

E06/S(HSS)/c

**2013/14 NHS STANDARD CONTRACT  
FOR LYSOSOMAL STORAGE DISORDERS SERVICE (CHILDREN)**

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

<b>Service Specification No.</b>	E06/S(HSS)/c for adult see Appendix 1
<b>Service</b>	Lysosomal storage disorders service (Children)
<b>Commissioner Lead</b>	
<b>Provider Lead</b>	
<b>Period</b>	12 months
<b>Date of Review</b>	

## 1. Population Needs

### 1.1 National/local context and evidence base

The aim of the service is to provide an inclusive, holistic, multi-disciplinary service for children with lysosomal storage disorders (LSDs). This should include the rapid diagnosis of patients suspected as having LSD, multidisciplinary assessment of disease burden, the provision of disease specific therapy, advice on symptom control and palliative care for patients with untreatable disorders and, in conjunction with patient advocacy groups, provide support for affected families.

The lysosome is an intracellular organelle with an acidic interior containing a range of hydrolytic enzymes such as glycosidases, proteases, sulfaphatases, lipases and phosphatases. These hydrolases together with a number of integral lysosomal membrane proteins, transporters and targeting motifs are responsible for much of the cells inherent recycling mechanism and defects in any of these components can result in the pathological storage of partially metabolised substrates within the cell. This, plus the pathological cascades initiated as a result of the lysosomal dysfunction, gives rise to a group of mongeneic disorders known as lysosomal storage disorders (LSDs).

Most LSDs are inherited as autosomal recessive traits. The exceptions are the X-linked enzyme deficiency disorders Fabry disease and Mucopolysaccharidosis type II (Hunter syndrome) and the X-linked disorder of lysosomal associated membrane protein 2 (LAMP2) known as Danon disease.

Although individual disorders are considered very rare there are a large number of them (over 50) and thus the prevalence of the group as a whole are about 14 per 100, 000 live births<sup>1</sup>.

The LSDs like many other genetic disorders show a remarkably varied phenotype. In

some patients the presentation may be in the newborn period, whereas in others, with the same disease (but a different genetic mutation), onset may be in late adulthood. Clinical disease may affect many organ systems and is usually progressive.

Management requires a coordinated approach from many different medical specialities as well as input from colleagues in professions allied to medicine. For some disorders management is purely palliative and involves symptom control alone whereas other disorders have disease specific therapies such as enzyme replacement therapy<sup>2</sup>. Cell based therapies including haematopoietic stem cell transplantation<sup>3</sup> and substrate reduction therapy<sup>4</sup> have a limited but important role in treatment. The LSDs, their genetic basis, clinical features and recommended therapies are illustrated in the Table outlined in the appendix.

Concentrating children with LSDs in specialist paediatric metabolic disease centres ensures that the multi-disciplinary team necessary to manage such patients will see sufficient numbers to main expertise so that patients will be treated efficiently and expensive therapies used more effectively. In addition, increasing expertise allows for the earlier recognition and treatment of potential complications hopefully leading to a reduced disease burden.

The target population includes all children with LSD although not all aspects of management are commissioned nationally. The service specification concentrates on the disorders that are currently managed by enzyme replacement therapy (ERT) or substrate reduction therapy (SRT). Haematopoietic stem cell therapy (HSCT) for LSD is excluded from this specification.

## **Evidence Base**

Fabry disease is an X-linked disorder caused by a deficiency of the lysosomal enzyme  $\alpha$ -Galactosidase A. The disorder is pan-ethnic, occurs with a prevalence of 1:117,000 births and neuropathic pain is most often the first sign of the disease in childhood although this is often misdiagnosed<sup>5, 6</sup>. Without treatment the condition progress throughout adult life to cause serious cardiac, neurological and renal disease<sup>7</sup>. A panel of physician experts have recommended that ERT be initiated as early as possible in all males with Fabry disease, including children<sup>8</sup>. There are two products available for enzyme replacement therapy, Agalsidase alpha (Replagal™, Shire Genetic Therapies, UK) and Agalsidase beta (Fabrazyme®, Genzyme Corp, USA). An approach to diagnosis and management has recently been published<sup>9</sup>.

Gaucher disease (GD) is an autosomal recessive disorder caused by a deficiency of the lysosomal enzyme Beta glucocerebrosidase. There are three types of Gaucher disease all of which occur in children. The first type, type 1, is the most common and patients in this group usually present with enlargement of the liver and spleen and haematological problems. There are no signs of brain involvement but without treatment serious skeletal complications can occur. In type 2 Gaucher disease, liver and spleen enlargement are apparent by 3 months of age and affected infants have central nervous system (CNS) damage and usually die by 2 years of age. In the third

category, called type 3, liver and spleen enlargement is variable, respiratory disease is common and signs of brain involvement such as seizures may become apparent over time. This type of Gaucher disease is also associated with a specific eye movement abnormality<sup>10</sup>

Both type I and type III (GD) respond favourably to ERT. Type II disease does not respond and ERT cannot prevent the inevitable neurological decline and is therefore not indicated in these patients. Two ERT products are currently licensed for use in GD, Imiglucerase (Cerezyme®, Genzyme Corp, USA) and Velaglucerase alfa (Vpriv®, Shire Genetic Therapies, UK). Individualised therapeutic goals may be necessary in children especially those with type III disease<sup>11</sup>. For patients deemed unsuitable for treatment with ERT the substrate inhibiting drug Miglustat (Zavesca®, Actelion Pharmaceuticals, UK) has a license for use in type I GD and has been shown to be an effective long term therapy for adults with type I disease<sup>12</sup>

Mucopolysaccharidoses (MPS) are a group of disorders associated with specific enzyme deficiencies. Most are inherited as autosomal recessive traits with the exception of MPS II (Hunter syndrome) which is X-linked. The treatment of the severe form of MPS I (Hurler syndrome) is by HSCT which is excluded from this specification. ERT is available for MPS I (non-Hurler patients) using Laronidase (Aldurazyme®, Genzyme Corp, USA), MPS II using Idursulfase (Elaprase®, Shire Genetic Therapies, UK) and MPS VI using Galsulfase (Naglazyme®, BioMarin, Novato USA). Clinical trials in MPS IV are at an advanced stage and a brief review of outcomes for MPS patients treated by ERT has been published<sup>13</sup>. Children with MPS have complex problems that affect many organ systems and illustrate graphically the need for multidisciplinary management of LSD patients<sup>14</sup>

Pompe disease (acid maltase deficiency, glycogen storage disease type II) is caused by a deficiency of the lysosomal enzyme acid glucosidase (acid maltase). Although milder variants do occur the commonest presentation in childhood is with severe infantile disease (often called “classical” Pompe disease). This disorder is associated with a rapidly progressive cardiomyopathy, generalised skeletal muscle weakness, respiratory failure and early death in the first few months of life<sup>15</sup>. Affected infants often require long periods of time on paediatric intensive care units and many go on to require long term mechanical ventilation. ERT with Alglucosidase alfa (Myozyme®, Genzyme Corp, USA) dramatically alters the natural history of the infantile disease but many patients still require complex long term follow up<sup>16</sup>

Niemann-Pick disease type C (NP-C) is associated with a late endosomal defect in cholesterol trafficking. Defects in two different proteins NP-C1 (95%) and NP-C2 (5%) can cause the severe neurovisceral disorder NP-C<sup>17</sup>. Heterogeneity can be extreme ranging from death in the newborn period due to liver failure to a presentation in adult life with purely psychiatric symptoms. Neurological abnormalities are common including gaze palsy and the development of cataplexy and narcolepsy, uncommon conditions that require specialist management. The NP-C2 protein is a lysosomal hydrolase and treatment by HSCT can be attempted. The NP-C1 protein is more complex and thought to act in conjunction with NP-C2 to

promote efflux of cholesterol out of the late endosomal system. In NP-C the primary storage products in the brain are gangliosides and not cholesterol<sup>17</sup>. The substrate inhibiting drug Miglustat (Zavesca®, Actelion Pharmaceuticals, UK) has been shown to stabilise disease progression in both adults and children with NP-C<sup>18, 19</sup>

Other disorders associated with the accumulation of gangliosides within the CNS (GM<sub>1</sub> and GM<sub>2</sub> gangliosidosis) have also been treated with the substrate inhibiting drug Miglustat (Zavesca®, Actelion Pharmaceuticals, UK). The indications in this area are very limited and this treatment is not routinely commissioned.

