B04/S(HSS)/b

2013/14 NHS STANDARD CONTRACT
FOR SEVERE IMMUNODEFICIENCY AND RELATED DISORDERS SERVICE (CHILDREN)

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

Service Specification No.	B04/S(HSS)/b
Service	Severe immunodeficiency and related disorders service (children)
Commissioner Lead	
Provider Lead	
Period	12 months
Date of Review	

1. Population Needs

1.1 National/local context and evidence base

The Severe Combined Immunodeficiency and Related Disorders (SCID), Autoimmune Gut Diseases (AGD) and Juvenile Idiopathic Arthritis (JIA) services aim to provide diagnosis, assessment and transplantation, where appropriate, of infants, children and adolescents with suspected or known immunodeficiencies, and severe inflammatory disorders affecting the gut or joints along with associated treatments and long term support.

Primary immunodeficiency disease

It is more than forty years since the first successful hematopoietic cell transplants (HCT) were reported in children with primary immunodeficiency disorders (PID) [GHatti et al 1968, Bach et al 1968]. Many advances have been made since that time such that most children with PID can now be cured from their otherwise lethal disorders through well-matched HCT procedures (Filipovich A 2008).

Autoimmune disease

The potential of Hematopoietic cell transplantation (HCT) for the treatment of autoimmune and inflammatory diseases was originally supported by almost three

decades of animal experiments and by the serendipitous remissions of autoimmune disease observed in patients undergoing transplantation for haematological disorders.
Hematopoietic stem cell transplantation (HSCT) over the last decade has been followed by increasing acceptance of HCT as an experimental treatment for severe autoimmune diseases that are resistant to conventional treatment. (Hough et al 2005).

Juvenile Idiopathic Arthritis (JIA)

Intensive immunosuppression followed by autologous HCT in an attempt to "reset" the immune system has resulted in sustained complete remission or marked improvement in 15 of 22 patients with progressive refractory JIA, although morbidity and mortality associated with the procedure has required adjustment in the initial protocols used. (Brinkman et al 2007)

Autoimmune Gut Diseases

In the 1990's a number of case reports of individuals with inflammatory bowel disease (IBD) who underwent HCT for haematological malignancy described a sustained improvement in the IBD following the transplant procedure (Drakos et al 1993), Lopez-Cubero et al 1998).
Many children with PID have an enteropathy that improves significantly with correction of the systemic immune deficiency.

Description of disease

SCID is the term used to cover the most serious types of primary immunodeficiency (see table 1); a group of conditions where various components of the body's defence system are defective, leaving the children prone to unusual and/or frequent infections. The immune system, which provides the body's defence against infection, is derived predominantly from white blood cells originating in the bone marrow and passing through the thymus, lymph nodes and spleen. AGD and JIA represent severe inflammatory diseases of the gut or joints respectively, and only a small minority of patients who do not respond to conventional immunosuppressive and biological modifying therapies are considered for HCT.

Treatment, involving HCT, offers the only hope of cure but usually entails a lengthy period of specialised high-dependency care. Children are treated in isolation rooms where the air is controlled through a special hepafiltration system to ensure an infection free environment.

Assessment is provided for all children suspected of having SCID or a related disorder to confirm diagnosis and assess the need for HCT, either early or delayed. Treatment includes specialised intensive care within a sterile environment, and either HCT, or full supportive therapy for those not requiring HCT or until such time as one

is carried out. A period of monitoring in early childhood may be necessary to define

the defect clearly at molecular level, and show the likely clinical course and possible need for HCT. Great Ormond Street Hospital for Children NHS Trust (GOSH) provides a molecular immunology diagnostic service for both designated SCID units. Follow-up is required, normally as an outpatient, frequently in the first 6-12 months following HCT, reducing to an annual visit in the longer-term.

Table 1. Immunodeficiencies included in the service specification

<table>
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<td>

Severe combined immunodeficiency (SCID)
<table>
<tr><td>Functional</td><td>Genetic</td></tr>
<tr><td>T- B- NK-</td><td>ADA deficiency
reticular dysgenesis</td></tr>
<tr><td>T- B- NK+</td><td>RAG deficiency
SCID with Artemis</td></tr>
<tr><td>T- B+ NK-</td><td>γc deficiency (X linked)
Jak 3 kinase deficiency (AR)</td></tr>
<tr><td>T- B+ NK+</td><td>IL7 Rα deficiency</td></tr>
</table>
- unspecified
- other
T cell immunodeficiency / SCID variants
- CD4 lymphopenia
- Zap 70 kinase deficiency
- MHC class II deficiency
- PNP deficiency
- Omenn’s syndrome
- Severe Di George complex (22q 11 del)
- CID with skeletal dysplasia
- Cartilage hair hypoplasia
- other

