NHS

VERSION TWO

Commissioning policy for all treating centres for the provision of intravenous and subcutaneous immunoglobulin to medium and low priority patients

National Specialised Commissioning Group
Model Commissioning Policy

1st July 2008 –30th June 2009

[Insert Organisation; if commissioning under a collaborative arrangement, include 'on behalf of X, Y etc. PCT']

Commissioning policy for IMMUNOGLOBULIN USE

VERSION TWO

Blue and grey Indications

National Specialised Commissioning Group

Taken from Clinical Guidelines for the Use of Intravenous Immunoglobulin, Department of Health, May 2008 (2nd Edition)

1st of 2 related documents

1. Introduction

1.1. This policy shall cover the period [date] to [date].

1.2. The policy provides the framework for the provision and supply of intravenous and subcutaneous immunoglobulin (IVIG/SCIG) for all categories other than red indications.

1.3. It is recognised that immunoglobulin is provided to the patient as a result of a partnership between a number of organisations:

Organisation	Roles and responsibilities
Providers	Clinical management of patient, initiation of funding requests and prescribing of IVIG/SCIG
Commissioners	Commissioning IVIG/SCIG, home delivery services and community administration of IVIG/SCIG
Home Delivery Services	Providing IVIG/SCIG to patients on long-term treatment
Primary and Community services	Supervising infusions when necessary and providing clinical support under shared care protocols

2. The aims of this policy

2.1 To target a scarce supply of IVIG/SCIG to those patients for whom this treatment is the preferred option and to ensure that IVIG/SCIG is used in a way that is effective and cost-effective.

2.2 To operate a robust mechanism for managing and prioritising access to treatment at times of short supply.

2.3 To ensure that funding is linked to the provision of data to the national IVIG/SCIG Database to improve the health communities' understanding of the current use of and demand for IVIG/SCIG.

3. Designated IVIG/SCIG responsible person

Any hospital in which IVIG/SCIG is likely to be prescribed should have a designated responsible person whose role it is:

- To ensure that this commissioning policy is operated by all clinicians within the provider trust
- To sign off funding requests for IVIG/SCIG to confirm that they comply with this commissioning policy
- [Insert a list of designated responsible persons for local providers]

4. Commissioning considerations

The supply of immunoglobulin has, over the last few years, reduced in volume and, at times, there are periods of short supply. The cost of this treatment has also risen significantly. At the same time, the indications for use of immunoglobulins have widened, often in the absence of robust evidence about clinical effectiveness. The cost-effectiveness of IVIG/SCIG for different indications has rarely been examined.

The Department of Health initiated a piece of work with clinicians that aimed to:

- develop a better understanding of how IVIG/SCIG is currently used nationally
- ensure better stock control of IVIG/SCIG
- develop a more evidence-based approach to IVIG/SCIG use

This piece of work has generated three main outputs:

1. A national IVIG/SCIG Database has been set up which will provide information about the epidemiology of target conditions and IVIG/SCIG use and enable tracking of IVIG/SCIG stock.

2. A set of clinical guidelines, produced by healthcare professionals, that have classified indications into Red, Blue or Grey based on clinical evidence and clinical opinion. (Clinical Guidelines for the use of Intravenous Immunoglobulin, DH, 2nd edition, May 2008)

    - Red indications are those for which there is evidence of good outcome and for which access should be guaranteed. These are a clearly defined group of patients whose treatment is considered the highest priority because of the risk to life without treatment. This group is subject to a separate commissioning policy.

    - Blue indications are those for which there is some evidence of benefit but for which there *may be* alternative treatments and *for which* treatment may be modified in times of supply shortages of immunoglobulin (by either delaying starting treatment, reducing treatment frequency or dose or substituting a less favourable alternative).

    - Grey indications are those for which the evidence is weak. These include rare disorders. Patients from this group should be considered on a case-by-case basis and their need prioritised against other competing demands.

3. A demand management plan that included a recommendation that providers establish IVIG/SCIG review panels to screen requests to use IVIG/SCIG. (Demand Management Plan for Immunoglobulin Use, DH, 2nd edition, May 2008)

Having presented this work to the Directors of Specialised Commissioning Teams, commissioners felt that it was important for commissioners to provide a clear statement of their commissioning position and the decision-making process for each category of treatment. In addition, it was also considered important that funding was linked to data provision to the national IVIG/SCIG Database.