## **2. Scope**

### **2.1 Aims and objectives of service**

#### **Objectives and Expected Outcomes**

The strategic objectives of the service are to provide children with LSDs rapid access to diagnostic testing, assessment and appropriate multi-disciplinary management for their underlying disorder.

#### **Key outcomes of the service:**

- Children with LSDs are diagnosed promptly and accurately.
- Patients are assessed and treated in designated centres by appropriately trained multi-disciplinary teams and managed under shared care protocols with local hospitals where appropriate.
- All patients should be provided with appropriate disease specific treatment – HSCT, ERT or SRT.
- The condition and its response to therapy should be monitored regularly and should be discontinued in patients that are not benefitting from treatment.
- Patients, parents and patient advocacy groups should be involved in improving the quality of the service.
- Equality of management across centres, treatment protocols, and common quality standards, are followed.

### **2.2 Service description/care pathway**

#### **Service description**

Services will be well organised to avoid repeat and unnecessary visits by families. The goal is to produce a “one-stop” service. The will be expected to deliver a rapid, accurate diagnosis, an assessment of disease burden at baseline and the provision of disease specific therapy where available. Patients will be followed up according to disease-specific protocols that are evidence based and have input from patient advocacy groups.

### **Laboratory facilities:**

- A specialised laboratory service should be capable of carrying out all the tests relevant for the diagnosis of inherited lysosomal disorders. Although histopathology services may contribute to the diagnosis, it is biochemical assay and molecular genetic studies, sometimes involving the study of cultured cells and biopsy specimens that are principally required for the evaluation of lysosomal storage disorders.
- There should be access to microbiology, virology, biochemistry, haematology and blood bank services.
- Access to diagnostic services should ensure that specific enzyme functions can be assayed, both in relation to the suspected diagnosis and also to screen for possible candidate diagnoses in a person with a LSD.
- Services should make pre-implantation genetic diagnosis available where appropriate.
- Laboratories must be able to analyse blood cells, cultured fibroblasts, biopsy tissue, plasma and urine samples.

### **Diagnostic support:**

- There should be access to a range of diagnostic imaging including ultrasound, computed tomography (CT) and Magnetic resonance imaging (MRI) imaging.
- There should be ready access to echocardiography and other specialised cardiac services.
- There should be ready access to pulmonary function tests and a sleep laboratory able to examine for sleep apnoea.
- There should be ready access to a physiotherapist experienced in assessing children with LSD.

### **Care and treatment**

#### **Care setting:**

- Children may be managed as outpatients in centres together with adult patients and their families (appropriate for disorders such as Fabry disease), or in children's hospitals. In all cases national standards for the care of children in hospital must be met.
- The provider will ensure that patients with LSD can be admitted without delay to a suitable ward staffed by personnel familiar with care of patients with LSD.
- Staff on admitting wards and in A&E departments will be aware of the provider's arrangements for care of patients with LSD and ensure prompt referral to the LSD team.
- Each centre will have a regular daily consultant-led ward round at a minimum of twice a week of for any LSD in-patients.

## **Team care**

### **Staffing**

The service will be staffed with a core staffing from a range of suitably qualified health professionals which will include the following people:

- a named service manager
- at least two paediatricians with a special interest in paediatric inherited metabolic diseases who are experienced in the management of LSDs
- a lead nurse supported by a nursing team capable of delivering the service.

Other members of the LSD team to be determined and accessed locally as deemed necessary for the LSD patient population served.

These may include :

- therapists including a dietician, physiotherapist and occupational therapist
- a dedicated pharmacist to support the LSD service
- appropriate administrative and clerical support for the proper management of the service.

The treatment of LSDs represents a lifetime commitment to the maintenance of life quality and health. Patients will require access to all the services commonly found in a regional paediatric hospital including suitably trained paediatric specialists as well as colleagues in professions allied to medicine.

Services will be consultant led by specialists with experience in genetic disorders affecting metabolism in infants, children and young people.

### **Range of interventions required**

The range of interventions required will differ depending upon the underlying diagnosis and this breakdown must serve as the minimum likely to be required. All patients are likely to require routine haematological and biochemical blood and urine tests which will differ in detail depending on the disease. These will be outlined in the disease specific guidelines for management which will be regularly reviewed by the clinical advisory group.

### **Fabry disease**

- cardiology opinion with Echocardiogram (ECG), 24 hour ECG,;
- urine protein excretion, Cr51-EDTA assessment of renal function;
- MRI scan of brain;
- ophthalmology assessment;
- audiology;
- insertion of port a cath for (ERT);
- access to chronic pain team.

## **Gaucher disease**

- cardiology opinion with ECG and Echocardiogram;
- X-Ray skeletal survey, Magnetic Resonance Imaging (MRI) scan spine, pelvis, femora and abdomen, ultrasound scan of abdomen;
- ophthalmology assessment including a detailed analysis of saccadic eye movements;
- pulmonary function tests;
- audiology;
- Electroencephalography (EEG) and neuropsychology;
- insertion of port a cath for ERT;
- selected patients may require liver biopsy and access to the full range of hepatic support services.

## **Mucopolysaccharidoses**

- patients with severe MPS I require access to Hematopoietic stem cell transplantation (HSCT);
- patients that are post-HSCT and patients with attenuated variants on ERT are likely to require the following interventions;
- a detailed endoscopic assessment of their airways by ENT and anaesthetic colleagues experienced in the management of the difficult paediatric airway;
- referral for tonsillectomy, adenoidectomy and grommet insertion;
- repair of hernias and insertion of port a cath for ERT;
- referral for dental assessment and treatment;
- ophthalmology assessment including measurement of intraocular pressure;
- access to corneal transplantation;
- access to neurophysiology assessments;
- respiratory function testing including sleep studies;
- cardiology assessment including assessment of valve disease and possible valve replacement;
- specialist spinal orthopaedic management including correction of spinal deformities, treatment of hip dysplasia, genu valgum, foot deformities and tight Achilles' tendons;
- neurosurgical correction of compression or instability at the cranio-cervical junction and in some patients shunt treatment for hydrocephalus;
- referral to psychological/psychiatric evaluation of severe behavioural disturbance where required;
- age appropriate developmental assessment;
- access to endocrine assessment of growth and glandular function in those patients treated by HSCT;
- A measure of functional outcome such as a six minute walk test or a stair climb test depending on the disorder and degree of cooperation.

## **Pompe disease**

Severe infantile patients are likely to require respiratory support either by invasive or non-invasive ventilation. This may be long term and involve admission to a paediatric intensive care unit or a high dependency unit.

- detailed cardiac evaluation, measurement of left ventricular mass index and left ventricular function. Management of life threatening cardiac arrhythmias;
- physiotherapy assessment involving specific motor function tests such as Alberta
- infant Motor Scales (AIMS), Peabody Developmental Motor Scale-2 (PDMS-2), paediatric Evaluation of Disability Inventory (PEDI);
- respiratory function testing including a formal sleep study;
- insertion of port a cath for ERT;
- some patients will require a tracheotomy and a gastrostomy;
- audiology.

## **Not included as part of the nationally commissioned service**

Placement of tracheotomy or a gastrostomy

## **Niemann-Pick C**

- neurological assessment (videoed when possible);
- speech and language therapy assessment with videofluoroscopy to assess swallowing when appropriate;
- access to audiology (age appropriate);
- physiotherapy assessment to measure disability Scale for NPC and Ambulatory Index or Six minute walk test;
- nerve conduction studies;
- visual evoked potentials and auditory evoked potentials;
- age appropriate developmental assessment;
- ophthalmology assessment including a measure of saccadic eye movements;
- insertion of gastrostomy.

## **Other disorders**

The other LSDs that are currently untreated by HSCT, ERT or SRT have many of the same interventions including the need for paediatric surgery, paediatric neurosurgery and specialist orthopaedics:

- palliative care should be provided for all LSDs as required;
- surgical Interventions/treatment;
- surgical Procedures and Interventions are not funded within this specification. LSD patients requiring surgical intervention are funded through normal commissioning arrangements.

## **Team Process:**

- all members of the multidisciplinary team will attend monthly audit meetings, in



- line with good clinical governance;
- minutes of multidisciplinary team meetings, including a register of attendance, will be recorded.