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CD40 ligand deficiency
WASP deficiency
XLP
Phagocytic cell disorders
- Griscelli disease
- Immunodeficiency with partial albinism
- IFN-γ receptor deficiency
- Kostmann disease *
- Shwachman’s syndrome *
- Granule deficiency
- LAD
- X-linked CGD *
- AR-CGD *
- Chediak-Higashi syndrome
Autoimmune lymphoproliferative syndrome (homozygotes)
Thymus and complex Thymus as a result of DiGeorge Syndrome.
complex cases of HLH associated with immune deficiency’

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** not all patients proceed to SCT*

Donor choice in order of preference MFD, 0-1 antigen mismatched UD and haploidentical related donor in those disorders indicated *.

2. Scope

2.1 Aims and objectives of service

Objectives:

- to provide the best possible holistic care, diagnosis and treatment to children with SCID and their families;
- continued development of the service to improve morbidity and mortality outcomes across our patient population;
- to provide an exemplary and comprehensive service for all eligible referred patients with SCIDS;
- expert management of patients with SCIDS through the use of the most up-to-date clinical protocols;
- to operate a rolling programme of clinical audit to test current practice and inform the evolution of care in the service;
- to provide care with a patient and family centred focus to maximise the patient experience of care within the nationally designated providers;
- to become Joint Accreditation Committee - accredited;
- to support local healthcare providers to manage patients with SCIDS whenever it is clinically appropriate and safe to do so;
- provide high quality information for patients, families and carers in appropriate and accessible formats and mediums;
- to develop the experience, knowledge and skills of the MDT to ensure high quality sustainable provision.

2.2 Service description/care pathway

The Blood and Marrow Transplant (BMT) Unit provides a comprehensive HCT service including autologous and allogeneic procedures for patients within the haematology, oncology, immunology, metabolic disease, rheumatology and gastroenterology services. This dynamic and progressive unit carries out approximately 70 transplant episodes per annum and is actively involved in developing national and international protocols and guidelines.

The BMT unit aims to continuously improve the quality of care that it delivers to children who require a Bone Marrow Transplant (BMT), by placing the child at the centre of care. The unit continues to build on its reputation for innovative, robust research and ensures that this research is closely linked to the development of its clinical services.

Patients with complete DiGeorge syndrome are treated with thymic epithelial transplantation instead of a BMT. The thymus is transplanted in the form of cultured slices to the quadriceps muscle of the leg and results in conferring the ability for the child to produce T-cells otherwise absent in the condition. Atypical DiGeorge

syndrome patients may undergo pre-treatment (conditioning) with Antithymocyte Globulins (ATG), however in most cases conditioning is not required.

Gene therapy offers an alternative treatment option to certain immunodeficiency conditions for which there is no well matched donor. Gene therapy is currently used in X-linked SCID, ADA SCID, Wiskatt Aldrich syndrome and compassionate use for children with X-linked chronic granulomatous disease (CGD).

Referrals

Patients are referred to the service through either a letter or phone call from either the child's local hospital or their GP. If a child is suffering from any of the conditions in table 1 of this specification then the referral is accepted.
Initial Assessment:
The national providers use a core multidisciplinary team (MDT) including (at least):

- BMT consultant
- immunologists
- gastroenterology consultant
- rheumatology consultant
- clinical nurse specialist

The service is should also access support from:

- neurology;
- respiratory;
- cardiology;
- nephrology;
- metabolic medicine;
- endocrinology;
- occupational therapy;
- physiotherapy;
- oncology;
- physiotherapy;
- dietetics;
- psychology;
- interventional radiology;
- molecular genetics;
- stem cell laboratory.

Clinics

Outpatient clinics are held weekly. Patients will always see one of the medical team, usually a consultant on their first visit, and clinics are also supported and led by the expert clinical nurse specialist team.

Interventions

Where appropriate patients are screened for viruses, liver and kidney function, Graft-

versus-host disease (GvHD), vital signs are monitored. Appropriate interventions are made if necessary including antibiotics, pre-transplant work-up and donor searches where applicable.

Inpatient activity

Patients are admitted one to two weeks prior to their transplant for preparation and conditioning. Patients are re-admitted if there are complications following their discharge which are usually picked up either in clinic or by the patient's local hospital.

Follow up

The follow-up process must run for the period of time agreed with the referring clinician. A clinical review will be required within three months after transplant between referring and transplant centre clinicians to enhance communication, to plan further treatment and to agree on transfer arrangements.

