A03/S(NHSS)c

NHS STANDARD CONTRACT
FOR ISLET TRANSPLANTATION SERVICE (ADULT)

SERVICE SPECIFICATIONS

Service Specification No.	A03/S(HSS)c
Service	Islet transplantation service (Adult)
Commissioner Lead	
Provider Lead	
Period	12 months
Date of Review	

1. Population Needs

1.1 National/local context and evidence base

Successful clinical transplantation of islets purified from cadaveric human donors was realised in North America in the late 1970s. Incremental progress was made, particularly during the 1990s, by several groups worldwide. In Oxford, nine patients with Type 1 diabetes and functional renal grafts each received purified islets from a single donor with evidence of graft function for up to 15 month in five recipients. In 2000 Shapiro and colleagues in Edmonton, Canada reported successful islet transplantation in seven individuals without renal failure but suffering recurrent severe hypoglycaemia despite optimised conventional therapy. Prevention of further significant hypoglycaemia in addition to insulin independence at one year post-transplant was achieved in all.

In a most recent publication, results in 65 islet recipients transplanted in Edmonton were reported (Ryan et al, 2005). The major clinical indications remained disabling hypoglycaemia and glucose lability. Evidence of long-term graft function (secretion of insulin C-peptide) was confirmed at longest current follow up of five years in 80% of recipients. Although up to 90% of individuals have returned to 'top up' insulin injections by five years, the primary end-points of excellent overall glucose control (mean HbA1C 8% pre-transplant; 6.5% post-transplant) without recurrence of major hypoglycaemia have been maintained in all with continuing graft function (Ryan et al, 2005). These results have been matched by the two leading US islet transplant centres, Minnesota and Miami (Froud et al, 2005; Sutherland et al, 2004; Pileggi et al, 2004; Shapiro et al, 2003). Bernhard Hering in Minnesota has confirmed the potential for insulin independence in the majority of recipients following transplantation of islets from a single donor (Hering et al, 2005). Camillo Ricordi in Miami has demonstrated clinical success both locally and following transport of

isolated islets to the transplant team.

2. Scope

2.1 Aims and objectives of service

Islet transplantation is of proven benefit for patients with Type 1 diabetes who suffer from recurrent episodes of severe hypoglycaemia. Successful transplantation can abolish episodes of hypoglycaemia unawareness and improve the quality of life of recipients, while also improving overall metabolic control. Patients who are already receiving immunosuppression for a kidney transplant may also benefit from islet transplantation through the improved metabolic control afforded by an islet after kidney transplant.

This service is commissioned to provide a cure for recurrent severe hypoglycaemia in patients with Type 1 diabetes who have persistent hypoglycaemia despite full education and multidisciplinary team intervention. Alternatives to transplantation will be explored to ensure that medical management of hypoglycaemia unawareness is fully explored before transplantation is considered.

The service will provide education and support for patients undergoing transplantation and will provide long-term management of the complications of diabetes and surveillance of transplant medication side effects. The service will regularly review patients awaiting transplantation.

Children will not ordinarily be considered for transplant given the potential long-term complications of immunosuppression.

Islet transplantation

The national islet transplantation service is commissioned to identify the patients suitable for islet transplantation and provide them with long lasting freedom from life threatening episodes of hypoglycaemia. This intervention aims to reduce the incidence of sudden death associated with recurrent severe hypoglycaemia and improve quality of life within this patient group.

Islet isolation

The nationally commissioned islet isolation laboratories extract insulin secreting islet cells from whole cadaveric pancreata to provide transplantable islet cell preparations to the network of islet transplant centres. Pancreas retrieval and allocation is the responsibility of NHS Blood and Transplant.

The overall aim of the national islet isolation and transplantation service is to provide patients with freedom from recurrent severe episodes of hypoglycaemia. Designated centres provide a cost-effective national program for islet transplantation.

Islet transplant assessment

The objective for the islet transplant assessment services is:

- to provide high level multidisciplinary assessment for all patients suitable for islet transplantation.

Islet transplantation

The objectives for the islet transplantation service are:

- to perform successful islet transplants
- and to provide long term follow up to transplant recipients.

Islet isolation

The objectives for the islet isolation laboratories are:

- to provide a national islet isolation service that complies with regulatory standards
- to provide a capability to isolate islet cells from whole cadaveric pancreata
- to prepare and supply high quality islets suitable for transplantation to the islet transplantation centres
- and to work towards reducing the isolation cost per product.

Pancreas retrieval and allocation is the responsibility of NHS Blood and Transplant.

