A03/S(HSS)/b

NHS STANDARD CONTRACT
FOR INSULIN-RESISTANT DIABETES SERVICES (ALL AGES)

PARTICULARS, SCHEDULE 2 – THE SERVICES, A- SERVICE SPECIFICATION

Service Specification No.	A03/S(HSS)/b
Service	Insulin-resistant diabetes services (All Ages)
Commissioner Lead	
Provider Lead	
Period	12 months
Date of Review	

1. Population Needs

The National Insulin Resistant Diabetes Service provides a multidisciplinary outpatient clinic at Cambridge University Hospitals NHS Foundation Trust (CUH) plus inpatient stays for initiation of therapy when indicated.

The aim of the service is to provide diagnostic, therapeutic and educational support for both patients and their local clinical carers, and to establish and disseminate evidence-based recommendations for the therapy of this severe group of conditions.

The purpose of the service is to improve outcomes for these patients through the following mechanisms:

- by providing a precise diagnosis wherever possible
- by the provision of targeted specialist delivered treatment interventions including both dietary and pharmacological therapies
- by educating patients, their relatives (where this is appropriate) and local health carers
- by raising the profile of severe insulin resistance/lipodystrophy as a clinical problem in order to improve access to optimal care for affected patients.

1.1 Diagnosis and Treatment :

The efficacy of recombinant human insulin-like growth factor (rhIGF1) and the dramatic impact of leptin in appropriately selected patients have been demonstrated in small clinical trials summarised in the above references.

Leptin therapy:
Experience in 35 patients treated for 1-8 yrs suggested that triglyceride levels fell from a mean of 10.2 to 4.2 mmol/L (59% reduction) and haemoglobin A1C (HBA1c) decreased from a mean of 8.4% to 6.9%. The latter effect comfortably exceeds the goal of a 1% reduction in

HBA1c for novel treatments for type 2 diabetes and is expected to significantly delay micro- and macrovascular complications, although long-term trial evidence documenting these benefits is yet to be accumulated. The magnitude of the changes observed in glycaemic control and dyslipidaemia are expected to result in substantial reductions in macrovascular complications of diabetes (based on United Kingdom Prospective Diabetes Study (UKPDS) data)(8). For example, a fall of HbA1c of 1.5% (the mean in the above study) would translate to a >10% reduction in major macro- or microvascular events (8). Patients with lipodystrophy also tend to develop proteinuria and this was also significantly reduced by leptin therapy (9). Leptin therapy also reduces admissions for serious acute complications such as pancreatitis which costs on average £2000 per admission – prior to commencing leptin therapy, 5/10 local patients experienced recurrent pancreatitis whereas since starting leptin in 2007/8 none of the 10 patients has had an episode of pancreatitis whilst on leptin.

Local experience with leptin:
Ten patients are currently using leptin therapy in England. All of these were commenced on therapy as adults due to the fact that leptin only recently (2008) became available to these patients in England. The absolute mean ± SD changes (all decreases i.e. improvements) in triglyceride (TG) levels, liver fat (LF) levels and HBA1c are as follows:

- TG – 1.2 ± 1.3 mmol/L;
- LF – 25 ± 29 %;
- HBA1c – 1.1 ± 1.6 %.

These are in line with published data.

rhIGF-1:
The very guarded prognosis of the rare syndromes of defective insulin receptor function (less than 1 year for Donohue syndrome, and approximately 5-20 years for Rabson Mendenhall syndrome) has led to the use of the insulin homologue IGF-1 in an attempt to circumvent the dysfunctional insulin receptors. Collectively, studies to date suggest that there is a clear and reproducible metabolic benefit from IGF-1 treatment, with the most impressive results having been reported with longer term use of very high doses, which have been reported to dramatically increase longevity in babies with Donohue Syndrome. Nevertheless the optimal dosage and timing of therapy remain to be determined. Evidence has also recently been provided which demonstrates that rhIGF1 can exert markedly beneficial metabolic effects in a variety of different forms of syndromic severe insulin resistance in adulthood (a mean 1.4% reduction in HbA1c was seen in 5 patients after 16 weeks therapy.