Discharge criteria

Patients are generally deemed appropriate for discharge once they are no longer reliant on IV medications or receiving total parenteral nutrition (TPN), they are clinically stable to do so and they have no ongoing complications e.g. GvHD. Patients will also usually have a neutrophil count above 0.5. A clearly defined after-care programme should be developed with the parents/patient and the referring provider unit. Communication with general practitioners and staff in primary care and the referring clinician should be timely, efficient and continuous. The general practitioner should be informed at all stages of the patient's treatment and should be informed on how to access advice.

Audit

Audit is an integral part of improving the delivery of care and an on-going audit programme provides the evidence to improve and enhance the delivery of the clinical care provided.

The providers will meet on a regular basis usually annually to undertake audit and review outcomes within the service. The results of the audit will be shared with NHS England.

The laboratories are open Monday- Friday 0900 – 1730 hours. An out of hours service is not provided, but arrangements are in place for samples to be received out of working hours by the other hospital laboratories providing a 24/7 service.

2.3 Population covered

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

At the moment, NHS England contract includes provision for the service to treat eligible overseas patients under S2 [Under European Union (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 NHS England contract.

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

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

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 are accepted for any patient sample affected by any of the conditions for which the laboratory may be able to provide testing after discussion with a consultant immunologist or senior clinical scientist.

2.5 Interdependencies with other services

Internally the SCIDS team should link into multiple clinical and administrative teams as a result of the composition of the broad MDT. Please refer to Appendix 1 (Lab specification)

Interdependencies

The SCID service depends upon adequate provision of a number of services including the following:

- BMT;
- immunology;
- gastroenterology;

- haematology;
- palliative care team;
- rheumatology;
- metabolic medicine;
- endocrinology;
- occupational therapy;
- physiotherapy;
- infectious diseases;
- oncology;
- physiotherapy;
- dietetics;
- psychology;
- interventional radiology;
- genetics

The service is also heavily reliant on tissue typing and cord blood services received from external organisations. Service Level Agreements (SLA) are in place with:

Barts Health NHS Trust
80 Newark Street
Royal London Hospital
Whitechapel
London E1 2ES

The Anthony Nolan Trust
Royal Free Hospital
Pond Street
Hampstead
London
NW3 2QG

Other providers include The National Blood Service, The Welsh Bone Marrow Registry and The British Bone Marrow Registry.

Relevant networks and screening programmes

The Primary Immunodeficiency Association (PIA) supports people with and promotes awareness of primary immunodeficiencies and disorders of the immune system. PIA exists to support people living with Primary Immunodeficiency; it liaises with clinicians and immunologists, funds relevant research and campaigns for the rights of its members in the UK.
There are also a range of international websites providing support for SCID patients and their families including SCID.net which has been set-up by the parent of an American SCID patient. The purpose of the site is to attempt to form a self-help support group, and a resource guide, to other families afflicted with SCID.

3. Applicable service standards

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

4. Key Service Outcomes

Quality Performance Indicator	***Threshold***	***Method of measurement***	***Consequence of breach***	***Report Due***
Outcomes	Severe combined immunodeficiency and related disorders • Number and percentage of patients treated successfully	Annual report (September of contract year) with data from previous financial year April to March		
	• Stem cell transplantation service for juvenile idiopathic arthritis and related connective disease tissue disorders • Number and percentage of patients treated successfully	Annual report (September of contract year) with data from previous financial year April to March		

5. Location of Provider Premises

Newcastle upon Tyne Hospitals NHS Foundation Trust
Great Ormond Street Hospital NHS Foundation Trust

Sub-contractors

The SCID service must have annually reviewed Service Level Agreements with appropriate sub contractors

These are:

- Barts Health NHS Trust;
- The Anthony Nolan Charity.

Appendix 1 : National Molecular Diagnostic Service for SCID.

Commissioned as part of: Paediatric Severe Combined Immunodeficiency and Related Disorders (SCID), Autoimmune Gut Diseases (AGD) & Juvenile Idiopathic Arthritis (JIA)

1. Purpose

1.1 Aims and General Overview

The laboratory service aims to provide diagnostic support to both centres (London and Newcastle) for aspects of the diagnosis of primary immune deficiency diseases that are transplantable.

Overview of Service

This is a UK service covering England. Samples are received from outside England, and appropriate funding arrangements should be made.

