Medical Data Solutions and Services

mdsas

Second National Immunoglobulin Database Report (2010–2011)

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NHS

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Executive summary

As the National Immunoglobulin Database approaches completion of its fourth year of data collection, this is a timely moment to review and assess the data again and describe the current prescribing practice of immunoglobulin in England. The development of the database was a major step forward in establishing the Department of Health (DH) Demand Management Programme for immunoglobulin. The first National Immunoglobulin Database Report in 2010 provided a baseline of immunoglobulin use for the first time and validated the key step of prioritisation of treatment indications to ensure that immunoglobulin will always be available to those for whom the treatment is life-saving, before major changes to the data. The database has continued to evolve to reflect the recommendations of the National Clinical Guidelines. This report captures the prescribing of immunoglobulin prior to the introduction of a number of significant changes within the National Clinical Guidelines, which include the introduction of selection criteria, changes to the definitions of duration of treatment, dosing recommendations and the move towards defining and recording outcome measures.

General findings

The data presented are for the 19-month period 1st June 2009 to 31st December 2011. Neurology remains the highest-using specialty (41% of volume), with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) accounting for 48% of volume. The data suggest that only 12% of prescribing in neurology was for life-threatening symptoms; this suggests that 88% of prescribing should have been considered for alternative treatments, such as therapeutic plasma exchange (although it is acknowledged that the service in London is inadequate for such purposes).

Immunology indications are the second largest user (29%), almost entirely for the treatment of primary immunodeficiency (PID), a life-threatening condition with no viable alternatives. PID and most neurological conditions require long-term treatment, and this is seen in the trend of increasing numbers of patients using immunoglobulin. The Guidelines now recommend dose reduction in stable patients, with the expectation that some patients will be able to reduce and stop therapy. The patterns of prescribing in neurology will be examined closely in the next report (due for publication in early 2013) to assess the impact of these new recommendations.

Haematology (including malignant disorders) accounts for 18% of immunoglobulin use, mostly for immune thrombocytopenia (ITP). New international management guidelines provide a new framework for ITP, which is reflected in the Second Edition Update of the *Clinical Guidelines for Immunoglobulin Use*, published in July 2011 (gateway reference 16290). Regarding dosing, new recommendations suggest initiating treatment at 1 g/kg, halving the initial dose of immunoglobulin that was previously widely used. Adherence to this advice in the new Guidelines should reduce immunoglobulin use for this high-volume indication by at least one third. In addition, the revised Guidelines also provide recommendations on various initiatives to reduce the volume of immunoglobulin used, in particular the need to consider using lean body weight dosing, strict starting and stopping criteria and dose reduction in stable patients on long-term immunomodulation.

Unity of effort

The overall number of patients entered into the database as this report goes to press has reached about 22,000. This represents a significant effort on behalf of most acute Trusts, and clinicians, pharmacists and others should be congratulated on this achievement.

Coping with shortages

During the time period for this report, two shortages occurred. The first shortage was due to a recall of product and subsequent suspension of the product's license for about 6 months by the MHRA. The advice provided was that new patients should be initiated on a different product, and that 15% of current patients should be switched to a different product. No serious adverse events from switching were reported; some patients reported a sense of change in efficacy. On the whole, the view formed was that patients were satisfied and remained with their new product.

The second shortage was due to a manufacturing problem, which resulted in a break in supply for 3 months. Many patients receiving this product had been long-term users, so the advice provide was that patients receiving immunoglobulin for 'Red' indications should have their supply maintained, but that patients being treated for 'Blue' indications should either have longer periods between treatments or should switch to a different immunoglobulin product. Again, no serious adverse events were reported.

The next phase

The DH initiated and funded the development and implementation of the Demand Management Programme for immunoglobulin. From April 1st 2012, the DH has stepped back from its role and the database has been transitioned to Specialised Commissioning Groups (SCGs), consistent with the SCGs commissioning the use of immunoglobulin as one of the subset of the Specialised Services National Definitions Set (SSNDS) ('Minimum Take') services from April 2012. By April 1st 2013, it is expected that immunoglobulin prescribing will fall in the various definition sets, e.g., neurology, immunology, cancer, and paediatrics.

There is an ongoing exercise to develop a Quality Dashboard for immunoglobulin prescribing and it is expected that a Quality Dashboard-related goal linked to achieving quality indicators for immunoglobulin prescribing will be set within the CQUIN payment framework.

The impact of the Second Edition Update of the *Clinical Guidelines for Immunoglobulin Use* published in July 2011 (gateway reference 16290), will be assessed and reported in a further report in early 2013.

Contents

Abbreviations

ALL	acute lymphoblastic leukaemia
ANCA	anti-neutrophil cytoplasmic antibody
BMT	bone marrow transplantation
CIDP	chronic inflammatory demyelinating polyradiculoneuropathy
CLL	chronic lymphocytic leukaemia
CVID	common variable immunodeficiency disorder
DH	Department of Health
GBS	Guillain-Barré syndrome
HPA	Health Protection Agency
HSCT	haematopoietic stem cell transplantation
ITP	idiopathic thrombocytopenic purpura
MDSAS	Medical Data Solutions and Services
MG	myasthenia gravis
MM	multiple myeloma
MMN	multifocal motor neuropathy
MMNCB	multifocal motor neuropathy with conduction block
MUD	matched unrelated donor
NSCG	National Specialised Commissioning Group
Panel	Immunoglobulin Assessment Panel
PCT	Primary Care Trust
PID	primary immunodeficiency disorder
RCT	randomised controlled trial
SCG	Specialised Commissioning Group
SHA	Strategic Health Authority
SLE	systemic lupus erythematosus

CHAPTER 1

Introduction

1.1 Background

In 2006, precipitated by a severe and prolonged shortage of immunoglobulin, the DH initiated a review that resulted in the DH publishing *Clinical Guidelines for Immunoglobulin Use* and *Demand Management Plan for Immunoglobulin Use* in May 2007. In May 2008, after further stakeholder involvement, revised versions of the *Clinical Guidelines for Immunoglobulin Use* and *Demand Management Plan for Immunoglobulin Use* (Gateway reference 10012 and 10013) were published. The DH issued a 'Dear Colleague' letter (DH 085234) at the same time to highlight the publication of these documents and the importance of the programme to maintain the security of supply of immunoglobulin. These documents can be accessed at www.ivig.nhs.uk.

> "Variable supply, high product costs, and an increasing demand for both established and off-label indications have made the Department of Health's development of a management programme for intravenous immunoglobulin use in the United Kingdom essential."
>
> **Fitzharris P, Hurst M. *BMJ* 2008; 337:a1851**

The National Immunoglobulin Database (Reference No. ROCR/ OR/0221) was launched in June 2008, with MDSAS contracted at launch to continue the database programme and to be responsible for working with a DH-sponsored database steering group to maintain and extend the solution.

The initial aims of this database were to provide:

a) An accurate assessment of immunoglobulin use for forecasting and tendering
b) An accurate picture of prescribing by indication
c) A tracking mechanism of individual batches for safety purposes

These aims were then developed further, to include monitoring of the **effects of shortages**, either due to manufacturing problems (which was the case in the BPL product shortage) or with actual product withdrawals (e.g., the case of Octapharma). The key was to ensure **treatment priority for 'Red' Indications**, in particular for those patients with PID.

Benefits of the database have included:

a) Better contracts with suppliers
b) Supporting local Trust management of immunoglobulin use or its alternatives (e.g., plasmapheresis)
c) Informing research to enable clinical trials of efficacy of therapy

1.2 Future of the database

The DH initiated and funded the development and implementation of the Demand Management Programme, chairing the various working groups that researched and wrote the Guidelines, the Demand Management Plan, and developed the database. From April 1st, 2012, the DH has stepped back from its role and the database has been transitioned to SCGs, consistent with the SCGs commissioning the use of immunoglobulins as one of the subset of the SSNDS ('Minimum Take') services from April 2012. By April 1st 2013, it is expected that immunoglobulin prescribing will fall in the various definition sets, e.g., neurology, immunology, cancer, and paediatrics. There is an ongoing exercise to develop a Quality Dashboard for immunoglobulin prescribing and it is expected that a Quality Dashboard-related goal linked to achieving quality indicators for immunoglobulin prescribing will be set within CQUIN payment framework. The database will play an increasingly important role and is fit for this purpose.