Immunosuppression:
Evidence of the benefits of immunosuppressive therapy in patients with acquired syndromes of extreme insulin resistance is limited to a series of case reports. These disorders are exceedingly rare so this is likely to remain true in the future. The service would provide a unique opportunity to collate such experience for future patient benefit.

Small scale evidence for the judicious use of acarbose, U500 insulin use), pump therapy and Glucagon-like peptide-1 (GLP1) agonists is available. However, there will never be large scale trial evidence of efficacy, and careful selection of patients and monitoring of therapy by a specialist team will be critical for improving i) patient health with available therapy and ii) treatment algorithms.

Education:

Whilst randomised controlled trial (RCT) evidence is lacking, considerable expertise in managing patients with severe insulin resistance/ lipodystrophy has been developed over time. This has shown how harmful (severe dyslipidaemia/ pancreatitis, hyperglycaemia and steatohepatitis) high fat diets can be in lipodystrophy; a fact which is often under-appreciated by clinicians/dieticians whose approach to diet is confounded by the apparent leanness of the patients. Specialist dietetics input is essential in the management of such patients.

2. Scope

2.1 Aims and objectives of service

The National Insulin Resistant Diabetes Service provides a multidisciplinary outpatient clinic at Cambridge University Hospitals NHS Foundation Trust (CUH) plus inpatient stays for initiation of therapy when indicated.

The aim of the service is to provide diagnostic, therapeutic and educational support for both patients and their local clinical carers, and to establish and disseminate evidence-based recommendations for the therapy of this severe group of conditions.

The service is targeted at patients with lipodystrophy and/or extreme insulin resistance as defined below (in 2.1). These are very rare but metabolically devastating disorders associated with significant long-term morbidity and mortality.

The purpose of the service is to improve outcomes for these patients through the following mechanisms:

- by providing a precise diagnosis wherever possible
- by the provision of targeted specialist delivered treatment interventions including both dietary and pharmacological therapies
- by educating patients, their relatives (where this is appropriate) and local health carers
- by raising the profile of severe insulin resistance/lipodystrophy as a clinical problem in order to improve access to optimal care for affected patients.

Objectives and expected outcomes

Diagnosis

Accurate clinical assessment is an essential step to putting the correct management strategies in place early for this group of patients. This requires close links to clinical biochemistry, molecular genetics and radiology services, to provide a complete, integrated package of clinical, biochemical and radiological evaluation as well as definitive molecular genetic diagnosis where appropriate.

Objective 1

- To provide a specific diagnosis to all patients with lipodystrophy/severe insulin resistance. This is not currently possible as the genetic basis of several of the disease

subtypes remains unknown but there is an aspiration to meet this objective in due course.

Outcome measure 1

Number and type of precise diagnoses made/number of referrals.

Patient Management

Where good metabolic control is maintained in referred patients, patient management will be delivered through annual reviews in the national service in conjunction with locally commissioned diabetes care. The nationally commissioned service will also provide a limited amount of specialist dietetic and nursing care directly to patients and by providing expert advice to local diabetes services. Expertise in the use of leptin is essentially only available through the nationally commissioned service within the UK. Additionally, this service has the greatest experience of the use of rhIGF1 in severe insulin resistance (4, 25). Where specialist therapies are introduced, several reviews at CUH per year may be required and will be undertaken in conjunction with local diabetes care where appropriate.

Objective 2

- To deliver specialist dietetic and nursing care targeted at these specific patients. This will require intensive efforts with the patients and local dieticians/specialist nurses and doctors.

Objective 3

- To provide suitable patients with targeted pharmacological therapies including leptin for severe lipodystrophy and IGF1 for patients with primary insulin receptoropathies. To advise local providers on the administration of immunosuppressive therapies in conjunction with specialist immunological input in patients with autoimmune forms of severe insulin resistance.