### **Monitoring and review**

A core MDT should meet monthly to review patients referred and assessed for ERT.

All patients on ERT should not continue to receive ERT unless there is evidence that the treatment is improving the patient's condition or preventing decline. This should be managed in line with disease management protocols and practice.

### **Collaboration with local hospitals**

Where possible, patients should be cared for in shared care arrangements with clinicians at local hospitals who operate in close liaison with the designated centres. Local clinicians will be kept well informed of individual patient status and are updated by letter following patient review.

There should be written guidelines and or nursing care plans for shared care between the specialist centre, local referring physician and general practitioner. Written guidelines or nursing care plans may also be needed for sharing care with other specialist centres (e.g. neuromuscular centres or liver units).

### **Collaboration with other designated trusts and audit**

All designated centres will meet at least twice a year jointly with the patient support groups to review outcomes, policies and protocols.

### **Discharge**

It is unlikely that any child will be discharged from the designated paediatric LSD service. Transition to adult services should be a planned, collaborative process involving the LSD teams, the young person and family. The process should include:

### **Early discussion of transition**

- Transition should be introduced at least a year before transfer to allow time to resolve concerns the young person or child may have.

### **Time of transfer**

- Timing should be flexible in accordance with individual needs.

### **In young people that are capable, independence and responsibility for their own care should be encouraged:**

- The emphasis in paediatric consultations should focus progressively on the young patient if capable but should not exclude the parents prematurely.

- The proposed procedure for transition should be discussed.
- The young person and family should be encouraged to make an informal visit to the adult centre.

### **Joint transition clinics**

- Joint clinics where the young person and family can meet the paediatrician and adult physician together should be held.
- Opportunities should be made for the family to meet other members of the adult LSD team.

### **Information**

- Written information about the adult centre should be provided.

### **Ward Environment**

- Sleeping and leisure facilities should be appropriate for a young person.

### **Risk management**

The provider will demonstrate a system for the identification of all risks which could compromise delivery of the highest standard of care. The provider is obliged to deliver services according to national and local requirements dictating the level and quality of services. There are many initiatives that contribute to these requirements and set the context for safe clinical activities. These include the National Service Frameworks (NSF), the Modernisation Agenda, the Health Care Annual Health Check, the Commission for Healthcare Audit and Inspection, the Department of Health guidelines, the National Health Service Litigation Authority Standards and Standards for Better Health.

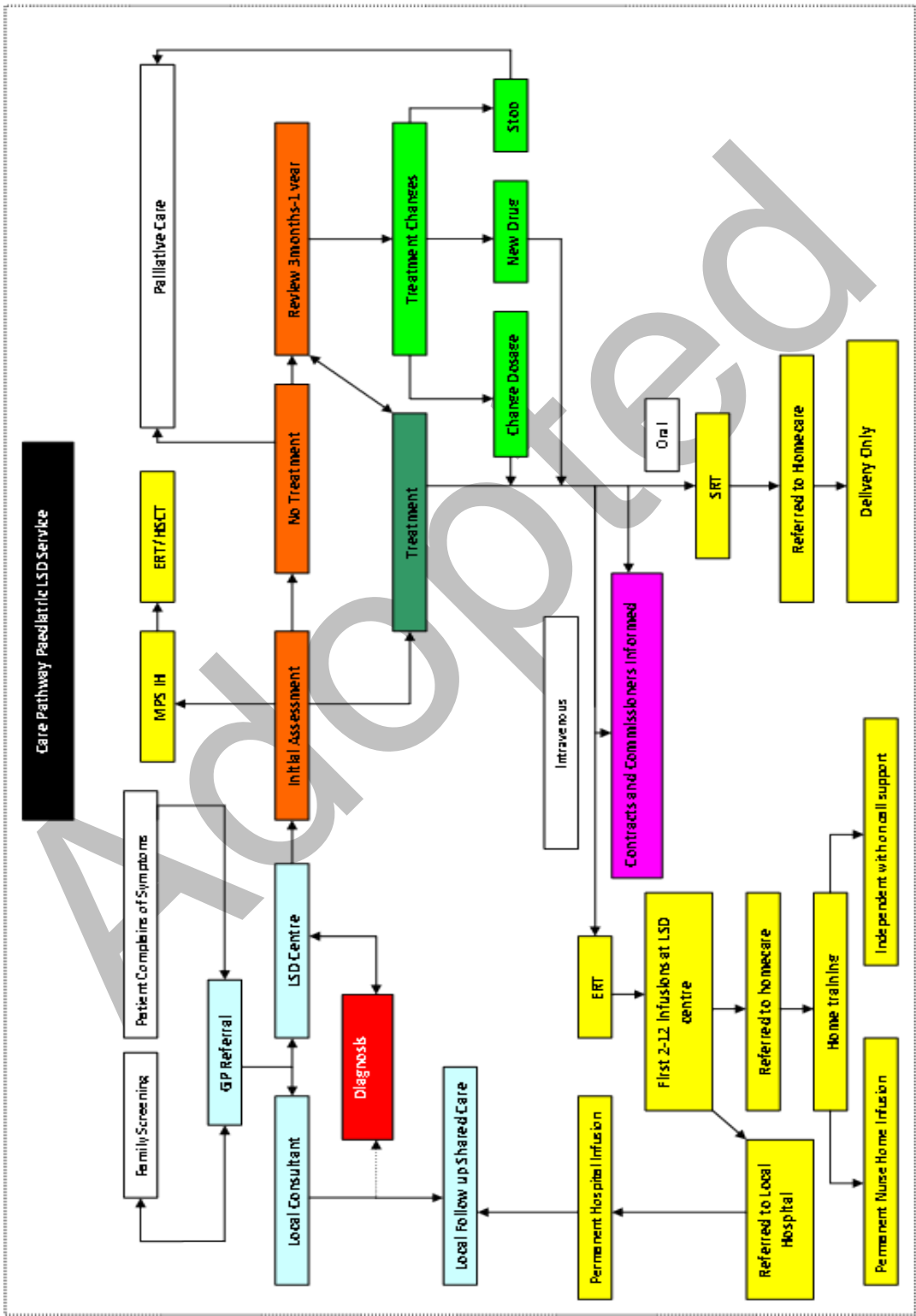
The provider will ensure that professionals within the trust adhere to the standards of their regulatory bodies.

Care delivered by the LSD service must be of a nature and quality to meet the care standards, specification and Agreement for the service. 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.

Patients must be managed in line with the specification and care standards. Any deviation from these which has not been approved by the 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 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.



## **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.

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

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.

Changes to the existing arrangements recommended in “Allocation of organs to non-UK EU residents” are under consideration by the Department of Health as part of a wider review of eligibility, allocation and funding of deceased organs donated for transplantation.

## **2.4 Any acceptance and exclusion criteria**

### **Referral criteria, sources and routes**

Referrals to the service come from:

- General Practitioners;
- clinicians in secondary care units;
- colleagues in other tertiary care specialties.

### **Exclusion criteria**

No child with LSD is excluded from referral and assessment but some elements of the service are not Nationally Commissioned. Specific exclusions:

- ERT for patients with severe MPS I (MPS IH) unless undergoing HSCT;
- ERT for patients with classical infantile Pompe disease if already requiring mechanical ventilation for muscle weakness prior to diagnosis.

Guidelines for the management of children with these and other disorders have been developed. Management outside of the guidelines requires a discussion with the

Commissioners prior to commencing therapy.

## 2.5 Interdependencies with other services

Providers will provide a service which integrates with existing services through communication with other professionals whilst at the same time minimising reduplication of effort.

- **primary care**  
general practitioner, community nursing staff, dieticians, physiotherapist, Speech and Language therapists, Occupational Therapists, dentist, wheel chair services
- **local hospital**  
general paediatrician, community paediatrician plus others seeing the child under shared care protocol
- **children's hospice**
- **local education authority**  
with community paediatrician and others providing information for statement of special educational needs
- **school SENCO**
- **social services**
- **laboratory services**  
National Metabolic Biochemistry Network (MetBioNet)
- **clinical services**  
British Inherited Metabolic Disease Group.