2.2 Service description/care pathway

The service will provide for isolation of islets from whole pancreata. Patients will be assessed for eligibility against the criteria listed in the service standards. The service will offer islet transplant and follow up.

The islet transplant program provides a tertiary referral service for Type 1 diabetic patients who have severe metabolic lability or recurrent episodes of hypoglycaemia.

Despite best medical management, some patients continue to have significant metabolic lability and require transplantation to resolve their episodes of severe hypoglycaemia. Patients are assessed and counselled in all modalities of pancreatic and islet transplantation. After physical and psychological assessment, a clinical consensus is reached by the transplant team of the patient's suitability for transplantation. Once a decision has been made to pursue transplantation, the patient is either listed locally for islet transplantation or referred for whole organ pancreas transplantation, depending on the choice of the patient and suitability for each modality.

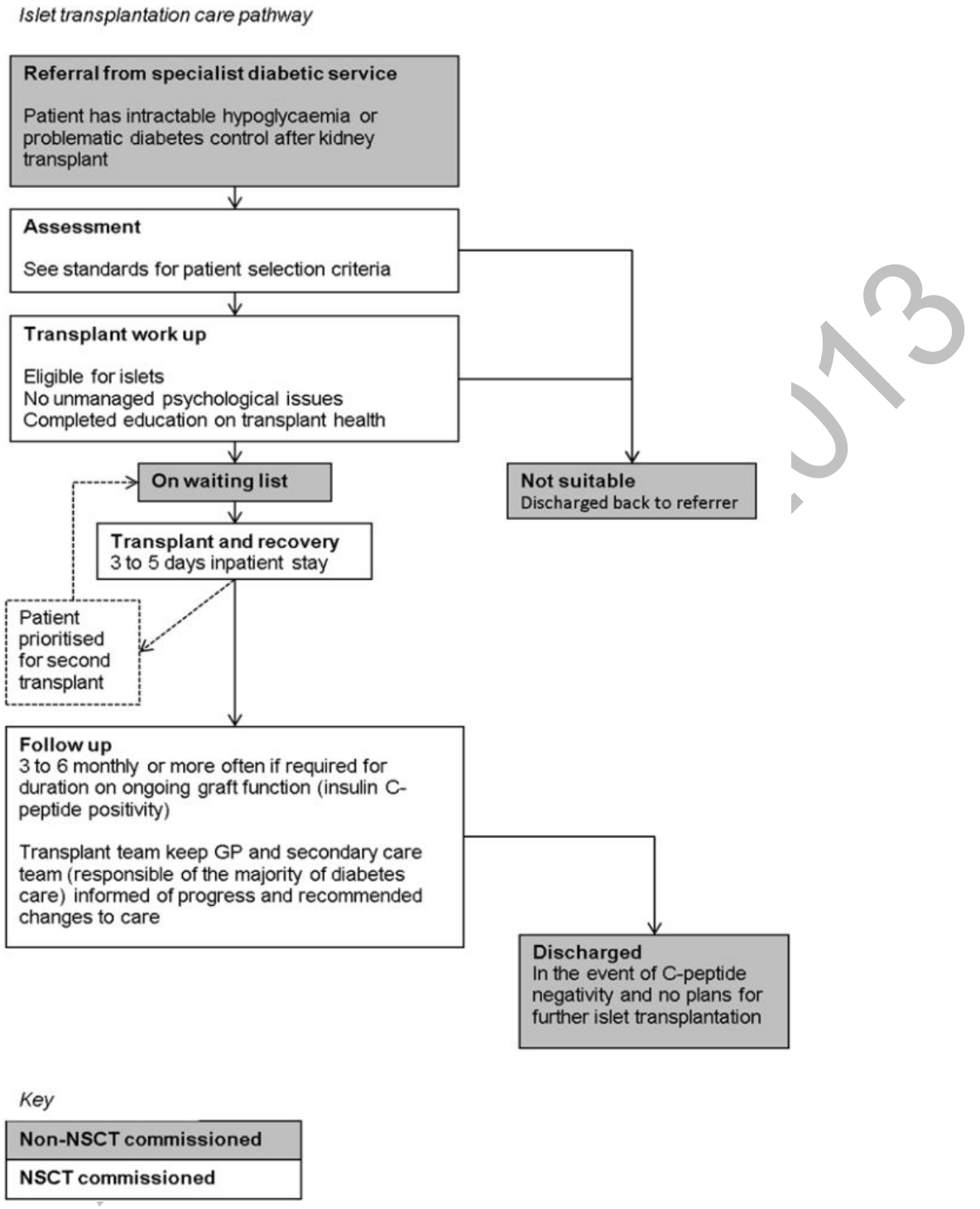
After transplantation, recipients of islet transplants are followed up within the transplant unit for assessment of long-term transplant graft function and the associated complications of transplantation. The patients undergo regular metabolic assessment of their transplant function, in the form of mixed meal testing, and all

metabolic data is fed back to the islet transplant consortium for assessment of centre performance.