1.3 The Second National Database Report

The *First National Database Report (2008–2009)* was published in January, 2010 (Gateway reference 13401). This report was an important step forward as it established, for the first time, a baseline of immunoglobulin use in the NHS in England. This was seen as a major step forward in establishing the DH Demand Management Programme and, in particular, validating the key step

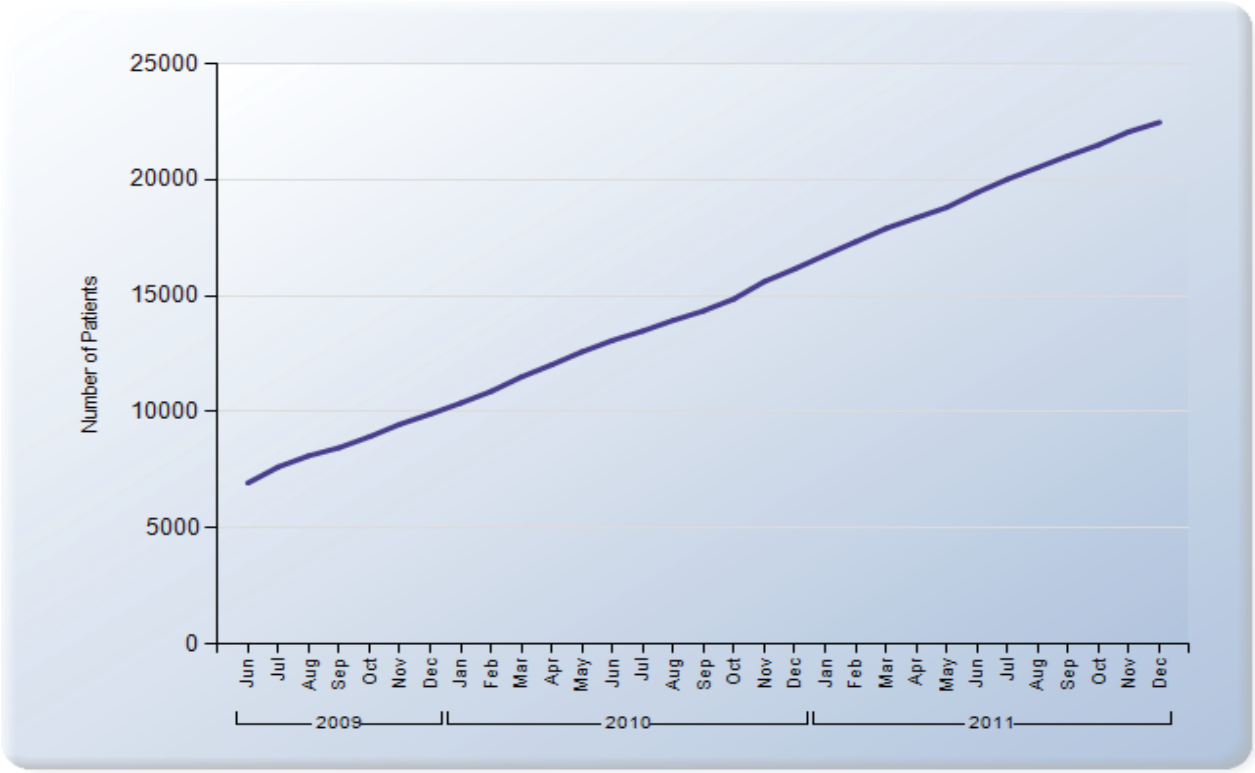
of prioritisation of treatment indications to ensure that immunoglobulin will always be available to those for which the treatment is life-saving.

This *Second National Database Report (2009–2011)* presents data prior to the update of the Clinical Guidelines introduced in late 2011 that now include the added requirement of measuring patient outcome. A *Third National Database Report (2011–2012)*, which will audit the implementation of the changes to the Guidelines and, in particular, the recording of outcomes for each disease category, will be published in early 2013.

1.4 Entries in the database

To date (April 2012), there are 22,478 patients registered and 165 NHS Trusts enrolled on the database. Not all Trusts are expected to enrol, as some will rarely use immunoglobulin. From database launch in June 2008, the database has grown consistently, both in the number of patients registered and the volume of immunoglobulin use recorded. The rate of increase in patient numbers for the period of this analysis is shown in Figure 1.4.

Figure 1.4 Patients registered on the database (1st June 2009 to 31st December 2011)



1.5 Immunoglobulin use in specialisms

As expected from the data analysis in the *First National Database Report (2008–2009)*, neurological conditions used the most immunoglobulin (41% by volume), with immunology the second highest user (29%) and haematology third (11%).

To accurately forecast future immunoglobulin use it will be necessary to closely monitor the rates of increase in patient numbers recorded on the database. Looking at the rate of increase of patients in Figure 1.5.2, it can be seen that neurology and haematology stand out as having a greater rate of increase in patient numbers. This may be accounted for by the long-term nature of some of the conditions under these specialisms.

Figure 1.5.1 Volume of immunoglobulin used for each specialism

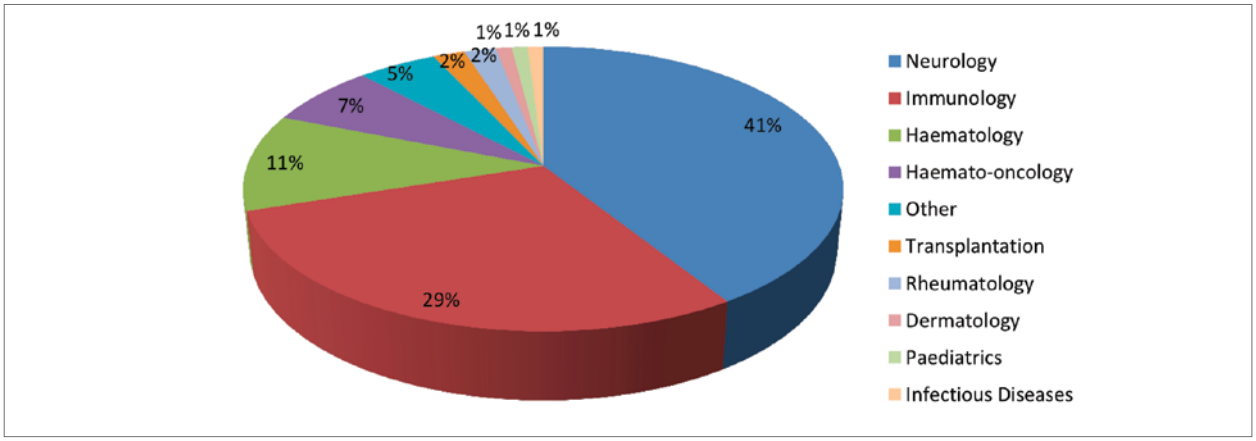
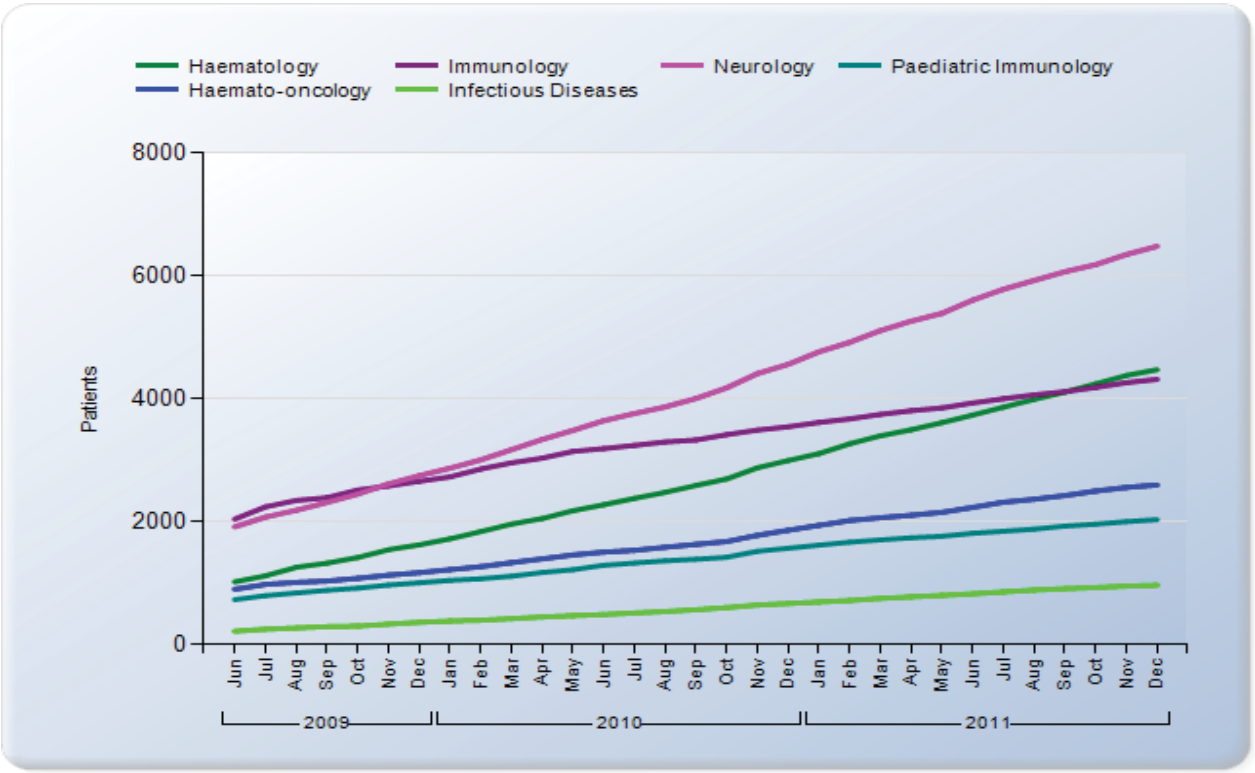


Figure 1.5.2 Number of patients using immunoglobulin in each specialism



1.6 Immunoglobulin use in individual Trusts

The number of patients entered by each Trust, and the volumes used, vary considerably. The largest number of patients registered remains by Imperial College Healthcare NHS Trust, where the majority of the prescribing is for transplantation and neurology patients.