Lysosomal storage disorders

1. Defect of Specific Lysosomal Hydrolases

**Mucopolysaccharidoses (MPS)**

DS; dermatan sulfate, HS; heparan sulfate, KS; keratan sulfate, CS; chondroitin sulfate, HA; hyaluran.  
AAS – atlanto-axial subluxation, CC – corneal clouding, CM – cardiomyopathy, CVD – cardiac valve disease, DM – dysostosis multiplex, HSM – hepatosplenomegaly, MR – mental retardation, RY – retinopathy  
HSCT – hematopoietic stem cell transplant, ERT – enzyme replacement therapy

Disease	Eponym	OMIM	Clinical phenotype	Locus	Gene and product	Storage material	Treatment
MPS I	Hurler (MPS IH)	607014	Severe, death <10years, MR HSM, DM, CM, CVD, CC Intermediate	4p16	<i>IDUA</i> α-L-iduronidase	DS, HS	HSCT
	Hurler/Scheie (MPS IH/S)	607015					ERT
	Scheie (MPS IS)	607016	Attenuated, normal IQ, joint, CC, RY,				ERT
MPS II	Hunter	309900	Severe, HSM, MR, CVD, death <15 years Attenuated – short stature, Variable clinical phenotype	Xq28	<i>IDS</i> Iduronate sulfatase	DS, HS	ERT
MPS IIIA	Sanfilippo A	252900	Severe MR, behaviour and sleep disturbance, mild somatic features	17q25	<i>SGS</i> Heparan N-sulfatase	HS	Palliative
MPS IIIB	Sanfilippo B	252920	Similar to III A	17q21	<i>NAGLU</i> N-acetyl glucosaminidase	HS	Palliative
MPS IIIC	Sanfilippo C	252930	Similar to III A	8p11	<i>HGSNAT</i> α-glucosaminide acetyl CoA transferase	HS	Palliative
MPS IIID	Sanfilippo D	252940	Similar to IIIA	12q14	<i>GNS</i> N-acetyl-glucosamine 6- sulfatase	HS	Palliative
MPS IVA	Morquio A	253000	severe skeletal dysplasia, odontoid dysplasia, AAS, CC, normal IQ	16q24	<i>GALNS</i> Galactosamine 6-sulfatase	KS	Surgery

reatment

urgery

RT

SCT

dy 1 patient

RT

SCT

lliative

lliative

RT or HSCT  
RT

### **3. Applicable Service Standards**

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

##### **Governance**

The nationally designated LSD providers must be fully integrated into their trust's corporate and clinical governance arrangements and must fully comply fully with Clinical Negligence Scheme for Trusts (CNST) and Care Quality Commission (CQC) requirements in terms of quality and governance. The hub centres are responsible for overseeing the governance arrangement of any spoke clinic provided under sub-contractual arrangements.

Each centre will ensure that:

- regular meetings take place with patient representatives;
- all practitioners participate in continuous professional development and networking;
- patient outcome data is recorded and audited across the service.

The commissioners and service will conduct a formal Joint Service Review at least every six months. All centres must participate in the national audit commissioned by the NHS England – e.g. audit meetings should address:

- clinical performance and outcome;
- process-related indicators, e.g. efficiency of the assessment process, prescribing policy, bed provision and occupancy, outpatient follow up etc.
- stakeholder satisfaction including feedback from patients, their families, referring clinicians and General Practitioners.

See also the NHS England Service Standards for the Paediatric LSD service

The service provider will ensure that they have a strong ethical position on governance and that they receive adequate medical advice to confirm that the LSD service they provide is safe, efficient, and reliable and meet national standards.

All practitioners involved within the service will to participate in continuous professional development and networking. This will be built into the roles within the service and forms part of the providers corporate and clinical mandatory training programmes.

The provider will be able to explain who provides clinical leadership and also demonstrate that they have appropriate clinical governance processes in place. The designated clinician who leads and is accountable for the LSD service will be known to all patients and staff so that at any time, when audited, any patient, parent or member of staff should be able to name the person who leads the service.



The key components will include<sup>20</sup>:

- ensuring effective clinical leadership
- maintaining the capacity and capability to deliver service
- proactively identifying clinical risk
- collecting and using “intelligent information” on clinical care
- involving professional groups in multi-professional clinical audit
- involving patients and the public in the delivery of services
- ensuring the quality of the patient experience
- improving services based on lessons from complaints
- improving services based on lessons from serious untoward incidents and “near misses”.

#### 4. Key Service Outcomes

Quality Performance Indicator	Threshold	Method of measurement	Consequence of breach	Report Due
HCAI control (Q) Will comply with Health & Social Care Act 2008: Code of practice for the NHS on the prevention & control of HCAIs	Fully compliant	Monthly data from Provider	As per NHS Standard Contract for Acute Services. 2010/11	Annual Report
Service User Experience (Q) Service user experience survey to be offered to every patient/family at the end of each episode	100% patients/families surveyed	annual patient satisfaction report with action plan	As per NHS Standard Contract for Acute Services.	Annual Report
Service User Experience (Q) Complaints are dealt with in accordance with NHS policy and improvement plans are implemented and actioned	Fully compliant	Audit	None	Annual Report

Improving Service Users & Carers Experience (Q) Patient experience surveys addressed and improvements noted.	Evidence that top areas of concern addressed.  Top areas of concern not replicated in subsequent years	Audit	None	Annual action plan
Reducing inequalities Equality Impact Assessments to be carried out (Q)	All actions to be addressed	EIA reports	As per NHS Standard Contract for Acute Services.	Annual report
Access (P) Length of time to see emergency referral	48 hours	Monthly data from provider	None	6 monthly report
Access (P) Length of time to see non-urgent new referral	2 days	Monthly data from provider	None	6 monthly meeting
Access (P) Length of time from referral to commencement of definitive treatment	4 weeks	Monthly data from provider	None	6 monthly meeting
Morbidity and mortality (P) Report all SUIs	100% compliance	Monthly data from provider	As per NHS Standard Contract for Acute Services. 2010/11	6 monthly meeting

## 5. Location of Provider Premises

The designated Paediatric LSD centres are based at:

Birmingham Children's Hospital NHS Foundation Trust  
Inherited Metabolic Disorders  
Steelhouse Lane Birmingham  
B4 6NH

Great Ormond Street Hospital for Children NHS Foundation Trust  
Metabolic Office, Level  
7 Southwood Building  
Great Ormond Street  
London WC1N 3JH

Central Manchester University Hospitals NHS Foundation Trust  
6th Floor  
St. Mary's Hospital  
Oxford Road  
Manchester  
M13 9WL

## References

1. Poorthuis BJ, Wevers RA, Kleijer WJ et al (1999) The frequency of lysosomal storage diseases in The Netherlands. *Human Genetics* **105(1-2)**:151-156.
2. Rohrbach M, Clarke JT (2007) Treatment of lysosomal storage disorders: progress with enzyme replacement therapy. *Drugs* **67**: 2697-2716
3. Prasad VK, Kurtzberg J. (2010) Cord blood and bone marrow transplantation in inherited metabolic diseases: scientific basis, current status and future directions. *British Journal of Haematology*. **148**:356-72.
4. Platt FM, Jeyakumar M. (2008) Substrate Reduction Therapy. *Acta Paediatrics Suppl* **97**: 88-93.
5. Marchesoni CL, Roa N, Pardal AM et al (2010) Misdiagnosis in Fabry disease. *Journal of Pediatrics*. **156**: 828-831.
6. Pintos-Morrell G, Beck M. (2009) Fabry disease in children and the effects of enzyme replacement therapy. *The European Journal of Pediatrics* **168**: 1355–1363.
7. Mehta A, Hughes DA (2008) Fabry Disease in Pagon R, Bird TC, Dolan CR, Stephens K, editors, *GeneReviews* [Internet]. Seattle (WA): University of Washington, Seattle; 1993-.
8. Desnick RJ, Brady R, Barranger J, et al (2003) Fabry disease, an under-recognized multisystemic disorder: expert recommendations for diagnosis, management, and enzyme replacement therapy. *Annual International Medicine*. **138**: 338–346.
9. Mehta A, Beck M, Eyskens F et al (2010) Fabry disease: a review of current management strategies. *Q Journal of Medicine*, **103**: 641–659.
10. Pastores GM, Hughes DA (2008) Gaucher Disease. in Pagon R, Bird TC, Dolan CR, Stephens K, editors, *GeneReviews* [Internet]. Seattle (WA): University of Washington, Seattle; 1993-.
11. Brunel-Guitton C, Rivard GE, Galipeau J et al (2009) Enzyme replacement therapy in paediatric patients with Gaucher disease: what should we use as maintenance dosage? *Molecular Genetics and Metabolism* **96**: 73-76.
12. Giraldo P, Alfonso P, Atutxa K et al (2009) Real-world clinical experience with long-term miglustat maintenance therapy in type 1 Gaucher disease: the

ZAGAL project. *Haematologica* **94**: 1771-1775.