Service model and care pathways

The service will provide for isolation of islets from whole pancreata. Patients will be assessed for eligibility against the criteria listed in the service standards:

- the service will offer transplant and follow up
- median duration of hospital admission for each islet transplant is envisaged to be three days patients will remain primarily under the care of their usual diabetes primary/secondary care teams both pre- and post-islet transplantation.



Days/hours of operation

The service is always open. Isolation laboratories operate a rota to ensure the service can provide a 24/7 response to cadaveric pancreas donation.

Discharge criteria & planning including any transition arrangements

Follow-up

Transplant-specific out-patient care will be provided by the multi-disciplinary islet transplant team with regular (3-6 monthly or more frequently as required) follow-up for the duration of ongoing graft function (insulin C-peptide positivity).

Discharge

Both GP and the secondary care team responsible for the majority of diabetes care will be kept informed of progress and any recommended changes in management by the multidisciplinary islet transplant team. In the event of C-peptide negativity and no plans for further islet transplantation, the patient will be discharged from NHS England-funded service.

2.3 Population covered

NHS England commissions the service for the population of England. Commissioning on behalf of other devolved administrations is reviewed annually, and a current list is available from NHS England commissioners or via the website.

At the moment, NHS England contract includes provision for the service to treat eligible overseas patients under S2* referral arrangements. Providers are reimbursed for appropriately referred and recorded activity as part of NHS England contract.

Trusts performing procedures on EU-based patients outside of S2 arrangements will need to continue to make the financial arrangements directly with the governments involved, separately from their contract with NHS England.

With regard to S2, the mechanism for recovery of costs has been via the Department for Work and Pensions Overseas Healthcare Team. They are responsible for agreeing reconciliation and recovery of costs with European administrations. These arrangements were implemented in October 2009, though a similar process existed previously. The financial flows are therefore back into the treasury rather than back to trusts.

*Under EU regulations, patients can be referred for state funded treatment to another European Economic Area (EEA) member state or Switzerland, under the form S2 (for EU member states) or the form E112 (for Iceland, Norway, Liechtenstein and Switzerland)

2.4 Any acceptance and exclusion criteria

NHS England commissions a range of services for devolved administrations, and these are renegotiated annually.

The provider regularly reviews potential transplant recipients, and works with the wider diabetes community, to ensure appropriate referrals and equity of access for all patients.

As a requirement of race, gender, sexual orientation, and religion and disability equality legislation, providers have a duty to co-operate with the commissioner inundertaking Equality Impact Assessments.

Referral criteria, sources and routes

Referrals are from specialist diabetes services. Referral criteria are described in the service standards. A summary is given below:

Established Type 1 diabetes:

- children will not ordinarily be considered for transplant given the potential long-term complications of immunosuppression
- insulin dependence for at least 5 years
- negative C-peptide (<0.16 nmol/l with no increment at 6 min after 1 mg glucagon IV).

Note: This is because the benefits of islet transplantation are associated with replacement of C-peptide positivity.

Intensive diabetes management:

Evidence of compliance with expert medical advice (with glucose testing 3 or more times daily), formal diabetes self-management re-education and intensified insulin therapy including optimised insulin regimens and where appropriate continuous subcutaneous insulin infusion pump therapy.

Absence of insulin resistance

Current islet replacement techniques are not sufficiently efficient to overcome insulin resistance. This is defined as an insulin requirement of more than 0.7units/kg body weight per day to achieve an HbA_{1c} < 9%. BMI should not be greater than 28kg/m^2. Chronic treatment with oral steroids is only permissible for those with renal grafts or Addison's disease and current prednisolone dose should be <5mg daily. Euglycaemic insulin clamps will be used in the early phases to assess insulin sensitivity.

Absence of contraindications to the use of the immunosuppressants:

- impaired renal function (creatinine > 135 μmol/l, or Cr clearance < 80 mls/min/1.73m2)
- macroalbuminuria (AER > 300 mg/24hr) or overt proteinuria
- uncontrolled hypertension
- uncontrolled dyslipidaemia (fasting LDL > 3.4 mmol/l; triglycerides > 2.4 mmol/l)
- active infection including Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), HIV, Tuberculosis (TB) or aspergillus within previous year
- any history of malignancy except completely resected squamous or basal cell carcinoma of skin
- high index of suspicion of non-compliance with conventional therapy
- pregnancy or plans for pregnancy (including fatherhood).