The highest volume user remains University College London Hospitals, which includes the National Hospital for Neurology and Neurosurgery. Interestingly, the addition of cases at Cambridge University Hospitals and Guy's and St Thomas' to the database has caused Southampton and Salford to fall in numbers registered. Barts and the London Hospitals as well as Guy's and St Thomas' Hospitals may have more patients registered, but Salford Royal and Leicester actually use more in volume.

Table 1.6.1 Number of patients registered in top 10 Trusts (1st June 2009 to 31st December 2011)

NHS Trust	Number of patients
Imperial College Healthcare NHS Trust	729
The Newcastle upon Tyne Hospitals NHS Foundation Trust	525
Guy's and St Thomas' NHS Foundation Trust	453
University College London Hospitals NHS Foundation Trust	437
Sheffield Teaching Hospitals NHS Foundation Trust	428
Cambridge University Hospitals NHS Foundation Trust	412
Oxford Radcliffe Hospitals NHS Trust	409
Leeds Teaching Hospitals NHS Trust	408
Royal Free Hampstead NHS Trust	396
Barts and the London NHS Trust	366
Total	**4563**

Table 1.6.2 Volume of immunoglobulin used in top 10 Trusts (1st June 2009 to 31st December 2011)

NHS Trust	Number of grams infused
University College London Hospitals NHS Foundation Trust	366742
The Newcastle upon Tyne Hospitals NHS Foundation Trust	292841
Royal Free Hampstead NHS Trust	274233
Oxford Radcliffe Hospitals NHS Trust	254143
Salford Royal NHS Foundation Trust	226496
Leeds Teaching Hospitals NHS Trust	222912
Imperial College Healthcare NHS Trust	208302
Sheffield Teaching Hospitals NHS Foundation Trust	208185
Cambridge University Hospitals NHS Foundation Trust	186183
University Hospitals of Leicester NHS Trust	177824
Total	**2417861**

1.7 Immunoglobulin use for top 10 individual diagnoses

PIDs, which are prioritised as Red within the DH Demand Management Programme, account for the highest proportion of patients recorded on the database (23.9%) and the largest volume used. The next highest disease is autoimmune thrombocytopenia.

The top 10 diagnoses (by volume) described in the analysis of the *First National Database Report (2008–2009)*, included two 'Grey' indications (secondary antibody deficiencies and antibody-mediated rejection following solid organ transplantation). This finding contributed to the review of the Clinical Guidelines and in the Second Edition Update of the *Clinical Guidelines for Immunoglobulin Use* published in July 2011 (gateway reference 16290), these indications were changed and reclassified as Blue within changed disease groupings.

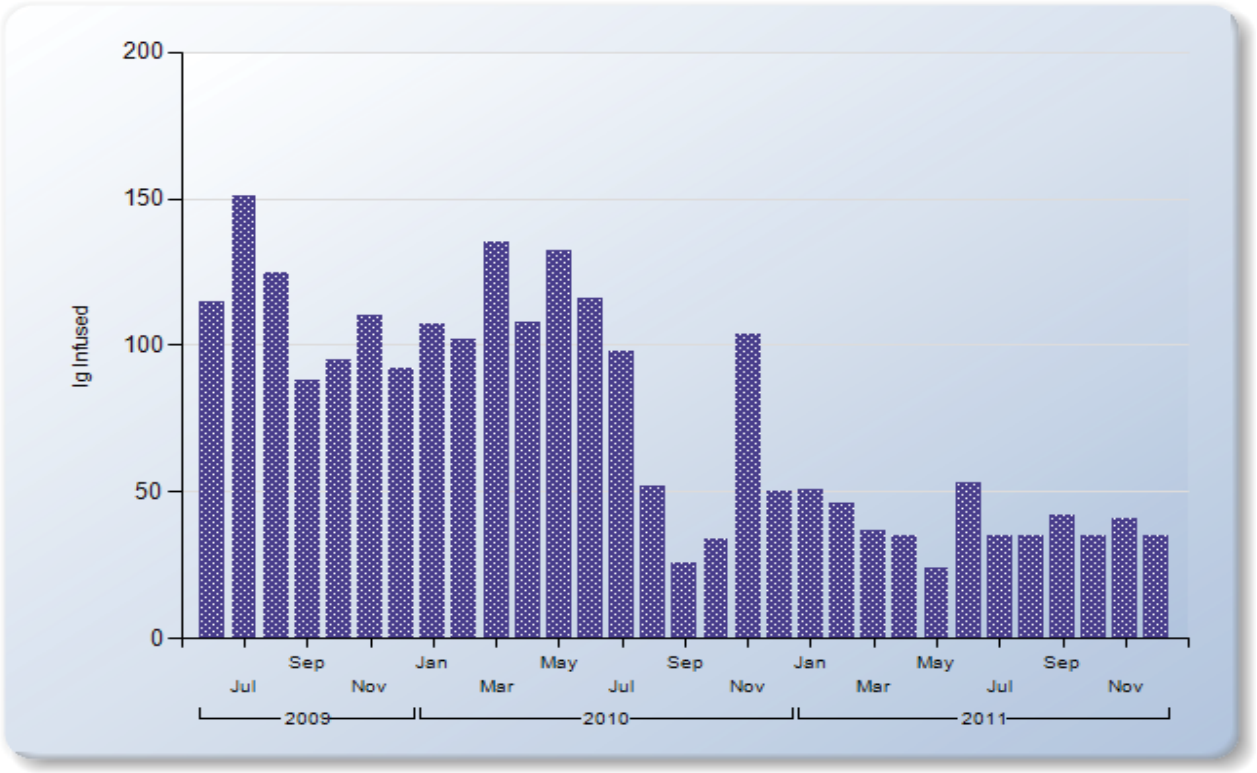
1.8 Immunoglobulin use for 'other' diagnoses

Considerable volumes of immunoglobulin were used and no specific condition recorded. Measures to address this have been taken by MDSAS and recent upgrades to the database have resulted in the removal of duplicate treatment episodes, reducing the number of 'other' diagnoses and ensuring all patients have a primary diagnosis.

Table 1.7 Number of patients for top 10 diagnoses (1st June 2009 to 31st December 2011)

Diagnosis	Number of patients
PID	2676
Autoimmune thrombocytopenia (see ITP)	2140
Guillain–Barré syndrome (GBS)	1433
CIDP	1333
Chronic lymphocytic leukaemia (CLL)	1009
Myasthenia gravis	722
Kawasaki disease	586
Multifocal motor neuropathy (MMN)	543
Low serum IgG levels following HSCT for malignancy	329
Severe or recurrent *Clostridium difficile* colitis	309

Figure 1.8 The number of 'other' diagnoses registered (1st June 2009 to 31st December 2011)



The strategies employed by MDSAS were:

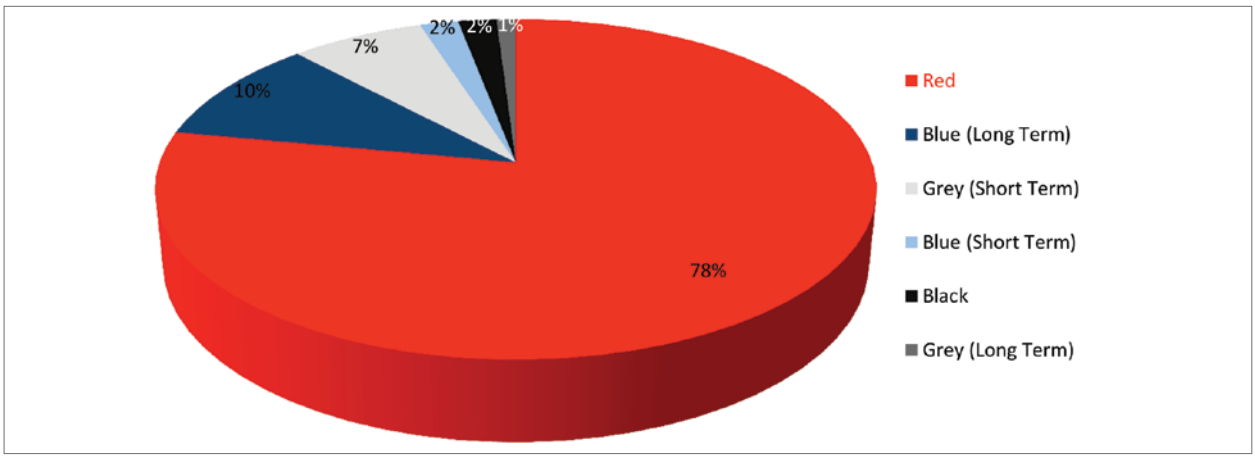
a) Removing all 'other' options for each specialism, but retaining a single 'other' option
b) If 'other' is selected, the user is forced to enter the diagnosis in a mandatory textbox
c) If 'other' is selected, the colour coding defaults to 'Grey', which requires Commissioner approval.

