

CPAG Summary Report for Clinical Panel – Total Pancreatectomy with Islet Autotransplantation for Chronic Pancreatitis – URN 1670

The Benefits of the Proposition			
Total pancreatectomy with islet autotransplantation with no comparators			
No	Metric	Grade of evidence	Summary from evidence review
1.	Survival	There is a survival benefit [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 by Dong et al reported mortality rates at 30 days of 2.1% (95% CI: 1.2-3.8%) and 5% (95% CI: 2 to 10%) respectively. They reported long-term and last follow-up mortality rate of 1.09 per 100 person-years (95% CI: 0.21-1.97) and 1.38¹ 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 alone were conflicting and both prone to selection bias.
2.	Progression free survival	Not measured	
3.	Mobility	Not measured	
4.	Self-care	Not measured	
5.	Usual	Not measured	

¹ 1.38/1.09 cases would be expected for 100 persons observed for 1 year

	activities		
6.	Pain	Benefit determined [A]	Pain reduction refers to any pain relief associated with chronic pancreatitis that patients get after total pancreatectomy with islet autotransplantation (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.
7.	Anxiety / Depression	Not measured	
8.	Replacement of more toxic treatment	Not measured	
9.	Dependency on care giver / supporting independence	Not measured	
10.	Safety	Adverse events identified [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 (low blood insulin levels) occurred in 42.3% of patients; renal failure in 12% and that 8.4% of patients had wound infections. In this study suggests low blood insulin levels were very common after TP/IAT. Without a control arm it is unclear how these results compare to TP alone, therefore the results of this study should be interpreted with caution.
11.	Delivery of intervention	Not measured	

Other health metrics determined by the evidence review Total pancreatectomy with islet autotransplantation with no comparators			
No	Metric	Grade of evidence	Summary from evidence review
1.	Metabolic measures	Grade A	Metabolic measures refer to control of diabetes. Removal of the pancreas by total pancreatectomy inevitably results in complete loss of endogenous insulin (insulin produced by the body) as well as other metabolic functions of the pancreatic islet cells. Patients who have total pancreatectomy (for example for trauma or cancer) are known to be prone, in the short term, to life threatening low blood sugars (hypoglycaemia) and diabetic coma from high blood sugar. In the long term, poor diabetic control is known to increase the risk of heart disease and stroke, blindness and kidney failure. The diabetes of total pancreatectomy is very difficult to control even with advanced techniques such as continuous glucose monitoring systems (CGMS) and feedback loops. The best measure of of endogenous insulin secretion (insulin produced by

			the body) in patients with diabetes is C-peptide levels. HbA1c is a form of haemoglobin that is measured primarily to give an indication of average plasma glucose concentration over a longer period (about 3 months). 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 as 1.7ng/mL and 1.4ng/mL: these are in the normal range (which 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, indicating ongoing insulin production by the transplanted islets. Wu et al 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%). These are in the recommended range for people at risk of hypoglycaemia, which includes those who have had a total pancreatectomy and subsequent insulin replacement 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 might 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.
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			This means that the benefits may have been exaggerated.
2.	Insulin independence	Grade 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.
3.	Quality of life	Grade 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 Physical quality of life 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 Psychological quality of life 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, both physical and psychological, improves significantly compared to baseline in patients who have undergone TP/IAT. However it is unclear how this compares with TP alone or other alternative interventions.

The Benefits of the Proposition

Total pancreatectomy with islet autotransplantation compared with total pancreatectomy alone

No	Metric	Grade of evidence	Summary from evidence review
1.	Survival	There is a survival benefit [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 alone (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 alone were conflicting; additionally this was an unrandomised retrospective study prone to selection bias.
2.	Progression free survival	Not measured	
3.	Mobility	Not measured	
4.	Self-care	Not measured	
5.	Usual activities	Not measured	
6.	Pain	Benefit determined [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 lower doses (one sixth the amount) of morphine required by a patient who has had TP alone. However these findings should be interpreted with caution as the baseline requirements were not reported and the ranges were quite wide.
7.	Anxiety / Depression	Not measured	
8.	Replacement of more toxic treatment	Not measured	
9.	Dependency on care giver / supporting independence	Not measured	
10.	Safety	Adverse events identified [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 that in their series of patients, there was a 41% major morbidity rate in patients with TP/IAT compared with 29% in patients who had TP alone ($p=0.02$). This study suggests that at some centres, 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. Also the high complication rates may not be typical of UK practice.
11.	Delivery of intervention	Not measured	

Draft for public consultation

Other health metrics determined by the evidence review Total pancreatectomy with islet autotransplantation compared with total pancreatectomy alone			
No	Metric	Grade of evidence	Summary from evidence review
1.	Metabolic control	Grade C	Removal of the pancreas by total pancreatectomy inevitably results in complete loss of endogenous insulin (insulin produced by the body) as well as other metabolic functions of the pancreatic islet cells. Patients who have total pancreatectomy (for example for trauma or cancer) are known to be prone, in the short term, to life threatening low blood sugars (hypoglycaemia) and diabetic coma from high blood sugar. In the long term, poor diabetic control is known to increase the risk of heart disease and stroke, blindness and kidney failure. The diabetes of total pancreatectomy is very difficult to control even with advanced techniques such as continuous glucose monitoring systems (CGMS) and feedback loops. Insulin requirement refers to the amount of insulin required by patients after surgery (TP/IAT or TP alone). This is however not regarded as a critical outcome. 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). Garcea et al 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.
2.	Cost-effectiveness	Grade C	Cost-effectiveness refers to whether TP/IAT is value for money compared to TP alone 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-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.
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Draft for public consultation