Absence of contraindications to surgery:

- untreated proliferative retinopathy
- recent myocardial infarction or uncorrected myocardial ischaemia
- portal hypertension, gall stones or liver haemangioma on baseline ultrasound
- anaemia / leucopenia / thrombocytopenia; coagulopathy
- on anticoagulants (excluding aspirin)
- active gastric or duodenal ulcer; pancreatitis
- abnormal liver function tests (persistently > 1.5 x upper limit of normal)
- panel of reactive antibody (>20% by flow cytometry).

Other contraindications:

- Addison's disease (untreated) or untreated malabsorptive disease
- inability to reach hospital within 2 hours of notification
- evidence of alcohol excess or other drug abuse.

Individuals with severe hypoglycaemia and normal renal function ('Edmonton profile')

As above but to include:

- experience of at least two episodes of severe hypoglycaemia requiring third party intervention within the last two years. Usually the rate of SH will be higher but this criterion is used to allow inclusion of patients who begin to experience recurrence of severe hypoglycaemia having previously obtained benefit from optimisation of therapy and those who have relaxed control in an attempt to avoid hypoglycaemia
- evidence of altered hypoglycaemia awareness
- (Clarke score ≥4; Ryan HYPO score ≥90th centile and evidence ofperasymptomatic biochemical hypoglycaemia on monitoring)
- or marked glycaemic lability as defined by Ryan Lability Index; continuous subcutaneous glucose monitoring profiles.

Individuals with sub-optimal control despite a functional renal graft

- islet transplantation may be considered in those >3 montNHS and <5 years post-renal transplant who are stable on tacrolimus-based immunosuppression (in combination with mycophenolate mofetil or sirolimus; with prednisolone dose < 5mg daily)
- all with severe hypoglycaemia or altered hypoglycaemia awareness would be eligible
- in addition any with HbA1c >7% or marked glycaemic lability
- Glomerular filtration rate (GFR) should not be <40 ml/min/1.73m and serum creatinine not >175µmol/L

This group of patients may also be considered for pancreas after kidney transplantation but only if without high cardiovascular risk precluding the more major whole organ transplant procedure, or previous prolonged peritoneal dialysis/other abdominal pathology adversely increasing operative risk. Children will not ordinarily be considered for transplant given the potential long-term complications of immunosuppression.

Exclusion criteria

See service standards for exclusions.

Response time & detail and prioritisation

The service will meet national wait times as appropriate. Wait times for transplant are dependent on organ availability.

2.5 Interdependencies with other services

Key relationships are with specialist diabetic services. Referrals are principally from secondary care and information regarding referral should be disseminated.

Relevant networks and screening programmes

UK Islet Transplant Consortium

3. Applicable Service Standards

3.1 Applicable national standards e.g. NICE, Royal College

The service will meet standard NHS governance requirements.

4. Key Service Outcomes

Quality Performance Indicator	***Threshold***	***Method of measurement***	***Consequence of breach***	***Report Due***
Outcomes	Elimination of hypoglycaemia	Significant variation from the national average or in 2 national centres significant variation from the outcomes achieved in the previous 3 years	Performance notice as set out in Clause 32.4 Review & action plan	NHS CB Annual report (September of contract year)

5. Location of Provider Premises

Provider	Islet transplant assessment	Islet transplantation	Islet isolation
King's College Hospital NHS Foundation Trust Denmark Hill, London SE5 9RS	**Yes**	**Yes**	**Yes**
Oxford University Hospitals NHS Trust Churchill Hospital, Headington, Oxford OX3 7LJ	**Yes**	**Yes**	**Yes**
Central Manchester and Manchester Children's University Hospitals NHS Foundation Trust Manchester Royal Infirmary, Cobbett House, Oxford Road, Manchester M13 9WL	**Yes**	**Yes**	**No**
The Newcastle upon Tyne Hospitals NHS Foundation Trust Freeman Hospital, High Heaton, Newcastle upon Tyne NE7 7DN	**Yes**	**Yes**	**No**
Royal Free Hampstead NHS Foundation Trust Pond Street, London NW3 2QG	**Yes**	**Yes**	**No**
North Bristol NHS Trust Trust Headquarters, Beckspool Road, Frenchay, Bristol BS16 1JE	**Yes**	**Yes**	**No**