The laboratory service is provided within the Immunology and Genetics laboratories of Great Ormond Street Hospital for Children NHS Trust. These laboratories are Clinical Pathology Accreditation accredited. The testing strategies are a combination of functional tests, protein detection by flow cytometry or immunoblot and genetic screening by sequence analysis and dosage analysis (Multiplex ligation-dependent probe amplification [MLPA]).

For each condition the testing strategy is designed to provide a timely diagnosis in the most cost efficient way. GOSH is the only laboratory providing comprehensive immunological assays and genetic tests within the UK.

Objectives and Expected Outcomes

- to provide a high quality, robust diagnostic service for patients with SCID;
- to continue to develop new assays to improve the diagnostic repertoire of the service;
- to review and modify all assays and methodologies to ensure that they are performed to maximise diagnostic yield and using most appropriate techniques and technologies;
- to support research into the diagnosis and treatment of SCID and related conditions.

Outcomes

A annual quality meeting is held which reviews

- number of tests undertaken;
- number of samples in which a meaningful result was obtained;
- correlation between different diagnostic methods (protein and genetics).

Expectations

Providers are expected to be actively involved in research and gathering an evidence base on which to base new and improving treatments.

2. Scope

2.1 Service Description

The Immunology and Genetics laboratories at GOSH provide comprehensive diagnostic services to the hospital, nationally and internationally. The molecular diagnostic service for primary immune deficiency was developed within these services in the mid 1990's, and has been NHS England funded since 1998.

Referrals

Samples for testing are referred from throughout the UK. Referrals are accepted from centres outside Newcastle and GOSH as many patients will be seen initially in other centres before transfer of their care to GOSH/Newcastle. Testing must be discussed and agreed with consultant or clinical scientists in Immunology before sending, to ensure that an optimal service is provided.

Quality and audit

Both laboratories should be Clinical Pathology Accreditation (CPA) accredited. All tests are fully evaluated in the laboratories before being used for routine diagnostics. The senior staff involved in running the service within genetics and immunology meet monthly to discuss all samples received in that period. An annual audit of the service is undertaken to review quality. Periodic audits of individual tests or other aspects of the service are undertaken as part of the laboratory quality management system.

Scope of Service

The following tests are currently provided as part of the service[1]. For individual patients, additional tests will be undertaken on a research basis to endeavour to elucidate the basis of their condition.

Disease	Functional Assay (Immunology)	Protein Tests (Immunology)	Genetic Tests

[1] A number of other tests to diagnose primary immune deficiency are provided within the laboratory services but are not funded as part of NHS ENGLAND-SCID programme.

X-SCID	STAT-5 tyrosine phosphorylation	Common gamma chain	Common gamma chain
Jak-3 SCID	STAT-5 tyrosine phosphorylation		Jak-3
XLP-1		SAP	SH2D1A
XLP-2		XIAP	XIAP
RAG SCID			RAG1/2
Artemis SCID			DCLRE1C
X-HyperIgM		CG154 expression	CD40LG (previously known as TNFSF5)

Disease	**Functional Assay (Immunology)**	**Protein Tests (Immunology)**	**Genetic Tests**
Wiskott Aldrich Syndrome		WASP	WAS
Chronic Granulomatous Disease		Gp91, p22, p67, p47	Sent to Amsterdam
ZAP-70 SCID		ZAP-70	
IL7R alpha SCID			IL7Ra

2.2 Accessibility/acceptability

The service is commissioned by NHS England for all eligible patients under 16 from England (or a minority of patients over 16 with relevant history). The service can be accessed by any eligible patient who has been confirmed to have SCIDS irrespective of gender, age, sex, disability, religious belief.

The service is expected to demonstrate equitable geographical access across the country and take actions to address gaps in access.

Providers are required to ensure staff to attend mandatory training on equality and diversity and the facilities provided offer appropriate disabled access for patients, family and carers.

When required providers are required to use translators and printed information must be made 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

2.3 Whole system relationships and interdependencies

The laboratory services link closely to other services. The tests provided as part of the service are an integral part of both laboratories repertoires, which ensures that the service is fully maintained throughout the year and not dependant on individual availability.

Full provision of the service in a cost effective manner is dependant on this integration. The laboratory services are fully integrated with the clinical BMT and Immunology teams, with regular attendance by Senior staff at ward rounds and other relevant MDTs

2.4 Relevant networks and screening programmes

The service works closely with researchers locally, nationally and internationally

and participates in discussions and working parties considering relevant testing for primary immune deficiencies.

GOSH : The service was granted national designation and funding from the 1st of April 1993. The laboratory service was included in this designation in 1998.

Newcastle : The service was granted national designation and funding from the 1st of April 1993.