13. Wraith JE (2009) Enzyme replacement therapy for the management of the mucopolysaccharidoses. *Int J Clin Pharmacol Ther.* **47 Suppl 1**:S63-65.
14. Muenzer J, Beck M, Eng CM et al (2009) Multidisciplinary management of Hunter syndrome. *Pediatrics* **124**:e1228-1239.
15. van den Hout HM, Hop W, van Diggelen OP et al (2003) The natural course of infantile Pompe's disease: 20 original cases compared with 133 cases from the literature. *Pediatrics* **112**: 332-340.
16. Chakrapani A, Vellodi A, Robinson P et al (2010) Treatment of infantile Pompe disease with aglucosidase alpha : the UK experience. *Journal of Inherited Metabolic Diseases.* (in press)
17. Vanier MT (2010) Niemann-Pick disease type C. *Orphanet Journal of Rare Diseases* Jun 3;5:16
18. Patterson MC, Vecchio D, Jacklin E et al (2010) Long-term miglustat therapy in children with Niemann-Pick disease type C. *Journal of Child Neurology* **25**: 300–305.
19. Wraith JE, Vecchio D, Jacklin E et al (2010) Miglustat in adult and juvenile patients with Niemann-Pick disease type C: long-term data from a clinical trial. *Molecular Genetics and Metabolism.* **99**: 351–357
20. Improving quality and safety, progress in implementing Clinical Governance in Primary care: Lessons for the New Primary Care Trusts (2007).

## APPENDIX 1

### 2013/14 NHS STANDARD CONTRACT FOR LYSOSOMAL STORAGE DISORDERS SERVICE FOR CHILDREN

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

<b>Service Specification No.</b>	E06/S(HSS)/c Appendix 1
<b>Service</b>	Lysosomal Storage Disorders service (adults)
<b>Commissioner Lead</b>	
<b>Provider Lead</b>	
<b>Period</b>	12 months
<b>Date of Review</b>	

#### 1. Population Needs

##### 1.1 National/local context and evidence base

The target population includes all adults with Lysosomal Storage Disorders (LSDs), regardless of whether specific therapy is available or not. The present service specification places special emphasis on the disorders that are currently managed by enzyme replacement therapy (ERT) or substrate reduction therapy (SRT). As treatments are developed for further LSDs, appropriate treatment guidelines will be produced by the LSD expert advisory group. Haematopoietic stem cell therapy (HSCT) for LSD is excluded from this specification

##### 1.2 Evidence base

Fabry disease is an X-linked disorder caused by a deficiency of the lysosomal enzyme  $\alpha$ -Galactosidase A. The disorder is pan-ethnic, occurs with a prevalence of 40:117,000 births and neuropathic pain is most often the first sign of the disease in childhood although this is often misdiagnosed<sup>5, 6</sup>. Without treatment the condition progress throughout adult life to cause serious cardiac, neurological and renal disease<sup>7</sup>. A panel of physician experts have recommended that ERT be initiated as early as possible in all males with Fabry disease, including children<sup>8</sup>. Many females develop significant disease manifestations and warrant enzyme treatment. Gaucher disease (GD) is an autosomal recessive disorder caused by a deficiency of the lysosomal enzyme Beta glucocerebrosidase. There are three types of Gaucher

disease. The vast majority of adult patients have type 1 disease. Patients in this group usually present with enlargement of the liver and spleen and haematological problems. There are no signs of brain involvement but without treatment serious

skeletal complications can occur. Type 2 Gaucher disease occurs exclusively in young children. In the third category, called type 3, liver and spleen enlargement is variable, respiratory disease is common and signs of brain involvement such as seizures may become apparent over time. This type of Gaucher disease is also associated with a specific eye movement abnormality<sup>10</sup>.

Both type I and type III (GD) respond favourably to ERT. For patients deemed unsuitable for treatment with ERT there is substrate inhibiting drugs available. Which have been shown to be an effective long term therapy for adults with type I disease<sup>12</sup>.

Mucopolysaccharidoses (MPS) are a group of disorders associated with specific enzyme deficiencies. Most are inherited as autosomal recessive traits with the exception of MPS II (Hunter syndrome) which is X-linked. The treatment of the severe form of MPS I (Hurler syndrome) is using HSCT which is excluded from this specification. ERT is available for MPS I (non-Hurler patients). Clinical trials in MPS IV are at an advanced stage. A brief review of outcomes for MPS patients treated by ERT has been published<sup>13</sup>. Patients with MPS may have complex problems that affect many organ systems and illustrate graphically the need for multidisciplinary management of LSD patients<sup>14</sup>.

Pompe disease (acid maltase deficiency, glycogen storage disease type II) is caused by a deficiency of the lysosomal enzyme acid glucosidase (acid maltase). Some patients present in infancy with severe disease (often called "classical" Pompe disease) which is characterised by a rapidly progressive cardiomyopathy, generalised skeletal muscle weakness, respiratory failure and early death in the first few months of life<sup>15</sup>. Other patients present later in life with a progressive skeletal myopathy with variable respiratory involvement. Treatment with ERT has been shown to stabilise and improve disease in these patients especially in early onset cases. (REF<sup>16</sup>)

Niemann-Pick disease type C (NP-C) is associated with a late endosomal defect in cholesterol trafficking. Defects in two different proteins NP-C1 (95%) and NP-C2 (5%) can cause the severe neurovisceral disorder NP-C<sup>17</sup>. Heterogeneity can be extreme ranging from death in the newborn period due to liver failure to a presentation in adult life with purely psychiatric symptoms. Neurological abnormalities are common including gaze palsy and the development of cataplexy and narcolepsy, uncommon conditions that require specialist management. The NP-C2 protein is a lysosomal hydrolase and treatment by HSCT can be attempted. The NP-C1 protein is more complex and thought to act in conjunction with NP-C2 to promote efflux of cholesterol of the late endosomal system. In NP-C the primary storage products in the brain are gangliosides and not cholesterol<sup>17</sup>. A substrate inhibiting drug is available which has been shown to stabilise disease progression in both adults and children with NP-C<sup>18, 19</sup>.

Other disorders associated with the accumulation of gangliosides within the CNS (GM<sub>1</sub> and GM<sub>2</sub> gangliosidosis) have treatment with the substrate inhibiting drug. The indications in this area are very limited and this treatment is not routinely commissioned.

The remaining LSDs for which ERT and SRT have either not been developed and follow up occurs within the specialised multi-disciplinary team are all listed in the Table in Appendix 1 as the disorders for which ERT or SRT is not available.

## **2. Scope**

### **2.1 Service Description**

The designated LSD centres will be expected to provide the full range of services required for the diagnosis and management of patients with LSDs. For diseases where specific treatment is available, management should be in accordance with NHS England protocols. For other LSDs, patients are expected to be managed to the highest possible standards based on current global practice. In order to achieve this, clinical staff in the centres should have experience in the management of a range of LSDs. The centres will be responsible for the initial assessment and periodic monitoring of all patients. Where other specialist input is required (e.g. cardiology, orthopaedics, ears, nose and throat (ENT), nephrology, imaging, ophthalmology, otology, sleep clinic etc) the LSD centres will work with other services, either in specialist units or, where appropriate, local to the patient, to develop expertise in the management of the relevant complications of LSDs. Many patients will live considerable distances away from their LSD centre. Centres will aim to identify clinicians at the patient's local hospital who can share care. In acute emergencies, clinicians from the LSD centres should be contactable and able to work with local health services to ensure appropriate management. Facilities should be available for transfer of patients requiring specialist input to hospital facilities where the LSD centre clinicians can have direct input to patient care.