The development of this IVIG/SCIG commissioning policy will be an iterative process and so will require an annual review. This is because there are a number of issues that still need resolving to the satisfaction of commissioners.

Firstly, there remains concern that cost-effectiveness has not been addressed. In the current climate, it is important that PCTs review what they currently commission to ensure that there is consistency in approach to priority setting. A piece of work has been commissioned from the HTA unit at Birmingham University to look at the 16 medium- to long-term blue indications in the first instance.

Secondly, there is recognition that clinical practice has been established for a number of indications for which the evidence is insufficient to fully judge both clinical effectiveness and cost-effectiveness. The Grey list comprises indications for which there is only case series data, some of which could be subject to more robust trials. As such, many commissioners would classify this subset of indications as experimental treatments and not generally fund patients outside the context of a robust trial. It has been agreed in the interim period to allow the grey list, as at the moment it is not known what the demand for this list is. However, the long-term goal is to reclassify grey indications as blue, black, or trial[1]. Commissioners are committed to reclassification based on high-quality clinical evidence.

With the above two points in mind, **great importance is attached to ensuring that there is provider compliance regarding data input to the national IVIG/SCIG Database as well as the participation of units in trials**.

[1]There will be a list of treatment indications for which a trial is required and for which formal efficacy endpoints will be pre-specified.

The possibility of establishing an 'n of 1' trial unit [1] will be explored. No such unit currently exists in the UK and so it is not possible to conduct n of 1 trials. Furthermore it is not clear at the moment which conditions are suitable for study through n of 1 trial methodology. In the meantime, it is recommended that as a minimum, where a trial period is funded, continuation criteria are agreed (clinical goals to be achieved) before the patient starts treatment. Trial periods might need to be of considerable duration.

Ongoing work is also needed to establish nationally agreed clinical criteria for initiating and stopping treatment, particularly for long-term use.

The potential use of subcutaneous preparations also needs to be fully explored. The important role of plasmapheresis therapy is acknowledged and a review of therapeutic plasma exchange services is a priority for 2009/10.

The practice of using different immunoglobulin preparations from different suppliers is encouraged to diversify risk in the event of a manufacturer restricting product supply.

Shortages must be reported via the IVIg website (www.ivig.nhs.uk). An example guideline on shortage management will be included in the next version of the Model Commissioning Policy.

A National IVIG/SCIG Working Group, which has Department of Health, commissioner and clinician representatives, will provide advice to the National Specialised Commissioning Group (NSCG) on further development of the service specification.

5. Key specifications

5.1 All applications for funding, even when retrospectively applied for, must be approved by the provider trust's designated IVIG/SCIG responsible person.

5.2 All new patients must be logged with the national IVIG/SCIG Database and their data provided as required. Existing patients must be logged during the next 12 months.

[1]An 'n of 1 trial' is a properly conducted trial in which the patient acts as his or her own control. The patient is given sequential periods of treatment and placebo and the course of the patient's illness is monitored against pre-agreed clinical outcomes. Both the patient and the clinician is blind to whether the patient is receiving active or placebo at any point in time. N of 1 trials in theory can be used to better target treatment to those individuals who will most benefit. They may also possibly help to inform policy-making about the value of treatments in particular patient groups. The true value of n of 1 trials is still to be determined.

An n of 1 trial is to be distinguished from 'a trial of treatment', which is often erroneously referred to as an n of 1 trial. These can be of variable quality but generally involve giving the patient a few doses of treatment and then seeing if they respond. At the very least, if patients are being given a trial run an appropriate length of treatment should be agreed, together with outcome indicators and criteria for continuation of treatment. Patients will also need to be consented as they clearly need to understand what is going to happen at the end of the 'test' period

6. The commissioning policy

6.1 Service developments and disinvestments Management of any changes to this commissioning policy

6.1.1 A service development is defined as any change that has resource implications. This includes new indications for treatment and new clinical criteria for treating patients.

6.1.2 In-year expansion to the list of indications for IVIG/SCIG use will not generally be considered. Individual funding requests are not considered an appropriate route to introduce service developments.