Outcomes for 2 & 3

Meeting these objectives will be reflected in patient clinical outcomes specified in item 7. Patients receiving leptin must be part of ongoing audit. Use of other specialist therapies must also be audited.

2.2 Service description/care pathway

Target patients:

- the service is aimed at patients with extreme insulin resistance and/or lipodystrophy. Specifically, referral criteria are:
  - Donohue Syndrome or Rabson Mendenhall Syndrome with confirmed extreme hyperinsulinaemia

  - clinically diagnosed lipodystrophy (generalised or partial)
- unexplained severe insulin resistance:
  - Body Mass Index (BMI)<30 kg/m2 AND acanthosis nigricans AND/OR severe hyperinsulinaemia*

*fasting insulin>150pM or peak plasma insulin on oral glucose tolerance testing >1,500pM

Overview of the service

The core element of service provided is a weekly multidisciplinary clinic consisting of (minimum requirement):

- consultant
- specialist nurse
- dietician
- genetic counsellor (only a strict requirement for all cases with a new genetic diagnosis and after that the genetic counsellor will be available according to individual patient requirements).

Patients presenting before the age of 16 years will be seen in conjunction with paediatric endocrine consultants supported by paediatric specialist nursing and dietetic input.

Liaison with local clinicians managing the patients is a key component of the service outside the weekly multidisciplinary teams (MDTs). These shared care arrangements will involve liaison with local carers (hospital specialists, GPs, specialist nurses and dieticians). This will allow the service to educate patients and local care teams to optimise the patient's care. New patients will be seen in clinics at CUH. Diagnostic results and management advice will then be communicated to the patient and their local medical team.

Most patients will not then require review at CUH but will require remote contact with the specialist dietician. The service will maintain contact with local specialists and GPs to provide advice as required. Patients receiving specialist therapies including leptin and IGF1 will be reviewed on a regular basis (up to quarterly) as indicated by their clinical progress.

Other patients will return to the care of their local specialists and GPs with remote support from the National Severe Insulin Resistance Service. Patients not receiving specialist therapies and thus not under regular follow up at CUH who experience particular clinical difficulties with for example poorly controlled diabetes or dyslipidaemia may be reviewed at CUH if this is requested by the local care team or if they later become eligible for specialist therapies (leptin, IGF1). This is likely to be a rare event.

In rare cases, where specific therapies (leptin or IGF1) are appropriate, patients will need to return to CUH for treatment initiation and regular follow-up – usually quarterly or biannually.

When required patients will be admitted to CUH for short stays of between five to ten days for initiation of specialist therapies such as rhIGF1, leptin, or multimodal immunosuppression.

Other inpatient care of complications of severe insulin resistance and lipodystrophy are outside the scope of this specification. These will be managed according to standard practice

guidelines with advice where necessary from NHS England .

Specialist investigations:

The clinical service will be supported by the provision of specialist biochemical and genetic assays and specialised imaging. These will include:

- determination of plasma markers of insulin action such as adiponectin
- assays such as the anti insulin receptor antibody assay
- MRI-based techniques to directly assess liver fat and fibrosis.

These investigations will be provided by the clinical biochemistry, molecular genetics and radiology services at CUH.

Specialist therapies:

- Dietary modification is an essential element in the management of patients with these disorders. Specialist input is required to adjust dietary advice for the unusual body composition associated with lipodystrophies and the need for strict calorie restriction in patients with apparently normal BMIs.
- Specialist nursing input, including education of local carers, will be required to support the initiation and on-going use of U500 insulin which will be required in many of the patients. This will involve extensive liaison with and education of GPs, community specialist nurses, and other relevant carers. This specification covers the initiation of U500 therapy and funding is provided for the first 3-months of therapy. Past 3 months funding responsibility for patients responding appropriately to U500 therapy will pass to the patient's responsible Clinical Commissioning Group (CCG) or other responsible commissioner.
- Recombinant leptin is specifically indicated for patients with severe lipodystrophy and low leptin levels (<10ug/L). The national service will select and treat patients with leptin as is clinically indicated. The cost of leptin is expressly excluded from the funding for this service.
- Recombinant human IGF-1: Subcutaneous recombinant human IGF-1 (rhIGF1) is effective in improving metabolic control, and possibly survival, in patients with Donohue Syndrome and Rabson Mendenhall Syndrome, rare paediatric conditions at the most severe end of the spectrum of genetic insulin receptor dysfunction. It has also been shown to be effective in older patients with a variety of different syndromic forms of severe insulin resistance (26).
- Immunosuppression - In addition to monogenic causes of extreme insulin resistance and lipodystrophy, these disorders may also develop as a result of autoimmune disease. In some cases the consequences can be life-threatening and require targeted immunosuppression.