1.9 Immunoglobulin use by colour-coded prioritisation

As expected, the highest usage recorded on the database is for 'Red' indications (78%). However, not all of these are recorded correctly. 'Red' identifies life-threatening diseases and clinical situations, but many patients with CIDP are receiving immunoglobulin when they could have an alternative treatment such as therapeutic plasma exchange and should be entered onto the database as Blue. ***The data are consistently incorrectly coded, so a decision has been made to link specific indications to a specific colour, which is then automatically assigned.***

'Grey' indications, which require referral for PCT approval, currently account for 8% (short term and long term) of all usage. There is still some usage (2%) for 'Black' indications, which are not approved under the Demand Management Programme.

Figure 1.9 Immunoglobulin usage by colour-coded prioritisation (1st June 2009 to 31st December 2011)



CHAPTER 2

Commissioning of Immunoglobulin

Intravenous and subcutaneous immunoglobulin is an expensive blood product used across a variety of clinical specialities. The critical need as well as effectiveness of treatment varies; it is life-saving for some patients for whom no alternative treatment exists, while others do have clinically effective and often more cost-effective alternatives available to them.

Treatment with immunoglobulin represents a substantial financial commitment for the health service, with an annual cost of about £80 million. These treatments remain a high-cost drug exclusion from the national tariffs and will be entirely funded by specialised Commissioners via the National Commissioning Board.

2.1 Model Commissioning Policy for immunoglobulin

In 2009, the Model Commissioning Policy was published and closely mirrored the aims of the DH Demand Management Programme for immunoglobulin. The policy aims to target the scarce supply of immunoglobulin to those patients for whom this treatment is the preferred option and to ensure that immunoglobulin is used in a way that is effective and cost effective. The commissioning policy required the operation of a robust mechanism, namely Immunoglobulin Assessment Panels (IAPs) for managing and prioritising access to immunoglobulin treatment at times of short supply (using the colour coding provided in the DH Demand Management Plan).

In addition, there was a requirement that all patient data be entered into the National Immunoglobulin Database, with a view to tying funding for immunoglobulin with accurate data entry.

A National Immunoglobulin Working Group, which has Commissioner and clinician representatives (and until recently a representative from DH) will continue to provide advice to the National SCG on further development of the service specification.

Figure 2.1 The approval process

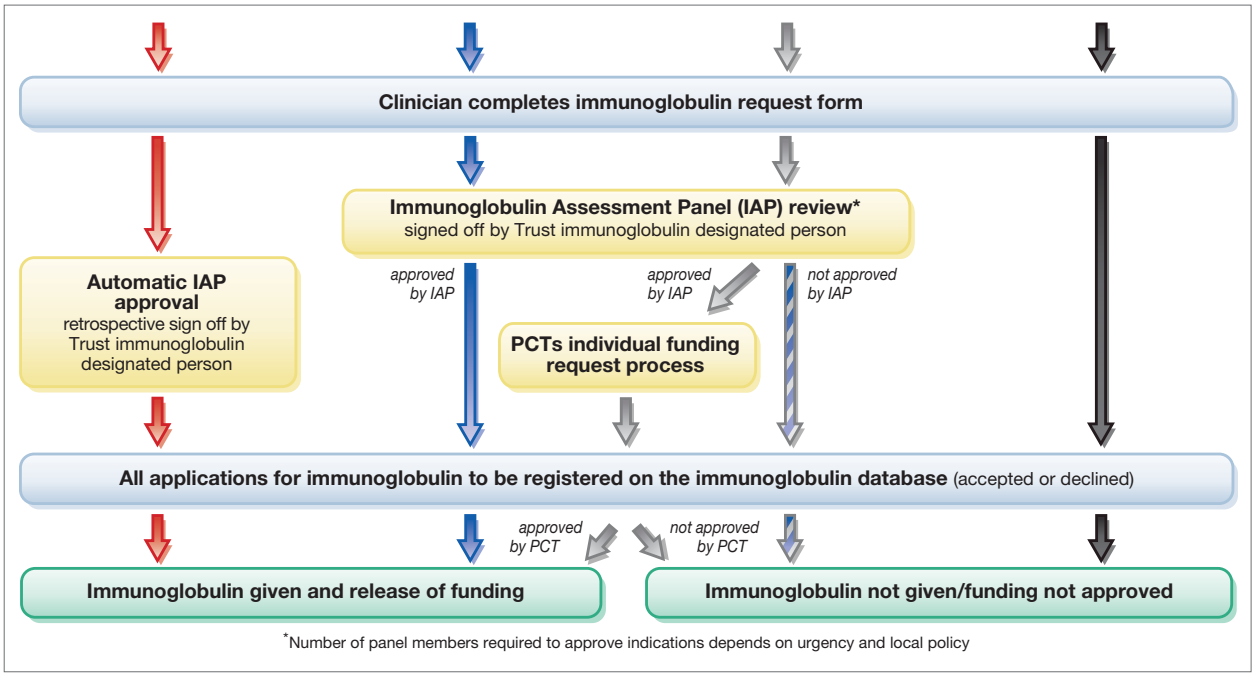
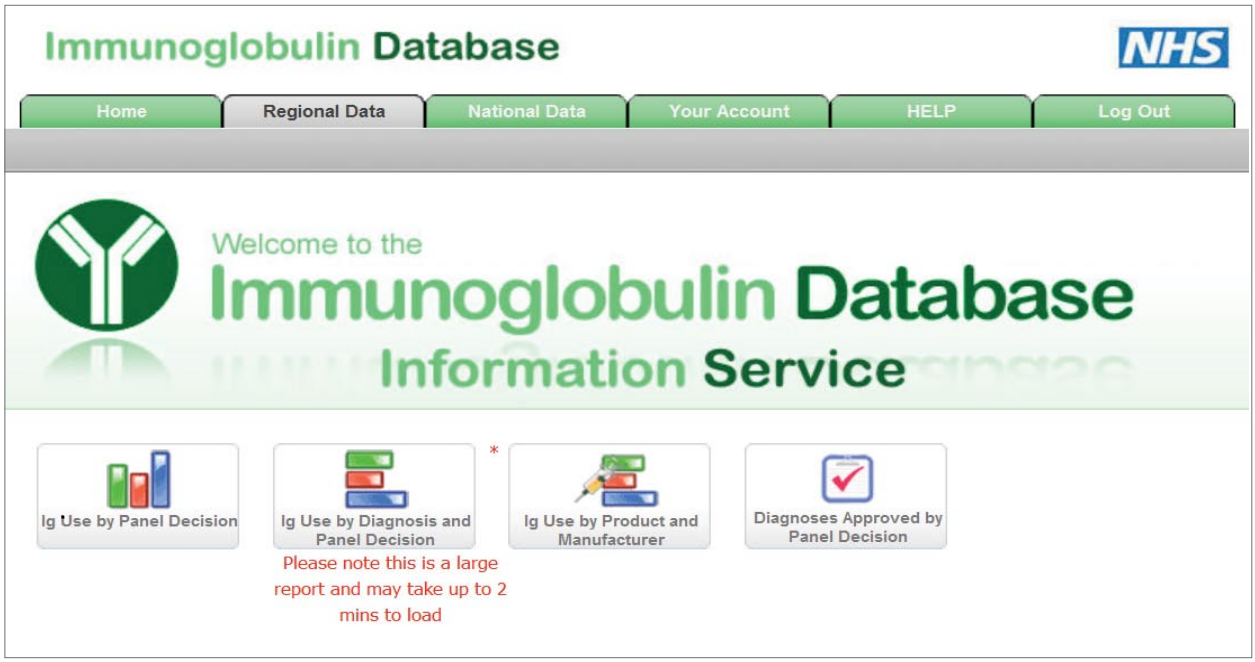


Figure 2.2.1 Commissioners database information system



2.2 Commissioner's database information service

As part of the database improvements launched in June 2009, the database was migrated onto the internal NHS N3 network, which uses industry-standard encryption. One of the key additions was the information service for Commissioners.

Figure 2.2.2 Location of patients' GPs attending London Trusts (1st June 2009 to 31st December 2011).

This has allowed access to data by region, subdivided by centres, as well as the ability to geographically map patients attending a particular centre. The London map highlights the specialist nature of services provided in London, with many patients attending London treatment centres from other parts of the country.

This service gives secure, real-time online access to reports and charts so there is now an opportunity to link immunoglobulin use to payment. For example, East Midlands SCG has incorporated a requirement for National Immunoglobulin Database completion as a condition for payment. Bespoke immunoglobulin prescribing reports are generated from the Commissioners' portal on the database, documenting total volume and cost of each product. This data is then used to calculate the 'spend' entered onto the database, and, if this does not correlate with actual volumes used, final payments are withheld.