6.1.3 Providers will notify commissioners at an early stage of any potential change in the use of IVIG/SCIG that has resource implications. All new indications for IVIG/SCIG will only be considered through a national process overseen by the NSCG on an annual basis. This includes proposed trials using IVIG/SCIG.

6.2 Indications for which IVIG/SCIG will NOT be funded

6.2.1 BLACK indications[1]

IVIG/SCIG use for the following indications will **not** be funded:

Haemato-oncology

Autologous bone marrow transplant

Neurology

Adrenoleukodystrophy
Alzheimer's disease
Amyotrophic lateral sclerosis
Autism (not included in the Clinical Guidelines)
Chronic fatigue syndrome
Critical illness neuropathy
Inclusion body myositis
Multiple sclerosis

Rheumatology

Inclusion body myositis
Rheumatoid arthritis

Paediatrics

Immunodeficiency secondary to paediatric HIV infection

[1]Black are indications for which there is evidence to suggest immunoglobulin is not an appropriate treatment and treatment is not recommended.

Infectious diseases

Neonatal sepsis (prevention or treatment)

Sepsis in intensive care unit not related to specific toxins or *Clostridium difficile*

Transplantation

Long-term use in CMV-induced pneumonitis following transplantation

Other

Asthma

Autoimmune uveitis

Graves' ophthalmopathy

IVF failure

Recurrent spontaneous pregnancy loss

6.2.1.2 Funding requests for this list of conditions are expected to be screened out by provider trust mechanisms.

6.2.1.3 It is not anticipated that exceptional circumstances will arise for patients with this list of conditions.

6.2.1.4 This list is not exhaustive.

6.2.2 Indications for which intended durations of treatment fall outside the recommendations in the Clinical Guidelines will NOT be funded[1]

6.2.2.1 Where the clinical intent to treat with IVIG/SCIG for a specified duration **falls outside** the recommendations made by the guidelines (duration as defined in the clinical guidelines[2]), treatment will **not** be funded for the following indications:

Immunology

Impaired specific antibody production

Kawasaki disease

[1]The intended duration of treatment is an important consideration for health commissioners because of the large financial implications of a short course of treatment compared with a long course; a long-course treatment can be 1000 times more expensive. Therefore, **the intended duration of treatment must be specified**. The expectation is that where appropriate, long-term treatment recommendations are reviewed for efficacy and safety after a short treatment course, before a long-term treatment plan is approved.

[2]Short-term treatment as specified in the clinical guidelines, consisting of a single course of treatment, which may comprise a number of doses up to a maximum of three. A single dose is defined as the appropriate dosage for the disease indication, usually in g/kg, which may be fractionated and delivered over 1–5 days.
Long-term treatment as specified in the clinical guidelines, consisting of one or more courses of IVIG/SCIG where further courses may be anticipated from the diagnosis before the initiation of treatment or decided upon following response to a single trial course.

Haematology

Acquired red cell aplasia due to parvovirus B19
Adult HIV-associated thrombocytopenia
Alloimmune thrombocytopenia
Autoimmune (acquired) haemophilia
Autoimmune haemolytic anaemia
Autoimmune thrombocytopenia
Evans' syndrome
Haemolytic disease of the foetus and newborn
Haemophagocytic lymphohistiocytosis
Idiopathic thrombocytopenic purpura
Post transfusion purpura

Haemato-oncology

Chronic lymphocytic leukaemia with recurrent infections associated with low serum Ig levels
Haemophagocytic lymphohistiocytosis
Multiple myeloma

Neurology

Guillain-Barré syndrome
Paraprotein-associated demyelinating neuropathy
Rasmussen syndrome
Stiff person syndrome

Paediatrics

Foetal hydrops
Toxin related infections in paediatric intensive care

Infectious diseases

Severe streptococcal group A disease
Staphylococcal toxic shock syndrome
Necrotising (PVL-associated) staphylococcal sepsis
Severe or recurrent *Clostridium difficile* colitis

6.3 Patients for whom funding will be routinely available BLUE indications

6.3.1 Funding will be provided for the following indications provided that the patient meets agreed clinical criteria set down by the provider's IVIG/SCIG Review Panel.

