at a given time period and survival rates refer to the percentage of patients who are alive after TP/IAT at a given time period. The results provide an estimate of the proportion of patients alive or have died after TP/IAT at given time periods. The meta-analyses by Wu et al and Dong et al found 11 and 11 studies respectively that reported 30-day

					mortality rates. They reported rates of 2.1% (95% CI: 1.2-3.8%) and 5% (95% CI: 2 to 10%) respectively. They also report long-term and last follow-up mortality rate of 1.09 per 100 person-years (95% CI: 0.21-1.97) and 1·38[gg] per 100 person-years (95% CI: 0·66-2·11) respectively. It is unclear whether these results are generalisable because the meta-analyses did not include any comparative studies; the results from unrandomised retrospective studies that compared mortality rates in TP/IAT and TP without IAT were conflicting and both prone to selection bias.
Quality of life (SF-12, SF-36)	Morgan et al 2015 Chinnakotla 2014a Chinnakotla 2014b Wilson 2014 Bellin 2011	6/10 6/10 7/10 7/10 7/10	Indirect Direct Direct Direct Direct	A	Quality of life is generally measured using the Short Form (36) Health Survey which is a 36-item, patient-reported survey of patient health. A shorter version is the SF-12 is used when only physical and mental health summary scores are adequate or required. The results provide an estimate of the improvement in quality of life compared to baseline in patients who have undergone TP/IAT. Morgan et al reported significant improvements in PhysQoL[hh] relative to baseline at one, two, and three years post-surgery of 7.1, 5.8, and 7.8 respectively ($p < 0.001$ for all). The percentage of patients with ≥ 3-point improvement was 65%, 60% & 61% at one, two, and three years respectively. They also reported significant improvements in PsychQoL[ii] relative to baseline at one year, two years, and three years post-surgery of 3.9, 4.9, and 6.6 ($p < 0.001$ for all). Percentage of patients with ≥ 3-point improvement was 49%, 58% & 66% at one, two, and three years respectively. These results suggest that quality of life improves significantly compared to baseline in patients who have undergone TP/IAT. However it is unclear how this compares with TP without IAT or other alternative interventions.

[gg] 1.38/1.09 cases would be expected for 100 persons observed for 1 year
[hh] PhysQoL - physical quality of life score
[ii] PsychQoL- psychological QoL score

Studies of TP/IAT compared with TP without IAT					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Pain reduction Median morphine usage per 24 hours	Garcea 2013	6/10	Direct	C	Pain reduction refers to any pain relief associated with chronic pancreatitis that patients get after TP/IAT surgery. This is measured by the reduction in the use of narcotic analgesia typically morphine in the studies included. The study provides an estimate of the reduction in narcotic use (morphine) after TP/IAT. Garcea et al report median morphine usage in patients who had TP/IAT vs. those who had TP alone of 10mg (range 0 to 920) vs. 60mg (range 0 to 460) p<0.001. These results suggest that patients who have had TP/IAT require one sixth the amount of morphine required by a patient who had had TP alone. However these findings should be interpreted with caution as the baseline requirements were not reported and the ranges were quite wide.
Insulin requirement	Garcea 2013	6/10	Direct	C	Insulin requirement refers to the amount of insulin required by patients after surgery (TP/IAT or TP alone). The study provides an estimate of how much insulin a patient requires in a 24 hour period. Garcea et al reported a higher rate of insulin independence (21.6%) after TP/IAT however figure for comparator was not reported. They also reported insulin requirement after TP/IAT vs. TP alone of 22 versus 35IU (p=0.002). They did not find a difference in HbA1c- details were not reported. Also they did not report any outcomes on C-peptide levels. The results suggest that patients require about 50% more insulin after TP alone compared to after TP/IAT. However these findings should be interpreted with caution because low insulin requirements do not necessarily mean good diabetic control and without any details of HbA1c and information on C-peptide levels it is not clear whether diabetes in these patients is well

					controlled,
Post-op complications/morbidity	Bhayani 2014	7/10	Indirect	B	Post-operative complications or morbidity refers to any adverse effects that occurred as a result of TP/IAT. The results provide an estimate of the complication and morbidity rates after TP/IAT. Bhayani et al reported a 41% major morbidity[jj] rate in patients with TP/IAT compared with 29% in patients who had TP alone (p=0.02). This study suggests that major complications were more common following TP/IAT than after TP alone. The results of this retrospective comparative study should be interpreted with caution because patients were not randomised which may have introduced bias.
Survival/Mortality rates	Bhayani 2014 Garcea 2013	7/10 6/10	Indirect Direct	B	Mortality rates refer to a measure of deaths after TP/IAT at a given time period and survival rates refer to the percentage of patients who are alive after TP/IAT at a given time period. The results provide an estimate of the proportion of patients alive or have died after TP/IAT at given time periods. Garcea et al reported longer survival in patients who had TP/IAT compared with those who had TP without IAT (16.6 vs. 12.9 years; p=0.011). It is unclear whether these results are generalisable because the results from the only other study that compared mortality rates in TP/IAT and TP without IAT were conflicting; additionally this was an unrandomised retrospective study prone to selection bias.
Cost-effectiveness	Garcea et al 2013	6/10	Direct	C	Cost-effectiveness refers to whether TP/IAT is value for money compared to TP without IAT and/or other interventions in patients with chronic pancreatitis. This cost study provides information on the cost of TP/IAT compared to no TP/IAT. Garcea et al reported that the cost of TP/IAT with attendant admission and analgesia costs over the 16-