LSD centres will be responsible for making decisions about the initiation, maintenance and termination of specific LSD therapy as per NHS England guidelines. Centres will have the facilities and staff required to perform ERT infusions. For patients who want to receive their infusions at home, the centres will work with homecare organisations to achieve this. Prescribing of these specific therapies will be by designated physicians from the LSD centres but treatment will be funded by the NHS England. Centres will put arrangements in place to ensure that NHS England are aware of all treatments being received by their patients, and to ensure that both Homecare organisations and NHS Trusts receive accurate and timely reimbursement of drug costs. Bone marrow transplantation and haemopoietic stem cell transplant for patients with LSDs is not included within the designated service.

The centres should provide a telephone helpline for patients and carers. The centres will work closely with patient groups to ensure a patient-responsive service.

## **Purchasing of Enzyme Replacement Therapy (ERT) & Substrate Replacement Therapy (SRT) Drugs**

All providers MUST purchase ERT/SRT drugs via the National Purchasing of Enzyme

(ERT) & Substrate Replacement Therapy (SRT) Drugs (commenced May 2012).

### **Provision of Homecare for patients on ERT**

All providers must access homecare provision via the NHS National Framework Agreement for the Supply of Home Delivery Service - Lysosomal Storage Disorders in England. (commenced 1 October 2012).

No alternative or separate purchasing arrangements can be agreed locally.

### **Laboratory facilities**

A specialised laboratory service will be capable of carrying out all the tests relevant for the diagnosis of inherited lysosomal disorders. Although histopathology services may contribute to the diagnosis, it is biochemical assay and molecular genetic studies, sometimes involving the study of cultured cells and biopsy specimens that are principally required for the evaluation of lysosomal storage disorders. There must be access to microbiology, virology, biochemistry, haematology and blood bank services.

Access to diagnostic services should ensure that specific enzyme functions can be assayed, both in relation to the suspected diagnosis and also to screen for possible candidate diagnoses in a person with a lysosomal storage disorder:

- patients should be referred for pre-implantation genetic diagnosis available where appropriate. This does not form part of the nationally designated service. Laboratories must be able to analyse blood cells, cultured fibroblasts, biopsy tissue, plasma and urine samples.
- laboratories undertaking activity referred by nationally designated LSD centres should not be separately charged for this is included in the contracting arrangements. Laboratories can only charge for LSD testing where the referrers for the testing are not nationally designated teams.

Routine blood tests, imaging and other assessments (e.g. echocardiography (ECG), pulmonary function tests, sleep studies etc), including those set out in the treatment guidelines where they exist, are covered by this service. Specialist diagnostic tests are to be performed in designated laboratories which will be separately commissioned.

### **Transition**

Appropriate transition processes should be in place involving both paediatric and adult staff. Each centre should demonstrate to commissioners that patients are well



supported during transition.

## **Staffing**

The service will be staffed with a core staffing from a range of suitably qualified health professionals should include the following people:

- a named service manager;
- at least one and preferably two consultant physicians with a special interest in and experience in the management of LSDs. Where there is only one lead physician, this centre must have formal arrangements for support from another designated LSD centre (either adult or paediatric);
- a Lead Nurse supported by a nursing team capable of delivering the service;
- a unit Secretary responsible for triaging telephone enquiries and correspondence.

Other MDT members of the LSD team to be determined and accessed locally as deemed necessary for the LSD patient population served.

These may include :

- therapists including a dietician, physiotherapist and occupational therapist;
- a dedicated pharmacist to support the LSD service;
- appropriate administrative and clerical support for the proper management of the service.

The treatment of LSDs represents a lifetime commitment to the maintenance of life quality and health. Patients will require access to all the services commonly found in a regional acute hospital including suitably trained colleagues in professions allied to medicine. This support will be outlined to local care providers by the nationally designated teams and may include physiotherapy, psychotherapy and occupational therapy.

## **Risk management**

The provider will ensure that professionals within the trust adhere to the standards of their regulatory bodies.

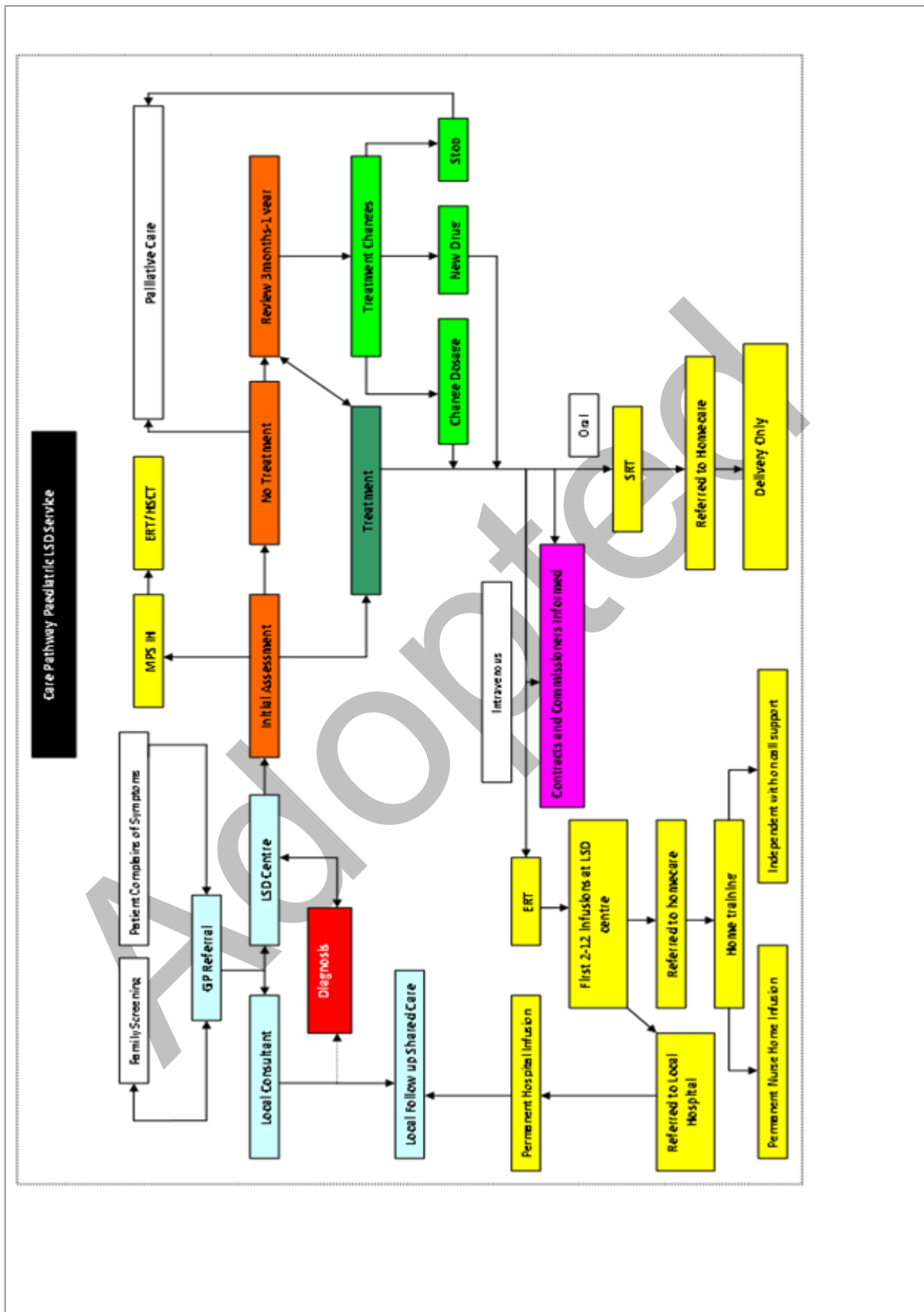
Care delivered by the LSD service must be of a nature and quality to meet the care standards, specification and Agreement for the service. It is the trust's responsibility to notify the commissioner on an exceptional basis should there be any breaches of the care standards. Where there are breaches any consequences will be deemed as being the trust's responsibility.

Patients must be managed in line with the specification and care standards. Any deviation from these which has not been approved by the 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 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.