In this setting, it is anticipated that the provider will manage acutely unwell patients with, for example, anti-insulin receptor or anti-insulin antibodies or autoimmune lipodystrophy, often in combination with other serious autoimmune disease such as systemic lupus erythematosis (S.L.E.), as inpatients at CUH. As with any severely insulin resistant or lipodystrophic patient, the decision to admit or transfer to CUH for inpatient care will be based purely on clinical need, irrespective of geographical location in England. Inpatient stays and specialist investigations required for the diagnostic work-up of these patients will be covered by the

service. However, if a diagnosis of acquired auto-immune disease is established, requiring immunosuppressive therapy, such therapy will be administered under the specialist guidance of colleagues with the necessary immunological expertise. Costs for these services and subsequent immunological therapies will not be covered by the National Severe Insulin Resistance Service. Recent experience suggests that targeted and sometimes aggressive immunosuppression in the hands of an expert metabolic and immunological team is required to bring disease under control and limit inpatient stays and to reduce complications both of the underlying disease and its therapy.

- GPL1 agonists may be prescribed according to NHS England protocol covering these drugs within this service. The protocol may be varied at the sole discretion of NHS England. Initiation of therapy, monitoring and cessation of therapy must all be carried out in accordance with the protocol. It is the trust's responsibility to notify the commissioner on an exceptional basis should there be any breaches of the care standards. Where there are breaches any consequences will be deemed as being the trust's responsibility. CUH will ensure that professionals within the trust adhere to the standards of their regulatory bodies.

Patients must be managed in line with the specification and care standards. Any deviation from these which has not been approved by NHS England is at the trust's risk both clinically and financially. It is the trust's responsibility to inform the commissioners of any such non-approved deviations on an exceptional basis.
Where a patient's presentation challenges the assumptions that underpin the specification, service standards and/or contractual arrangements it is the Trust's responsibility to inform the commissioners on an exceptional basis, prior to any treatment (except for emergency treatment) so that the implications of the patient's requirements can be considered. This does not affect situations where the Individual Funding Application process applies.

Days/hours of operation

Weekly clinic, DSN and dietician will be available at clinic appointments and for liaison throughout the working week. Similarly, consultant advice is available every weekday.

Discharge criteria & planning including any transition arrangements

This is largely not applicable given the proposed clinical pathways. The provider will aim to maintain contact with patients and their local care teams but most of this will be done remotely.

2.3 Population covered

This service covers patients registered with an English General Practitioner, resident in the European Union and eligible for treatment in the NHS under reciprocal arrangements. Patients from Scotland, Wales and Northern Ireland are not part of this commissioned service and the trust must have separate arrangements in place.

2.4 Any acceptance and exclusion criteria

The service is accessible to all patients in England either registered with an English GP or normally resident in England regardless of sex, race, or gender**.** Staff within the service are

required to attend the trust's mandatory training on equality and diversity and the facilities provided offer appropriate disabled access for patients, family and carers.

When required the service will use translators and printed information is available in multiple languages.

The provider has a duty to co-operate with the commissioner in undertaking Equality Impact Assessments as a requirement of race, gender, sexual orientation, religion and disability equality legislation

Referral criteria, sources and routes

Patients with lipodystrophy and syndromic forms of severe insulin resistance are generally clinically recognisable and so specialist investigations are not required prior to referral.