2.3 Improving the clarity of data entry

"Increased clarity regarding patient selection criteria and the need for prescribers to report clinical outcome after treatment are strongly supported"

When the first edition of the Demand Management Programme (both Guidelines and Demand Management Plan) were published in the UK, a similar group of stakeholders in Australia published their guidelines, which contained strict selection criteria as well as specified outcomes that were to be used to assess treatment success.

As well as 'starting criteria', there are also 'stopping criteria'. There will be automated email alerts and automatic stopping rules through database locking to prevent inappropriate unsanctioned use. This will also make it possible to link payment for immunoglobulin to appropriate prescribing as recorded in the National Immunoglobulin Database.

"For most diseases the treatment duration is short term (<3 months). The treatment episode ends at 3 months; treatment re-initiation will be regarded as a new treatment episode, based on a new IAP decision. Effective IAPs are important to monitor adherence to these new selection criteria in routine clinical practice"

In addition, for patients on long-term immunomodulatory doses, there is now a requirement that *attempts should be made to reduce the dose* either by increasing the dosing interval or by reducing the dose, and, for patients with a high body mass index, adjusted-body-weight dosing should be used.

Where the database has not been so successful is the capture of data regarding efficacy of immunoglobulin. Panels were encouraged to request up to three parameters by which efficacy could be determined in each patient (e.g., platelet count in patients with ITP). The last update now specifies the **outcome(s) measures** but not the degree in improvement of outcome(s) required to constitute treatment success. Over the next year(s), Commissioners will be working with expert clinicians to refine these outcomes and generate '**treatment success**' measures where possible.

CHAPTER 3

Immunology

Antibody deficiencies may arise as primary disorders with a known or suspected genetic basis or secondary to a variety of other diseases, drugs and environmental or iatrogenic factors. They may occur in isolation or in association with defects in other effector components of the immune system (combined defects).

3.1 Primary immunodeficiency

Significant primary antibody deficiencies collectively account for the majority of PID syndromes encountered in clinical practice, and can present at any age.

Diagnostic aims are to:

a) Identify, or exclude, significant antibody deficiency
b) Differentiate primary from secondary disease
c) Delineate, where possible, a precise diagnosis

Management aims are to:

a) Prevent complications or retard their progression
b) Optimise quality of life, working capacity and life expectancy
c) In children, ensure optimal growth and development

The hallmark clinical presentation is recurrent or persistent bacterial infection, but these disorders are also associated with a heterogeneous variety of other infectious and non-infectious complications and with a high incidence of chronic, structural tissue damage, particularly in the respiratory tract.

Replacement therapy with polyclonal human normal immunoglobulin is the cornerstone of management for significant primary antibody deficiency disorders. No viable alternatives exist to this essential, basic component of treatment, particularly in the context of severe, persistent or recurrent bacterial infections. ***For most patients, replacement therapy is a lifelong requirement***. Existing formulations replace deficient IgG only and are given by either intravenous or subcutaneous infusion, which are therapeutically equivalent.

Immunology indications account for 29% of total use by volume, with PID collectively accounting for at least 87% of this. Immunoglobulin replacement is the mainstay of treatment for patients with PID. The efficacy of immunoglobulin in established PID is supported by a strong evidence base provided by retrospective surveys and controlled studies (level IIb evidence). No alternative is available in patients who have clear-cut established PID, which is therefore prioritised as Red by the National Demand Management Programme.

3.2 Secondary antibody deficiency

Secondary antibody defects are found in a wide range of circumstances (in association with drugs, malignant disease, chronic infections, protein-losing states, systemic inflammatory diseases, trauma and iatrogenic factors such as splenectomy).

Infections associated with low measured antibody levels appear to be relatively uncommon in secondary deficiencies, with the exceptions of hypogammaglobulinaemia linked with haematological malignant disease, occasional cases of drug-associated deficiency and rare cases of nephrotic syndrome.

The selection criteria for immunoglobulin to treat hypogammaglobulinaemia linked to haematological malignancy includes the requirement to document the failure of serum antibody response to unconjugated pneumococcal or other polysaccharide vaccine challenge. Although this may sound onerous from a practical point of view, the intention is simply to ensure that a patient's response is included as a component of the evaluation for immunoglobulin therapy. For example, if a patient received a polysaccharide vaccine 3 months ago and their specific antibodies are low, it would seem reasonable to prescribe immunoglobulin. However, if the patient was vaccinated may years previously, it would be reasonable to re-vaccinate and assess the functional antibody response before immunoglobulin was prescribed.

Table 3.2 Selection criteria and outcome measures for secondary antibody deficiency (any cause)

Selection criteria	Outcomes for review	Dosing
Underlying cause of hypogammaglobulinaemia cannot be reversed or reversal is contraindicated OR hypogammaglobulinaemia associated with non-Hodgkin's lymphoma, CLL, multiple myeloma (MM) or other relevant B-cell malignancy confirmed by haematologist AND – recurrent or severe bacterial infection despite continuous oral antibiotic therapy for 3 months – IgG <5 g/L (excluding paraprotein) – documented failure of serum antibody response to unconjugated pneumococcal or other polysaccharide vaccine challenge	Number of infections and days in hospital recorded prior to treatment, and 6 monthly thereafter	0.4 g/kg/month modified to achieve an IgG trough level of at least the lower limit of the age-specific serum IgG reference range

CHAPTER 4

Neurology

Before the institution of the National Immunoglobulin Database, neurology was known to be a heavy user of immunoglobulin and there was concern about the proliferation of usage for large numbers of rare and unusual diagnoses, where the evidence base for efficacy was not strong, or was positively lacking.

4.1 Use of immunoglobulin in neurology

The use of immunoglobulin for neurological indications accounts for more than 40% of the total usage of immunoglobulin and 25% of all patients receiving treatment, making neurology the largest individual specialism user. Neurology is the specialism with the greatest number of indications for treatment with immunoglobulin, of which four indications account for 85% of all patients treated and 87% of the immunoglobulin given to neurology patients. The use of immunoglobulin in these four indications is supported by RCT evidence, which for CIDP, GBS and MMNCB is of high quality.

Table 4.1.1 Number of patients treated for the top four neurology conditions

Diagnosis	Grams used	% of total
CIDP	473,649	48%
MMN	224,303	23%
GBS	97,814	10%
Myasthenia gravis	69,221	7%

The information in the database confirms that only 12% is actually for life-threatening conditions and 88% could have alternative treatment, or a delay in treatment, in a shortage situation.

4.2 Ascertainment of patients

Ascertainment to the database in the first year was recognised as an issue. It was estimated from PASA/NHS-CMU that around 1000 kg of immunoglobulin (40% of total use) was unaccounted for in the database. This estimate was supported by the total use of immunoglobulin in GBS, where accurate incidence figures are available and there is strong evidence for the use of immunoglobulin treatment in patients with significant and deteriorating disability. With an incidence of GBS of 1.2–1.5 per 100,000 population, between 720 and 900 cases of GBS would be expected per year. Given that 60% of these require treatment with immunoglobulin, the database would be expected to contain between 430 and 540 cases of GBS. In 2009 there were 260 GBS patients in the database, suggesting case ascertainment between 48% and 60%. Now, there are 633 cases, which is suggestive of 90% ascertainment

Table 4.1.2 Colour-coded prioritisation by volume for top four neurology indications

Diagnosis	Red (short-term)	Blue (long-term)	Blue (short-term)
CIDP	4154	438,680	
GBS	96,354		
MMN		204,486	24,722
Myasthenia gravis		31,601	38,375

Table 4.3.1 Selection criteria for inflammatory myopathies with required outcome criteria

Inflammatory myopathies DM, PM, inclusion body myositis (IBM)	Diagnosis by a neurologist, rheumatologist, or immunologist of: – Patients with PM or DM who have significant muscle weakness, OR – dysphagia and have not responded to corticosteroids and other immuno-suppressive agents; OR – Patients with IBM who have dysphagia affecting nutrition (NOT patients with rapidly progressive IBM)	**1.** Improvement in functional scores (activities of daily living; ADLs) or quantitative muscle scores or MRC muscle assessment; OR up and go 10 m walk (in seconds) **2.** Stabilisation of disease as defined by stable ADLs or quantitative muscle scores or MRC muscle assessment OR up and go 10 m walk after previous evidence of deterioration in one of these scores

4.3 Updates in neurology

The Second Edition Update did not review and revise all of the content of the Second Edition, but limited itself to three key areas:

a) Defining selection criteria for appropriate use
b) Efficacy outcomes to assess treatment success
c) Reassignment of existing indications /inclusion of new indications

For example, polymyositis (PM) was grouped with dermatomyositis (DM) as **Myositis**.