## **2.2 Service description/care pathway**

Adopted



Lysosomal storage disorders						
1. Defect of Specific Lysosomal Hydrolases						
<p><b>Mucopolysaccharidoses (MPS)</b>  DS; dermatan sulfate, HS; heparan sulfate, KS; keratan sulfate, CS; chondroitin sulfate, HA; hyaluron.  AAS – atlanto-axial subluxation, CC – corneal clouding, CM – cardiomyopathy, CVD – cardiac valve disease, DM – dysostosis multiplex, HSM – hepatosplenomegaly, MR – mental retardation, RY – retinopathy.  HSCT – hematopoietic stem cell transplant, ERT – enzyme replacement therapy</p>						
Disease	Eponym	OMIM	Clinical phenotype	Locus	Gene and product	Treatment
MPS I	Hurler (MPS IH)	607014	Severe, death <10 years, MR HSM, DM, CM, CVD, CC Intermediate	4p16	IDUA α-L-iduronidase	HSCT
	Hurler/Scheie (MPS IH/S)	607015				ERT
	Scheie (MPS IS)	607016	Attenuated, normal IQ, joint CC, RY,			ERT
MPS II	Hunter	309900	Severe, HSM, MR, CVD, death <15 years Attenuated – short stature, Variable clinical phenotype	Xq28	IDJ Iduronate sulfatase	ERT
MPS IIIA	Sanfilippo A	252900	Severe MR, behaviour and sleep disturbance, mild somatic features	17q25	SGS Heparan N-sulfatase	Palliative
MPS IIIB	Sanfilippo B	252920	Similar to III A	17q21	NAGLU N-acetylglucosaminidase	Palliative
MPS IIIC	Sanfilippo C	252930	Similar to III A	8p11	HGNCAT α-glucosaminide acetyl CoA transferase	Palliative
MPS IIID	Sanfilippo D	252940	Similar to IIIA	12q14	GNS N-acetylglucosamine 6- sulfatase	Palliative
MPS IVA	Morquio A	253000	severe skeletal dysplasia, odontoid dysplasia, AAS, CC, normal IQ	16q24	GALNS Galactosamine 6-sulfatase	Surgery

Disease	Eponym (other name)	OMIM	Clinical phenotype	Locus	Gene and product	Storage material	Treatment
MPS IVB	Marquio B	253010	Similar to IVA	3p21	<i>GLB1</i> beta-galactosidase	KS	Surgery
MPS VI	Maroteaux-Lamy	253200	Mild and attenuated forms AAS, CC, normal IQ, CVD, DM	5q12	<i>ARSB</i> arylsulfatase B	DS	ERT
MPS VII	Sly	253220	HF, severe like MPS IH	7q21	<i>GUSB</i> Beta-glucuronidase	DS, HS	HSCT
MPS IX	Narowicz	601492	short stature, pericardial swelling, mild dysmorphism	3p21	<i>HYAL1</i> Hyaluronidase	HA	only 1 patient
<b>Sphingolipidoses</b> CER; ceramide, Gb3; globotriaosylceramide, gangliosides GM1 and GM2, GalCer; galactosylceramide, SM; sphingomyelin BD – bone disease, CM – cardiomyopathy, CRF – chronic renal failure, HSM – hepatosplenomegaly, PA – pancytopenia							
Fabry	Anderson-Fabry	301500	acroparaesthesiae, angiokeratoma CM, CRF, stroke, atypical variants, symptomatic heterozygotes	Xq22	<i>GLA</i> alpha-galactosidase A	Gb3	ERT
Fabry	Lipogranulomatosis	228000	subcutaneous nodules, arthritis, hoarse cry, severe MR	8p22	<i>ALAH</i> acid ceramidase	CER	HSCT
Gaucher	Glucoylceramidosis	608013	“Colloidion”, ichthyosis, neonatal death Type II acute neuronopathic, death <2 years Type III, chronic neuronopathic, Type I, adult onset, no CNS disease, HSM, PA, BD	1q21	<i>GBA</i>	GlcCer	Palliative Palliative ERT or HSCT ERT

Disease	Eponym	OMIM	Clinical phenotype	Locus	Gene and product	Storage material	Treatment
<b>Sphingolipidoses (continued), other lipidoses and glycogen storage disease</b>							
CER; ceramide, GalCer, glucosylceramide, Gb3; globotriaosylceramide, gangliosides; GM1 and GM2, GalCer, galactosylceramide, GSL; glycosphingolipids, SM; sphingomyelinase; CM – cardiomyopathy, DM – dysostosis multiplex, HSM – hepatosplenomegaly, MR – mental retardation, RF – resp. failure, RI – resp. infiltration, SRT – substrate reduction therapy							
GM1-gangliosidosis		230500	infantile – HF, Hurler-facies HSM, CM, DM, death <2 years	3p21	GLB1 β-galactosidase	GM1-ganglioside	Palliative
GM1-gangliosidosis B	Tyrr-Sachs disease	272800	severe – CNS disease, seizures, hyperacusis, death <4 years juvenile and adult forms	15q23	HEXA β-hexosaminidase α subunit	GM1-ganglioside	Palliative
GM1-gangliosidosis O	Sandhoff disease	268800	Similar to Tyrr-Sachs disease	5q13	HEXB β-hexosaminidase β subunit	GM1-ganglioside	Palliative
Globoid cell Leucodystrophy	Krabbe disease	245200	severe neurodegeneration with central and peripheral NS disease, seizures and irritability; death <4y juvenile and adult variants	14q31	GALC β-galactosylceramidase	GalCer	Palliative
Metachromatic Leucodystrophy		250100	infantile – dementia, seizures, death <4 years juvenile and adult forms – less rapidly progressive	22q13	ARSA Arylsulfatase A	Sulfatide	Palliative
Niemann-Pick A and B		257200	type A – severe HSM, MR, death <4 years Type B – no CNS disease, HSM, RI	11p15	SPMPT1 Acid sphingomyelinase	SM	Palliative
Niemann-Pick C(2)		607625	like NPC1 but often with severe RI	14q24	HEV Epithelial Secretory Protein	Cholesterol GSL	ERT (soon) SRT
Cholesterol Ester Storage Disease (CESD)	Wichman disease (WD)	278000	severe form (WD), HSM, adrenal calcification, RI attenuated form (CESD), HSM, coronary artery disease	10q24	LIPA Acid lipase	Cholesterol esters	HSCT
Glycogen Storage Pompe disease Disease II		232300	infantile – severe CM untreated death <12 months juvenile and adult – skeletal muscle myopathy, RF	17q25	GAA α-glucosidase	Glycogen	ERT ERT

## Glycoproteinoses

AK – angiokeratoma, CF – coarse facies, CRSM – cherry red spot myoclonus syndrome, DM – dysostosis multiplex, HSCT – haematopoietic stem cell therapy, ID – immune deficient, MR – mental retardation, NAD – neuroaxonal dystrophy.

Disease	Eponym (other name)	OMIM	Clinical phenotype	Locus	Gene and product	Storage material	Treatment
Aspartylglucosaminuria		208400	slowly progressive, MR, CF	4q32	AGA N-aspartyl-beta-glucosaminidase	aspartylglucosamine	HSCT
Fucosidosis		230000	MR, AK, mild DM	1p34	FUCA Fucosidase	Fucose-rich oligos	Palliative
alpha-mannosidosis		248500	slowly progressive, ID, mild to moderate MR, arthropathy	19q12	MAN2B1 alpha-mannosidase	Mannose-rich oligos	HSCT
beta-mannosidosis		248510	variable; severe patients: death <2 years, MR, seizures Milder patients – CF, AK and MR	4q22	MAN2B4 beta-mannosidase	Mannose-rich oligos	Palliative
Neuraminidase Deficiency	Suldisia (mucopolidosis I)	236530	Type I – CRSM, myoclonus, mild to moderate MR and DM Type II – severe MPS like features Severe MR and early death	6p21	NEU1 Neuraminidase	Sialic acid	Palliative
NAGA Deficiency	Schindler disease  Kanzaki disease	609241	infantile – NAD, severe MR  Type II – AK, mild MR	22q13	NAGA A-N-acetyl-glucosaminidase	N-acetylated glycolipids	Palliative