For other patients with severe insulin resistance, acanthosis nigricans is a very specific clinical sign and is sufficient to guide referral in non-obese (BMI<30) patients. However, it is not always present, in which case referrals should include measures of fasting insulin levels or insulin levels during a Glucose Tolerance Test (OGTT).

Referrals will be triaged by the lead consultants in all cases.

Exclusion criteria

All patients within the target population can be referred for assessment. There are no exclusion criteria for patients within this remit.

Conceivably the most common cause for confusion will relate to obese patients with features of severe insulin resistance. Some patients with lipodystrophy or syndromic severe insulin resistance may have a BMI of >30kg/m2 – these will be seen, but other obese patients with severe insulin resistance are not currently covered by this service.

Response time & detail and prioritisation

The clinic will be accessible on a weekly basis but most patients do not need to be seen within a specified timeline as these are largely chronic metabolic disorders. Patients with extreme metabolic derangements such as extreme hyperglycaemia or hypertriglyceridaemia will be prioritised accordingly.

2.5 Interdependencies with other services

The service is specifically aimed at providing patients with a specific diagnosis and management advice. Care will then largely be devolved to local specialists (i.e. diabetes specialists in most cases) and carers. On-going remote support will be provided. In cases, where leptin or IGF1 therapy is instituted, the provider will continue to see patients regularly although some of their standard care such as eye screening for people with diabetes is devolved to local carers.

The provider will also offer patients direct contact with the service via remote communication

(by phone, email and/or letter) in order to facilitate dietary interventions and other management plans.

Relevant networks and screening programmes

The CUH Clinical Biochemistry Laboratory offers a Specialist Assay Service for insulin measurements. This serves as a useful screening platform for detecting patients with severe hyperinsulinaemia. The aim is to ensure that all laboratories nationally, are aware of the service so that it can aid assessment of all patients with severe hyperinsulinaemia who are not obese (BMI>30 kg/m2).

3. Applicable Service Standards

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

The National Severe Insulin Resistance Service must be fully integrated into the trust's corporate and clinical governance arrangements.

The commissioners and service will conduct a formal Joint Service Review at least every six months.

NHS England and the service will develop service standards to be incorporated into the agreement in 2013/14.

4. Key Service Outcomes

- Number and type of precise diagnoses made/number of referrals.
- Patients receiving leptin must be part of ongoing audit. Use of other specialist therapies must also be audited.

Quality Performance Indicator	***Threshold***	***Method of measurement***	***Consequence of breach***	***Report Due***
Diabetes onset if not already present				
HBA1c (glycated haemoglobin)				
Fasting triglycerides				
HDL cholesterol				
Appearance/progression of neuropathy/nephropathy/retinopathy				
Appearance/progression of macrovascular disease				
Episodes of Pancreatitis				
Fertility				

Pregnancy outcome				
Severity of Clinical Hyperandrogenism (Ferriman Galwey/Subjective)				
Emergency Admissions due to complications of severe IR/LD				
Development of any malignancy (e.g. hepatocellular Ca, colorectal Ca)				
Mortality/Age at Death				

Supplementary Table Showing the Time Interval Suggested for Measurement of Outcome Variables

Outcome	Period between measurements
Diabetes onset if not already present	12 months
HBA1c (glycated haemoglobin)	6 months
Fasting triglycerides	6 months
HDL cholesterol	6 months
Appearance/progression of neuropathy/nephropathy/retinopathy	12 months
Appearance/progression of macrovascular disease	12 months
Episodes of Pancreatitis	12 months
Fertility	Case by case over 12 months
Pregnancy outcome	Case by case over 12 months
Severity of Clinical Hyperandrogenism (Ferriman Galwey/Subjective)	12 months
Emergency Admissions due to complications of severe IR/LD	12 months
Development of malignancy	12 months
Mortality/Age at Death	Case by case over 12 months

5. Location of Provider Premises

Cambridge University Hospitals NHS Foundation Trust