6.3.2 When national clinical criteria are agreed these will be incorporated into this commissioning policy. Once incorporated, national criteria will override existing local criteria.

Current indications for short-term treatment (18 indications)

Haematology

- Acquired red cell aplasia due to parvovirus B19
- Adult HIV-associated thrombocytopenia
- Autoimmune (acquired) haemophilia
- Autoimmune haemolytic anaemia
- Evans' syndrome
- Haemophagocytic lymphohistiocytosis
- Post transfusion purpura

Neurology

- Lambert Eaton myasthenic syndrome
- Multifocal motor neuropathy
- Myasthenia gravis

Other

- Immunobullous diseases

Paediatrics

- Foetal hydrops
- Haemolytic disease of the foetus and newborn
- Toxin-related infection in paediatric intensive care

Infections diseases

- Severe streptococcal group A disease
- Staphylococcal toxic shock syndrome
- Necrotising (PVL-associated) staphylococcal sepsis
- Severe or recurrent *Clostridium difficile* colitis

Current indications for medium- to long-term treatment (16 indications)

Immunology

- Impaired specific antibody production (with severe symptoms)

Haemato-oncology

- Low serum IgG levels following stem cell transplant
- Chronic lymphocytic leukaemia with recurrent infections associated with low serum Ig levels
- Multiple myeloma (plateau phase only with recurrent infections)

Neurology

- Chronic inflammatory demyelinating polyradiculoneuropathy
- Dermatomyositis
- Lambert Eaton myasthenic syndrome
- Multifocal motor neuropathy
- Myasthenia gravis

- IgM paraprotein-associated demyelinating neuropathy
- IgG or IgA paraprotein-associated demyelinating neuropathy
- Rasmussen syndrome
- Stiff person syndrome

Paediatrics

- Juvenille dermatomyositis

Other

- Immunobullous diseases
- Toxic epidermal necrolysis/Stevens-Johnson syndrome

Trials currently open and supported by the NSCG

None at the moment

6.3.3 Decision-making protocol

6.3.3.1 No prior approval is required before commencing treatment for Blue indications. However funding will not be released until all required information has been received and the application has been signed by the designated IVIG/SCIG responsible person. The information MUST include an IVIG/SCIG Database number.

6.3.3.2 [Insert local arrangements for dealing with funding requests and to whom they should be directed. Where funding has been put into contracts and does not occur on a case-by-case basis, the commissioner will have to agree locally how compliance and registration with the national IVIG/SCIG Database will be monitored.]