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Adopted



2. Defects in post translational modification of lysosomal proteins CM – cardiomyopathy, GAGs – glycosaminoglycans, MR – mental retardation, SD – skeletal dysplasia							
Disease	Eponym (other name)	OMIM	Clinical phenotype	Locus	Gene and product	Storage material	T treatment
Multiple Sulfatase Deficiency	Austin disease	272200	severe MR, spasticity, early death	3p26	SUMF1 Formyl-glycine generating enzyme	sulfatide, GAGs	Palliative
Mucopolipidosis II	I cell disease	252500	severe-Hurler CM, early death	12q23	GNPTAB UDP-GlcNAc- phosphotransferase α/β subunit	multiple (lipids and oligos)	Palliative
Mucopolipidosis IIIA	Pseudo-Hurler polydystrophy	252600	mild to moderate MR, joint stiffness, SD	12q23	GNPTAB as ML II	as ML II	Palliative
Mucopolipidosis IIIC	as IIIA	352605	as IIIA	16p	GNPTG UDP-GlcNAc- phosphotransferase γ-subunit	as ML II	Palliative
3. Defects in activator proteins HSM – hepatosplenomegaly, MR – mental retardation							
GM <sub>1</sub> -Gangliosidosis AB variant	Tay-Sachs AB variant	272750	as Tay-Sachs disease	5q32	GM2A GM <sub>1</sub> -activator protein	GM <sub>1</sub> -ganglioside	Palliative
Prosaposin Deficiency		611721	myoclonus, severe MR HSM, early death	10q22	PSAP Prosaposin	multiple glycolipids	Palliative
Saposin A	Krabbe variant	611722	Similar to infantile Krabbe	10q22	PSAP Saposin A	GalCer	Palliative
Saposin B	MLD variant	249900	Similar to late infantile MLD	10q22	PSAP Saposin B	Sulfatide	Palliative
Saposin C	Gaucher variant	610539	Similar to GD III	10q22	PSAP Saposin C	GlcCer	HSCT

4. Defects in structural lysosomal membrane proteins, protective proteins, transporters and trafficking  
 AMRF – action myoclonus renal failure, CC – corneal clouding, CF – coarse facies, CM – cardiomyopathy, GbCer – glucosylceramide, CRS – cherry red spot, DM – dystonia  
 multiplex, HF – hydrops fetalis, HSM – hepatosplenomegaly, Ma – myopia, MR – mental retardation, NH – neonatal hepatitis, PR – pigmentary retinopathy, SD – skeletal  
 dysplasia

Disease	Eponym (other name)	OMIM	Clinical phenotype	Locus	Gene and product	Storage material	Treatment
LAMP2	Danon disease	300257	CM, SKM Ma, PR, variable MR	Xq24	LAMP2 LAMP2	autophagic vacs	Palliative
LIMP2	AMRF	602257	AMRF	4q13q21	LIMP2 LIMP2	GbCer	Palliative
Cathepsin A Deficiency	Galactosialidosis	256540	CC, HSM, severe MR, CRS, DM, HF	20q13.1	PPGB Cathepsin A	Oligos, sialic acid	Palliative
Mucopolipidosis IV deficiency	TRPM1	252650	CC, severe MR,	19p13.3	MCOLN7 TRPM1	GM2, 3 GD3	Palliative
Cystinosis		219800	infantile nephropathic	17p13	CTNS Cystinosis	Cystine	Cys teamine
Infantile sialic acid storage disease	ISSD	269920	CF, HF, HSM, MR, early death	6q14-q15	JLC17A5 Sialin	sialic acid	Palliative
Salla disease		269920	moderate MR, athetosis spasticity, dementia, ataxia	6q14-q15	JLC17A5 Sialin	sialic acid	Palliative
Niemann-Pick Disease type C1	NPC1	257220	NH, ataxia, dementia, cataplexy, seizures, dementia	18q11	NPC1	cholesterol Gm1 and GM2	Palliative
5. Miscellaneous OS – osteosclerosis,							
Pycnodysostosis	Cathepsin K Deficiency	265800	OS, bone fragility, deformity of skull Maxilla, phalanges	1q21	Cathepsin K CTSK	collagen fibrils	Palliative

## **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.

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

Changes to the existing arrangements recommended in “Allocation of organs to non-UK EU residents” are under consideration by the Department of Health as part of a wider review of eligibility, allocation and funding of deceased organs donated for transplantation.

## **2.4 Any acceptance and exclusion criteria**

### **Referrals**

Referrals to the service are accepted from

- General Practitioners;
- clinicians in secondary care units;
- colleagues in other tertiary care specialties.

Patients should be diagnosed or suspected of an LSD listed in pages 5-11.

The service is commissioned by the NHS England for all eligible patients from England and Scotland. (Scottish patients are only seen in centres for on-going management – ERT is funded by Scotland directly) Patients from other devolved administrations i.e. Wales & Northern Ireland must have been granted prior agreement from the appropriate health boards before being accepted. Separate

commissioning arrangements are in place for these. In addition patients living outside of the UK must have an S2 form or agreement for access from the referring country.

The clinic can be accessed by any eligible patient who is either suspected of having LSD or has been confirmed to have LSD listed in the specification irrespective of gender, age, sex, disability, religious belief. Interpreters or use of a language line will be provided for families for whom English is not their first language or where the command of English is not sufficient to enable quality communication.

The service is expected to demonstrate equitable geographical access across the country and take actions to address gaps in access. Patients will be able to choose which centre they attend.

The provider will provide information to patients on public transport access and accommodation for patients and relatives as needed.

The provider will have a comprehensive Equality and Diversity framework to guide staff in providing equal opportunities on both service delivery and employment. The provider will have in place equality and diversity training programme as part of their mandatory corporate training programme.

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

### **Exclusion criteria**

Patients with Neuronal Ceroid Lipofuscinosis (Batten disease) and Cystinosis are excluded from the service.

### **Response time & detail and prioritisation**

Emergency referrals will be seen within 48 hours of referral. Routine referrals should be seen in a timely manner, being offered an appointment within four weeks of referral. Once a definite diagnosis has been made, the assessment of eligibility for treatment should be completed within two months and, if eligible, patients desiring treatment should start therapy within three months of either initial referral for those already diagnosed or firm diagnosis for those referred to the designated centres for further testing.

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

### **3. Applicable Service Standards**

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

### **4. Key Service Outcomes**

<b>Quality Performance Indicator</b>	<b>Threshold</b>	<b>Method of measurement</b>	<b>Consequence of breach</b>	<b>Report Due</b>
HCAI control (Q) Will comply with Health & Social Care Act 2008: Code of practice for the NHS on the prevention & control of HCAIs	Fully compliant	Monthly data from Provider	As per NHS Standard Contract for Acute Services. 2010/11	Annual Report
Service User	All	Annual patient	As per	Annual

Experience (Q) Service user experience survey to be offered to every patient/family at the end of each episode	patients/families to be sent annual satisfaction survey	satisfaction report with action plan	NHS Standard Contract for Acute Services.	Report
Service User Experience (Q) Complaints are dealt with in accordance with NHS policy and improvement plans are implemented.	Fully compliant	Audit	None	Annual Report
Improving Service Users & Carers Experience (Q) Patient experience surveys addressed and improvements noted.	Evidence that top areas of concern addressed.  Top areas of concern not replicated in subsequent years	Audit	None	Annual action plan
Reducing inequalities Equality Impact Assessments to be carried out (Q)	All actions to be addressed	EIA reports	As per NHS Standard Contract for Acute Services. 2010/11	Annual report
Access (P) Length of time to see emergency referral	48 hours	Monthly data from provider	None	6 monthly report
Access (P) Length of time to see non-urgent new referral	4 weeks	Monthly data from provider	None	6 monthly meeting
Access (P) Length of time from referral or diagnosis to commencement of definitive treatment	3 months	Monthly data from provider	None	6 monthly meeting

Morbidity and mortality (P) Report all SUIs	100% compliance	Monthly data from provider	As per NHS Standard Contract for Acute Services. 2010/11	6 monthly meeting	
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## 5. Location of Provider Premises

The designated Adult LSD centres are based at:

### **Cambridge University Hospitals NHS Foundation Trust**

Addenbrooke's Hospital  
Cambridge Biomedical Campus  
Hills Road  
Cambridge

### **University Hospitals Birmingham NHS Foundation Trust**

Mindelsohn Way  
Edgbaston  
Birmingham, B15 2WB

### **National Hospital for Neurology & Neurosurgery, UCLH**

Queen Square  
London  
WC1N 3BG

### **The Royal Free London NHS Foundation Trust**

Pond Street  
London  
NW3 2QG

### **Salford Royal NHS Foundation Trust**

Stott Lane  
Salford  
M6 8HD