Changes were also made to '**Grey**' **indications**, with two groupings specified:

a) Immune-mediated disorders with limited evidence of immunoglobulin efficacy
b) Presumed immune-mediated disorders with little or no evidence of efficacy

Table 4.3.2 Summary of 'Grey' conditions in neurology

Immune-mediated disorders with limited evidence of immunoglobulin efficacy	Immune-mediated disorders with little or no evidence of immunoglobulin efficacy
Acute disseminated encephalomyelitis (if high dose steroids have failed)	Acquired red cell aplasia NOT due to parvovirus B19
Autoimmune encephalitis (including NMDA and VGKC antibodies, among others)	Acute idiopathic dysautonomia
Catastrophic antiphospholipid syndrome	Aplastic anaemia/pancytopenia
Cerebral infarction with antiphospholipid antibodies	Atopic dermatitis/eczema
CNS vasculitis	Autoimmune neutropenia
Intractable childhood epilepsy	Chronic facial pain
Neuromyotonia	Diabetic proximal neuropathy (likely to be vascular)
Post-exposure prophylaxis for viral or pathogenic infection if intramuscular injection is contraindicated, or when hyper-immune immunoglobulins are unavailable	Paraneoplastic disorders (that are not clearly autoimmune)
Opsoclonus myoclonus	PANDAS
Pyoderma gangrenosum	Haemolytic uraemic syndrome
Systemic juvenile idiopathic arthritis	POEMS
Systemic vasculitides and ANCA disorders	SLE without secondary immunocytopenias
Urticaria (severe intractable)	Vasculitic neuropathy

4.4 Measuring outcomes

"This update provides efficacy outcomes to be measured in all indications. Efficacy outcomes are expected to play an important role in the IAP decision-making process for patients. This change reflects the wider change of focus in the NHS to patient outcomes, as presented in The NHS Outcomes Framework."

Previously, the database was not successful in the capture of data regarding the efficacy of immunoglobulin and patient outcomes. Panels were encouraged to request up to three parameters by which efficacy could be determined in each patient. The purpose of this exercise was both to obtain preliminary data about efficacy in various conditions and to provide feedback to individual Panels about the quality of their decision making. The decision has been taken to introduce efficacy outcomes for most indications in neurology.

Neurological diseases often result in chronic impairment, and measures of health-related outcomes such as disability, handicap and quality of life are important in the evaluation of therapeutic efficacy, in this case of immunoglobulin. To ensure sound measurement of outcomes, the instruments used to measure the outcomes must be fully evaluated in terms of their clinical appropriateness but also with respect to their scientific qualities.

The Clinical Guidelines now make recommendations on outcomes to be recorded using the best currently available. For example, for patients with CIDP who fulfil the diagnostic criteria, Trusts are now expected to record three outcome scores from five. These are:

- MRC score [seven pairs of muscles in upper and lower limb scored from 0 to 5 (max 70)]
- Sensory sum score
- Overall Neuropathy Limitation Scale
- 10 m walk
- Any other validated disability measure

Going forward, the ongoing PeriNomS study, which finished recruiting in January 2012, may provide better and more rigorous scientific outcomes to track for cases of peripheral neuropathy.

PeriNomS study

The PeriNomS (Peripheral Neuropathy Outcome Measures Standardisation) study compares tests (e.g., strength measurements, sensory tests) and questionnaires using international guidelines. The purpose of this study is to increase knowledge about tests, instruments and questionnaires (outcome measures). Ultimately, this will improve future research and daily clinical practice by constructing and selecting the best outcome measures.

The PeriNomS study is mainly performed in patients with inflammatory neuropathies like GBS, CIDP, MMN, and gammopathy related neuropathy.

CHAPTER 5

Haematology

5.1 Use of immunoglobulin in haematology

The Deloitte survey commissioned by the DH in 2006 estimated that 18% of immunoglobulin use in the UK was for the treatment of haematological diseases (both malignant and non-malignant), thus identifying haematology as a major immunoglobulin-using specialism. The National Immunoglobulin Database shows that non-malignant haematology indications account for 11% of the total use of immunoglobulin by volume, of which 58% is used by patients with the diagnosis of ITP.

5.2 Immune thrombocytopenia (ITP)

Short-term treatment of ITP is the only haematology disease for which prioritisation in the Demand Management Programme is Red. This reflects that in certain cases, the degree and severity of thrombocytopenia is life-threatening and therapeutic intervention with immunoglobulin is potentially life-saving, with no equivalent alternative treatment available. The ability of immunoglobulin to increase the platelet count in ITP is supported by numerous studies and, importantly, there are randomised data confirming the advantage of immunoglobulin over systemic corticosteroids.

Figure 5.1 Immunoglobulin use for individual diagnoses: volume of immunoglobulin

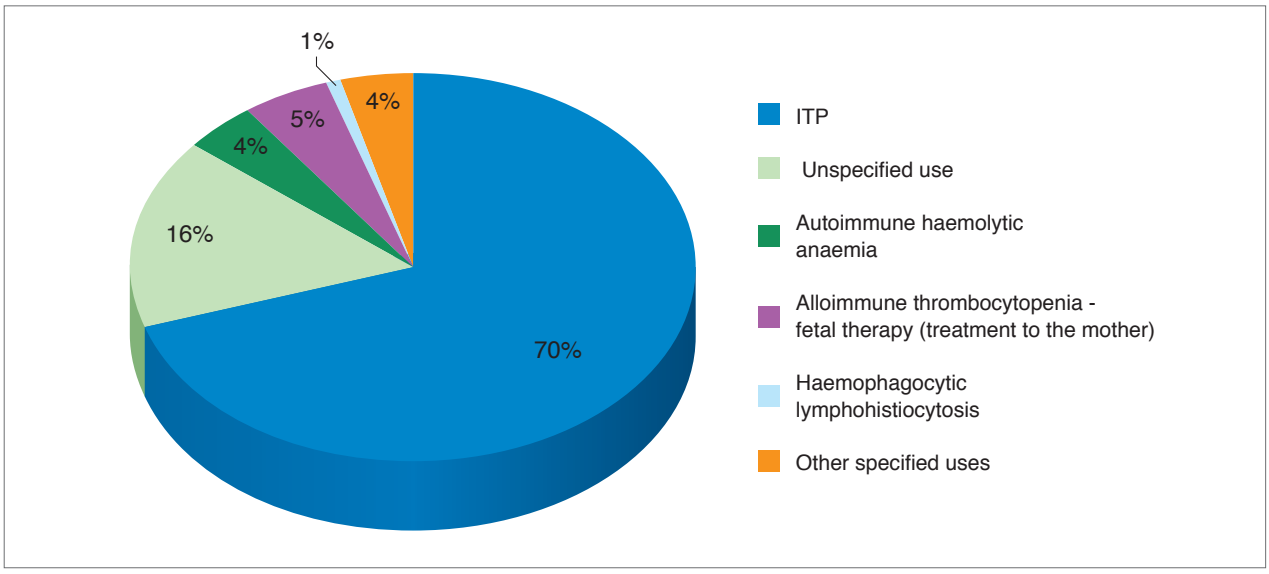


Table 5.2.1 Overview of medical management of ITP

Clinical situation	Therapy option
First line (initial treatment for newly diagnosed diagnosed ITP in adults or to cover patients with chronic ITP that require surgery or bleeding)	Corticosteroids: dexamethasone, methylprednisolone, prednisolon Intravenous immunoglobulin* (Anti-D)
Second line	Azathioprine Cyclosporin A Cyclophosphamide Danazol Dapsone Mycophenolate mofetil Rituximab Splenectomy Thrombopoietin-receptor agonists** Vinca alkaloids
Treatment for refractory ITP patients (patients failing first- and second-line therapies)	**Category A: treatment options with sufficient data** Thrombopoietin-receptor agonists **Category B: options with minimal data and potential for toxicity** Campath-1H Combination of first- and second-line therapies Combination chemotherapy Haematopoietic stem cell transplantation

*Immunoglobulin is also used to cover patients with chronic ITP that require surgery or have a severe bleeding event. It is therefore prioritised as a 'Red' indication and may only be given for <3 months. If severe ITP persists then IAP and Commissioner approval should be sought as for any other 'Grey' indication. Evidence will be required that other treatments have been tried and failed.

5.2.1 Terminology of immune thrombocytopenia (ITP)

An International Expert Working Group published a consensus document on the treatment of ITP. The consensus standardised the terminology for ITP [1]. The term 'idiopathic' was avoided, preferring 'immune', to emphasize the immune-mediated mechanism of the disease and 'primary' (as opposed to idiopathic) to indicate the absence of any obvious initiating and/or underlying cause. The term 'purpura' was also felt inappropriate, because bleeding symptoms are absent or minimal in a large proportion of cases. The acronym ITP (now standing for immune thrombocytopenia) was preserved because of its widespread and time-honoured use and taking into account its utility for literature searches. The term 'secondary immune thrombocytopenia' or 'secondary ITP' was proposed to broadly include all forms of immune-mediated thrombocytopenias except primary ITP.

A platelet count $<100 \times 10^9$/L was established as the threshold for diagnosis. A uniform predefined cut-off, instead of local normal ranges or other thresholds based on frequency distribution, is more convenient for practical use and comparisons across studies. This threshold was preferred to the more commonly used level of $<150 \times 10^9$/L.