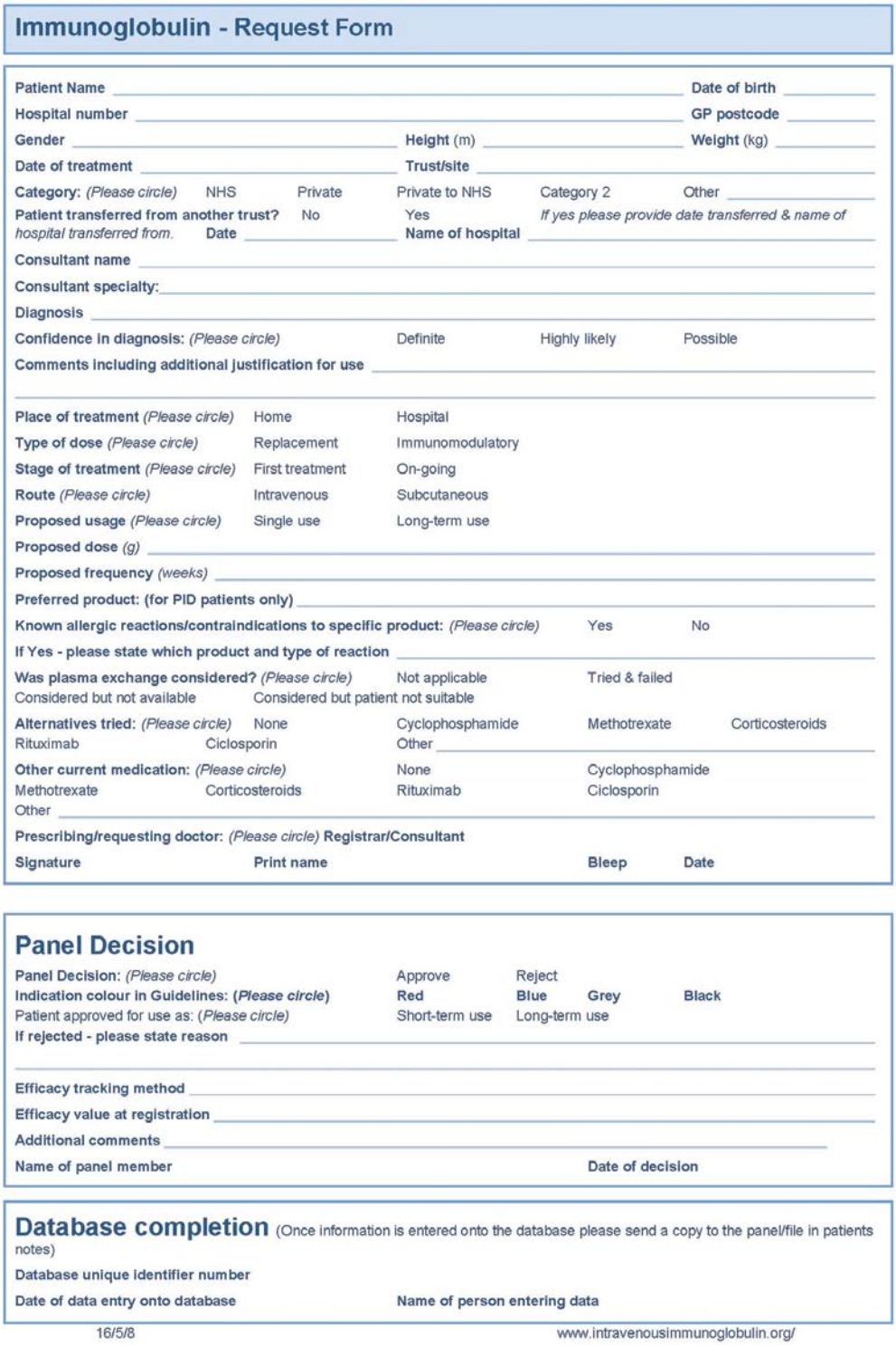
6.3.3.3 Requests for release of funding for new patients should be done by forwarding a photocopy of the front sheet of the national database form (Figure 1). All entries should be complete, including the database number. The trust's designated IVIG/SCIG responsible person should sign the form.

6.4 Individual funding requests GREY indications[1]

6.4.1 A trust wishing to treat a patient with the indications listed under 6.4.3 should complete a funding request. The funding request must consist of a clinical letter making the case for funding, setting out the following:

- The clinical information
- The case for treating this particular patient including the evidence base/rationale

[1] Grey indications are those for which the evidence base is weak, in many cases because the disease is rare; IVIG/SCIG treatment should be considered on a case-by-case basis, prioritised against other competing demands.



Immunoglobulin - Request Form

Patient Name _____ **Date of birth** _____
Hospital number _____ **GP postcode** _____
Gender _____ **Height** (m) _____ **Weight** (kg) _____
Date of treatment _____ **Trust/site** _____
Category: *(Please circle)* NHS Private Private to NHS Category 2 Other _____
Patient transferred from another trust? No Yes *If yes please provide date transferred & name of hospital transferred from.* **Date** _____ **Name of hospital** _____
Consultant name _____
Consultant specialty: _____
Diagnosis _____
Confidence in diagnosis: *(Please circle)* Definite Highly likely Possible
Comments including additional justification for use _____

Place of treatment *(Please circle)* Home Hospital
Type of dose *(Please circle)* Replacement Immunomodulatory
Stage of treatment *(Please circle)* First treatment On-going
Route *(Please circle)* Intravenous Subcutaneous
Proposed usage *(Please circle)* Single use Long-term use
Proposed dose *(g)* _____
Proposed frequency *(weeks)* _____
Preferred product: (for PID patients only) _____
Known allergic reactions/contraindications to specific product: *(Please circle)* Yes No
If Yes - please state which product and type of reaction _____
Was plasma exchange considered? *(Please circle)* Not applicable Tried & failed Considered but not available Considered but patient not suitable
Alternatives tried: *(Please circle)* None Cyclophosphamide Methotrexate Corticosteroids Rituximab Ciclosporin Other _____
Other current medication: *(Please circle)* None Cyclophosphamide Methotrexate Corticosteroids Rituximab Ciclosporin Other _____
Prescribing/requesting doctor: *(Please circle)* **Registrar/Consultant**
Signature **Print name** **Bleep** **Date**