[jj] Major morbidity was defined as re-intubation, prolonged intubation, pneumonia, cardiac arrest, myocardial infarction, renal failure requiring dialysis, deep or organ space infection, pulmonary embolus, transfusion requirement, sepsis, shock, stroke or coma.

					year survival period was £110,445 compared with £101,608 estimated 16-year costs if no TP/IAT was undertaken. These results should be interpreted with caution because they were not based on comparative trial data. The authors assumed that benefits would be sustained beyond that studied. Costs were computed based on broad and generalised assumptions but no sensitivity analyses were carried out to see how much these assumptions could have affected the results. The baseline outcome and costs data were based on extrapolation of retrospectively collected three year pre-operative data. This makes the assumptions on improved outcomes less reliable.

8 Literature Search Terms

Search strategy Indicate all terms used in the search	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	Patients of all ages with uncontrolled pain (i.e. pain resistance to other forms of treatment such as opioids) due to small duct chronic pancreatitis
I – Intervention Which intervention, treatment or approach should be used?	Total pancreatectomy with islet auto transplant
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	1. Total pancreatectomy without islet auto transplant 2. Other more limited surgical interventions 3. Best medical therapy
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use.	*Critical to decision-making:* Pain relief and reducing or stopping opioid use Measures of diabetic control such as: HbA1c level, islet function through C-peptide level, avoidance of severe hypoglycaemia, Diabetic Keto Acidosis and hypo-unawareness. **Insulin independence is not a critical outcome** Duration of benefit Quality of life *Important to decision-making:* Adverse effects (risks) of surgery Cost effectiveness (NB if studies report outcomes separately for patients with small duct chronic pancreatitis due to genetic factors, the results are to be presented separately – see research questions below).
Assumptions / limits applied to search *Inclusion and exclusion criteria e.g. study design, date limits, patients, intervention, language, setting, country etc.* The review should use broad criteria not restricted to randomised controlled studies. It should include meta-analyses and systematic reviews such as Total pancreatectomy and Islet auto transplantation for chronic pancreatitis by Beilman G Pancreapedia 2015 The background will include information on the natural history of chronic pancreatitis but this will not be based on a separate search and review of the natural history literature. The review should be limited to high volume centres in the modern era and exclude reports from centres which have performed fewer than 10 TP-IAT cumulatively. . Reports prior to 2007 should be excluded. Only peer-reviewed studies published in the English language must be included.	

9 Search Strategy

We searched PubMed, Embase, Cochrane Library, TRIP and NICE Evidence, limiting the search to papers published in English since 1st January 2005 to 24th March 2017. We excluded conference abstracts, commentaries, letters, editorials, case reports and studies with less than 10 patients.

Search Date: 24th March 2017

# ▲	Searches
1	*pancreatitis/ or alcoholic pancreatitis/ or autoimmune pancreatitis/ or chronic pancreatitis/
2	pancreatitis.ti,ab.
3	1 or 2
4	*pancreas resection/
5	exp pancreatitis/su [Surgery]
6	total pancreatectom*.ti,ab. or (pancreatectom* or pancreas resection or pancreatic resection).ti.
7	4 or 5 or 6
8	autotransplantation/ and (pancreas islet transplantation/ or pancreas islet/)
9	(islet adj3 (autotransplant* or auto transplant* or autologous transplant*)).ti,ab.
10	8 or 9
11	7 and 10
12	(tpiat or tp?iat).ti,ab.
13	11 or 12
14	(pain* or narcotic* or opioid* or opiate* or analgesi*).mp.
15	3 and 13 and 14
16	limit 15 to (english language and yr="2005 -Current")
17	3 and 13
18	limit 17 to (english language and yr="2005 -Current")
19	18 not 16

10 Evidence Selection

- Total number of publications reviewed: 60
- Total number of publications considered potentially relevant: 24
- Total number of publications selected for inclusion in this briefing: 14

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12 Appendix 1

The Short Form (36) Health Survey - (SF-36)

The original SF-36 came out from the Medical Outcome Study, MOS, done by the RAND Corporation. The SF-36 consists of eight scaled scores, which are the weighted sums of the questions in their section. Each scale is directly transformed into a 0-100 scale on the assumption that each question carries equal weight. The lower the score the more disability, the higher the score the less disability i.e., a score of zero is equivalent to maximum disability and a score of 100 is equivalent to no disability.

The eight sections are:

- vitality
- physical functioning
- bodily pain
- general health perceptions
- physical role functioning
- emotional role functioning
- social role functioning
- mental health