Definition of the different phases and severity of the disease were updated. The term 'newly diagnosed ITP' is used for all cases at diagnosis. A new category, called 'persistent ITP,' was introduced for patients with ITP to define the period lasting between 3 and 12 months from diagnosis. This category includes patients not achieving spontaneous remission or not maintaining their response after stopping treatment between 3 and 12 months from diagnosis. The term 'chronic ITP' is to be reserved for patients with ITP lasting for >12 months.

Definitions of disease severity were also updated. The term 'severe ITP' is reserved for patients who have clinically relevant bleeding, defined in the consensus as "the presence of bleeding symptoms at presentation sufficient to mandate treatment, or by the occurrence of new bleeding symptoms requiring additional therapeutic intervention with a different platelet-enhancing agent or an increased dose". Refractory disease is defined as when splenectomy has failed, or there has been relapse thereafter, and there is still severe ITP or a risk of bleeding.

5.2.2 Dosing schedule for severe immune thrombocytopenia (ITP) in adults

In the *First National Immunoglobulin Database Report (2008–2009)*, there was a realisation that some clinicians were using the old regimen of 2 g/kg over 5 days whist others would give a 1 g/kg dose on one day and wait a week before considering a second dose if the first had failed. The updated Guidelines now recommend using only 0.8 (children) to 1.0 g/kg and to wait for response, as the majority of patients will respond to this lower dose.

Over the next year, the National Database will record the individual doses and the recorded outcomes of resolution of bleeding (yes/no) as well as pre and post platelet counts.

REFERENCES

1. Rodeghiero F, Stasi R, Gernsheimer T, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. *Blood* 2009;113:2386–93.

CHAPTER 6

Haemato-oncology and Transplantation

6.1 Updated colour-coded prioritisation

The database review identified two of the top 10 immunoglobulin-using indications that had been prioritised as Grey (because the evidence base regarding prophylaxis with immunoglobulin was lacking). These were ***secondary antibody deficiencies and antibody-mediated rejection following solid organ transplantation***. In many Trusts, Commissioners had permitted pre-approval of immunoglobulin use for these indications despite the limited evidence base. Therefore, these indications were reviewed in detail and the evidence base was reassessed. The outcome of this review is that use of immunoglobulin for these indications is appropriate and is now listed as Blue.

6.2 Secondary immunodeficiency

Secondary antibody deficiencies were identified by a number of stakeholders as a key area for revision. Haemato-oncology historically has used 6% of all immunoglobulin and 70% of that use has been for CLL and MM, as well as other B-cell malignancies such as non-Hodgkin's lymphoma. The conclusion was to change the colour coding to Blue, but on the understanding that:

a) The IAPs ensured fulfilment of the selection criteria:
The underlying cause of hypogammaglobulinaemia cannot be reversed or reversal is contraindicated; OR
Hypogammaglobulinaemia associated with non-Hodgkin's lymphoma, CLL, MM or other relevant B-cell malignancy is confirmed by a haematologist; AND

- Recurrent or severe bacterial infection despite continuous oral antibiotic therapy for 3 months
- IgG <5 g/L (excluding paraprotein)
- Documented failure of serum antibody response to unconjugated pneumococcal or other polysaccharide vaccine challenge

b) The IAPs ensured completed records of the specific outcomes:
The number of infections and days in hospital pre-treatment and 6 monthly thereafter, AND documentation of failure of vaccine/challenge (which could be removed after 50 complete records, demonstrating that this is an unnecessary step).

6.3 Transplantation

The British Transplantation Society made a strong case to change certain defined transplantation cases to Blue, despite limited high-quality evidence for some of the clinical scenarios. The Update Working Group accepted the Society's view on the understanding that:

a) The IAPs ensure fulfilment of the selection criteria:

- Antibody incompatible transplant (AIT): patients in whom renal, heart or lung transplant is prevented because of antibodies
- Antibody-mediated rejection (AMR): patients experiencing steroid-resistant rejection or where other therapies are contraindicated after renal, heart and/or lung transplantation
- Viral pneumonitis: patients experiencing viral pneumonitis following heart and/or lung transplant (viruses to include HSV, VZV, CMV, RSV, but excluding Influenza virus)

b) The IAPs/Transplantation Society ensure completed records of specific outcomes:

Table 6.3 The agreed outcome data to be collected

AIT and AMR Renal	AIT and AMR Cardiothoracic	Viral pneumonitis Cardiothoracic
Type of renal transplant	HLA class DSA	Virus type
HLA class donor-specific antibodies (DSA)	Patient survival	Reversal of radiological infiltrates
Rejection episodes	Length of ITU and hospital stay	Length of hospital stay
Patient survival	Graft function (heart=ejection fraction; lung=spirometry)	Survival
Graft survival		
Renal function = eGFR (MDRD)		

CHAPTER 7

The National Database

The National Immunoglobulin Database (Reference number ROCR/OR/0221) was launched on 2nd June 2008, with MDSAS contracted at launch to continue to manage and develop the National Database and to be responsible for working with a DH-sponsored database Steering Group to maintain and extend the solution. See www.ivig.nhs.uk to access relevant immunoglobulin documents.

In July 2011, the Second Edition Update of the *Clinical Guidelines for Immunoglobulin Use* was published (gateway reference 16290). The update was to provide guidance for efficacy tracking and also to include amended prioritisation indication colour coding for some diagnoses. The latest update to the Guidelines in 2011 is now supported by the database.

7.1 Aims of the database

The initial aims of the database were to allow more accurate assessment of immunoglobulin use to provide an accurate picture of prescribing for forecasting, tendering and tracking.

These aims have developed further, and additional uses of the database are also being explored such as the support of patient access schemes for new treatments. Suggestions for new uses of the database are actively encouraged.

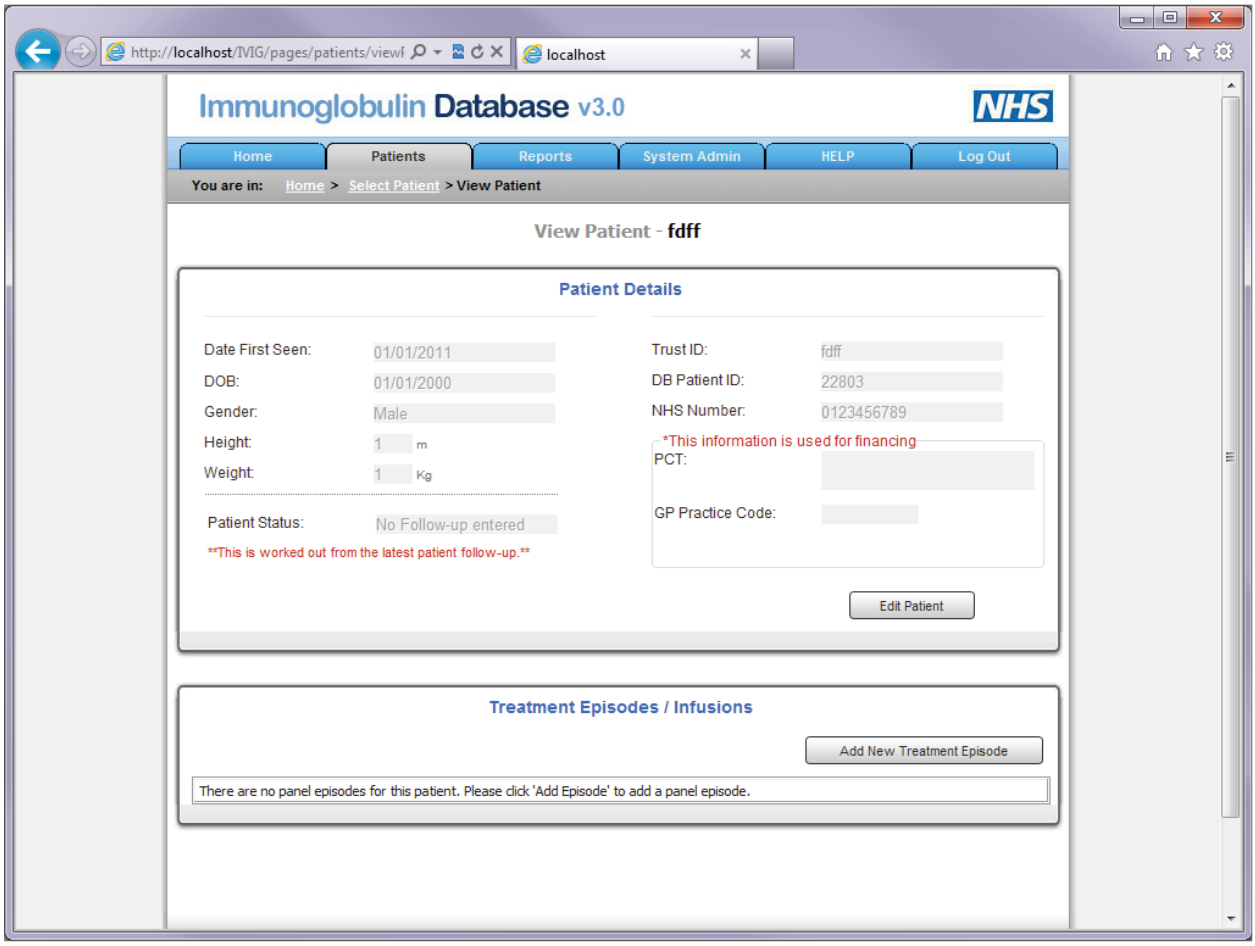
7.2 Database management

MDSAS is an award winning* health informatics consultancy delivering national and international healthcare projects using the very latest technology. Within the UK, MDSAS manage registries for haemophilia, ITP, haemoglobinopathy and TTP, and within 28 countries in Europe a Haemophilia Adverse Events Surveillance System, which is now being tried in Canada and Australia.