Panel Decision

Panel Decision: *(Please circle)* Approve Reject
Indication colour in Guidelines: (Please circle) **Red** **Blue** **Grey** **Black**
Patient approved for use as: *(Please circle)* Short-term use Long-term use
If rejected - please state reason _____
Efficacy tracking method _____
Efficacy value at registration _____
Additional comments _____
Name of panel member **Date of decision**

Database completion (Once information is entered onto the database please send a copy to the panel/file in patients notes)

Database unique identifier number
Date of data entry onto database **Name of person entering data**

16/5/8 www.intravenousimmunoglobulin.org/

Figure 1. Immunoglobulin Request Form

- The expected clinical outcomes
- For medium- to long-term treatment, how a trial of benefit will be tested

6.4.2 If agreed, funding will only be released if the commissioning team is confident that a valid database number has been provided.

6.4.3 The following have been identified as possible indications for funding:

Immunology

- Secondary antibody deficiencies

Haematology

- Acquired red cell aplasia not due to B19 parvovirus
- Aplastic anaemia or pancytopenia
- Autoimmune neutropenia
- Haemolytic uraemic syndrome
- Acquired von Willebrand disease
- Post exposure prophylaxis for viral infection if intramuscular injection is contraindicated, or treatment when hyperimmune immunoglobulins are unavailable
- Post-transfusion hyperhaemolysis (usually in patients with sickle cell disease)

Haemato-oncology

- Graft versus host disease following allogeneic bone marrow or haematopoietic stem cell transplant
- Infection following allogeneic bone marrow or haematopoietic stem cell transplant
- Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes (POEMS)

Neurology

- Acute disseminated encephalomyelitis
- Acute idiopathic dysautonomia
- Bickerstaff's brainstem encephalitis
- Cerebral infarctions with antiphospholipid antibodies
- CNS vasculitis
- Vasculitic neuropathy
- Systemic vasculitides and ANCA disorders
- Neuromyotonia
- Paraneoplastic disorders
- Polymyositis
- Short-term use in potassium channel antibody-associated, non-neoplastic limbic encephalitis

Paediatrics

- Intractable childhood epilepsy
- Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS)

- Juvenile systemic lupus erythematosus
- Other systemic vasculitides
- Systemic juvenile idiopathic arthritis

Other

- Catastrophic antiphospholipid syndrome
- Autoimmune diabetic proximal neuropathy
- Atopic dermatis / eczema
- Pyoderma gangrenosum
- Urticaria
- Systemic lupus erythematosus

Transplantation

- Antibody incompatible transplantation
- Treatment of acute antibody-mediated rejection following solid organ transplantation

6.4.4 The above list is not exhaustive.

6.4.5 Funding in these instances cannot be guaranteed. Each individual case will need to be taken on its own merits and prioritised against other competing demands for the available resource.

6.5 Application for exceptionality under sections 6.2 and 6.3

6.5.1 There may be instances in which a provider trust may wish to apply for funding for patients who do not fulfil the criteria for funding but who are considered, both by the treating clinician AND the designated IVIG/SCIG responsible person, to have exceptional circumstances. Under these circumstances an individual funding request may be made to the commissioner for consideration.

6.5.2 The funding request must set out the case for ***exceptionality*** and this must be signed by the trust's designated IVIG/SCIG responsible person. It should be noted that:

- Responsibility for demonstrating exceptionality rests with the requesting clinician.
- Only evidence of clinical need will be considered. Factors such as gender, ethnicity, age, lifestyle or other social factors such as employment or parenthood will not be considered.
- In order to demonstrate exceptionality the patient must be significantly different from the reference population (i.e. all other patients with the same condition who do not fulfil the treatment criteria) **and** there must be good grounds to believe that this patient is likely to gain significantly more benefit from this intervention than might be expected for the average patient with that condition. The fact that the treatment might be efficacious for the patient is not, in itself, grounds for exceptionality. This in essence requires the clinician to make a case why this particular patient should be funded when others will not receive treatment.

- In submitting a funding request the trust must forward a photocopy of the front sheet of the national database form (Figure 1). All items in the first two boxes should be complete. The trust's designated IVIG/SCIG responsible person should sign the form. In addition, the trust must forward a clinical letter making the case for funding, setting out why this patient should be treated when other patients are excluded from funding.

6.6 Trial pick-up or compassionate funding pick-up

6.6.1 The PCT will not pick up the funding of patients coming off drug trials or who are on drug company sponsored treatment programmes unless prior arrangements have been made at the time the patient is entered into the trial. It is seen as the responsibility of those running trials to ensure that there is a proper exit strategy for the trial and that patients understand what that is. PCTs will consider the funding of new indications following an agreed change to this commissioning policy.[2]

6.7 Existing patients

6.7.1 Patients currently receiving IVIG/SCIG who do not fall into the patient selection criteria indicated in the sections above should have the option to continue therapy until they and their clinicians consider it appropriate to stop. Ongoing treatment should be reviewed at the annual review.

7. Quality

7.1 All decisions will be undertaken by a consultant who has specialist knowledge of the use of IVIG/SCIG. This consultant will have ongoing responsibility for IVIG/SCIG prescribing until treatment is stopped.

7.2 It is expected that, where clinically appropriate, subcutaneous delivery will be considered.

7.3 It is expected that, where clinically appropriate, cost minimisation will be applied.

7.4 Patients on long-term treatment will be required to have an annual review of their treatment.

[2] National Specialised Commissioning Group Commissioning Support Document: *Funding for patients leaving clinical trials* March 2008

7.5 For patients who receive treatment on a shared care basis:

- The specialist clinical team initiating treatment will retain overall clinical responsibility for the management of the patient including the prescribing of IVIG/SCIG and the annual review.
- The specialist clinical team has the responsibility for ensuring that a satisfactory shared care arrangement is in place between itself and any local provider or community based service.
- Providers should ensure that patients understand the precise nature of the shared care arrangements including which person to contact when problems arise.

7.7 There will be no GP prescribing of these treatments.

7.8 The specialist clinical team responsible for prescribing will be expected to monitor communications from the Department of Health concerning any risks to supply and understand the mechanism for managing supplies of IVIG/SCIG at times of shortages.

7.9 Patients should have been fully informed about how supply shortages will be managed and what the implications might be for them. This should include clear written information. Patients should sign a consent form indicating that they understand that their treatment cannot be guaranteed, or in the case of a trial treatment period, that they understand the basis of treatment being continued.

7.10 Centres are expected, ***without exception***, to provide a complete dataset to the Department of Health IVIG/SCIG Database in line with information requests from the team overseeing the IVIG/SCIG Database. This will be monitored and ongoing failure to provide data may lead to penalty payments.

7.11 Developments in healthcare

The provider will notify the commissioner at an early stage of any change in the use of IVIG/SCIG that has resource implications.

All new indications for IVIG/SCIG will only be considered through a national process overseen by the NSCG on an annual basis.

In-year expansion to the list of Blue indications will not normally be considered.

Any requests for changes to the policy should be directed to the National Working Group (contact point: daphne.austin@wmsc.nhs.uk).

8.0 Mechanism of funding

8.1 The PCT responsible for funding of IVIG/SCID is identified by the General Practitioner's post code.

8.2 [It is recommended that the following monthly or quarterly monitoring requirements are required in order to track usage. A regular dataset might include:

- Database ID number
- Patient initials
- NHS Number
- PCT code
- Drug and dose
- Notification of changes to drugs and dosage
- Take-off date
- Reason for take off
- Monthly cost
- Annual cost

9. [Annual reporting]

[Insert performance management requirements]

10. Review of the Commissioning Policy

This commissioning policy will be reviewed annually by a National IVIG/SCIG Working Group set up under the auspices of the NSCG. Recommendations of changes will be put to primary care trusts through the NSCG. Any additional conditions will have to be considered as part of the annual commissioning round.

Commissioning contact for PCTs and SCTs: daphne.austin@wmsc.nhs.uk