In January 2012, in response to the updated Guidelines, a new system was launched. The database is built around the very latest technologies, utilising Microsoft products as used by the NHS IT Connecting for Health Programme. These include SQL Server (2008 R2 version), Reporting Services and ASP.NET. The database has a data entry portal and a National Information Service.

The National Immunoglobulin Database allows Trusts to enter and review immunoglobulin use on a patient-by-patient basis. The database follows the demand management plan, registering patients' details and recording Panels' decisions, and diagnosis and colour indications of each treatment episode.

Figure 7.2.1 Registration page



Patient infusions are recorded down to batch number level, allowing the system to be used for patient safety (batch tracking). The 2012 version also records the efficacy values at initiation and follow-up.

Reports are provided for each centre specifically to analyse their data and aid in the management of their patients. Reports include 'Monthly net usage', 'Patients by diagnosis', and 'Patients requiring a follow-up'.

There is a continuous effort to improve the quality of data held in the database. Recent upgrades to the database have resulted in the removal of duplicate treatment episodes, reducing the number of 'other' diagnoses and ensuring all patients have a primary diagnosis.

Figure 7.2.2 Data entry

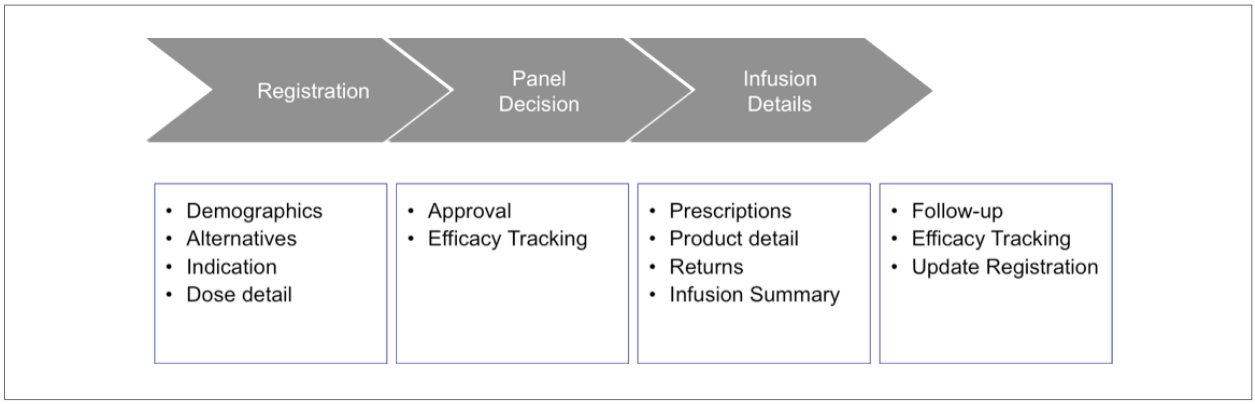
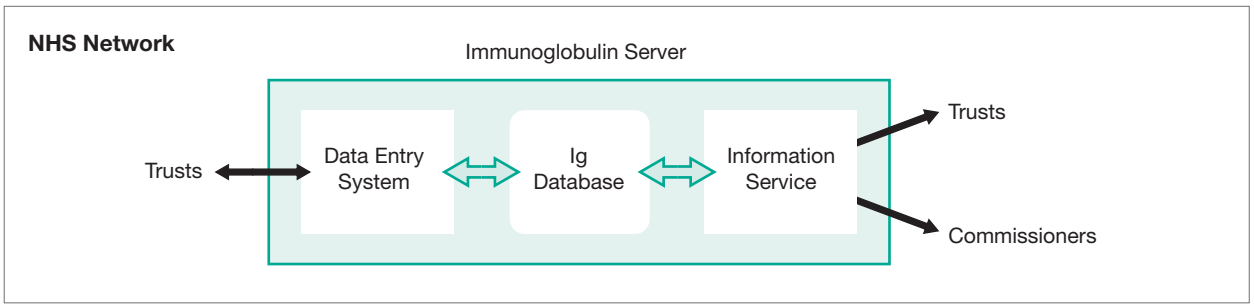


Figure 7.3 Architecture of the Database



7.3 The Database architecture

The real benefit of the database is that the SQL server (2008 R2) resides within the security of the NHS Network (N3) and offers high speed of data transfer. It is real-time and accessible by Trusts, Commissioners and the Steering Group. The ability to export data locally for analysis facilitates local and national benchmarking.

7.4 Data held

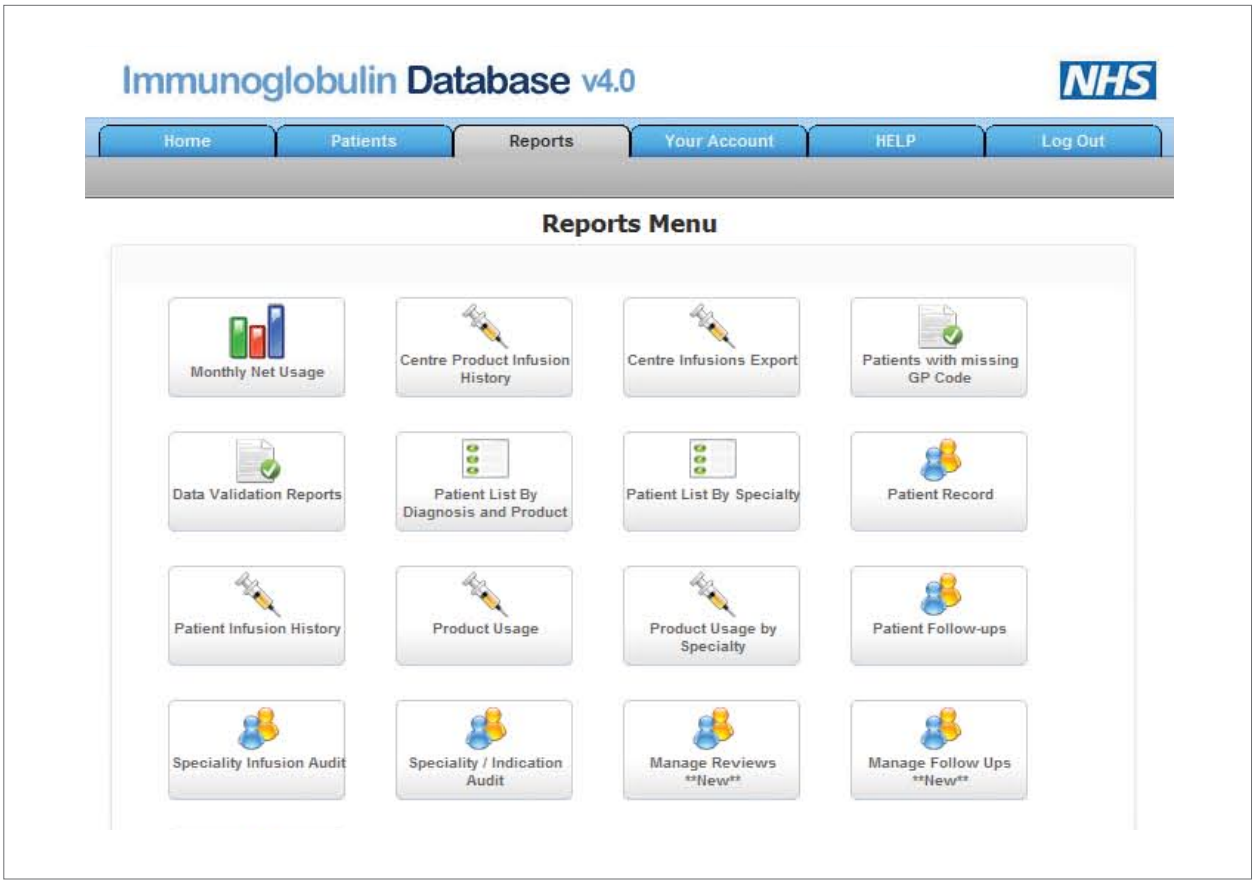
The data regarding the actual patient is only available to the patients Trust. The anonymised data held currently are:

- Infusion details including product and manufacturer
- Short- and long-term treatment
- Diagnosis
- Alternatives
- Outcome
- Weight/height
- GP Practice code
- Follow-up details

7.5 Reports available

Many of the reports required by Trusts over the past few years have become automatic. Currently there are 12 automatic reports available to Trusts (see Figure 7.5).

Figure 7.5 Database reports for local Trusts



7.6 The Information Service

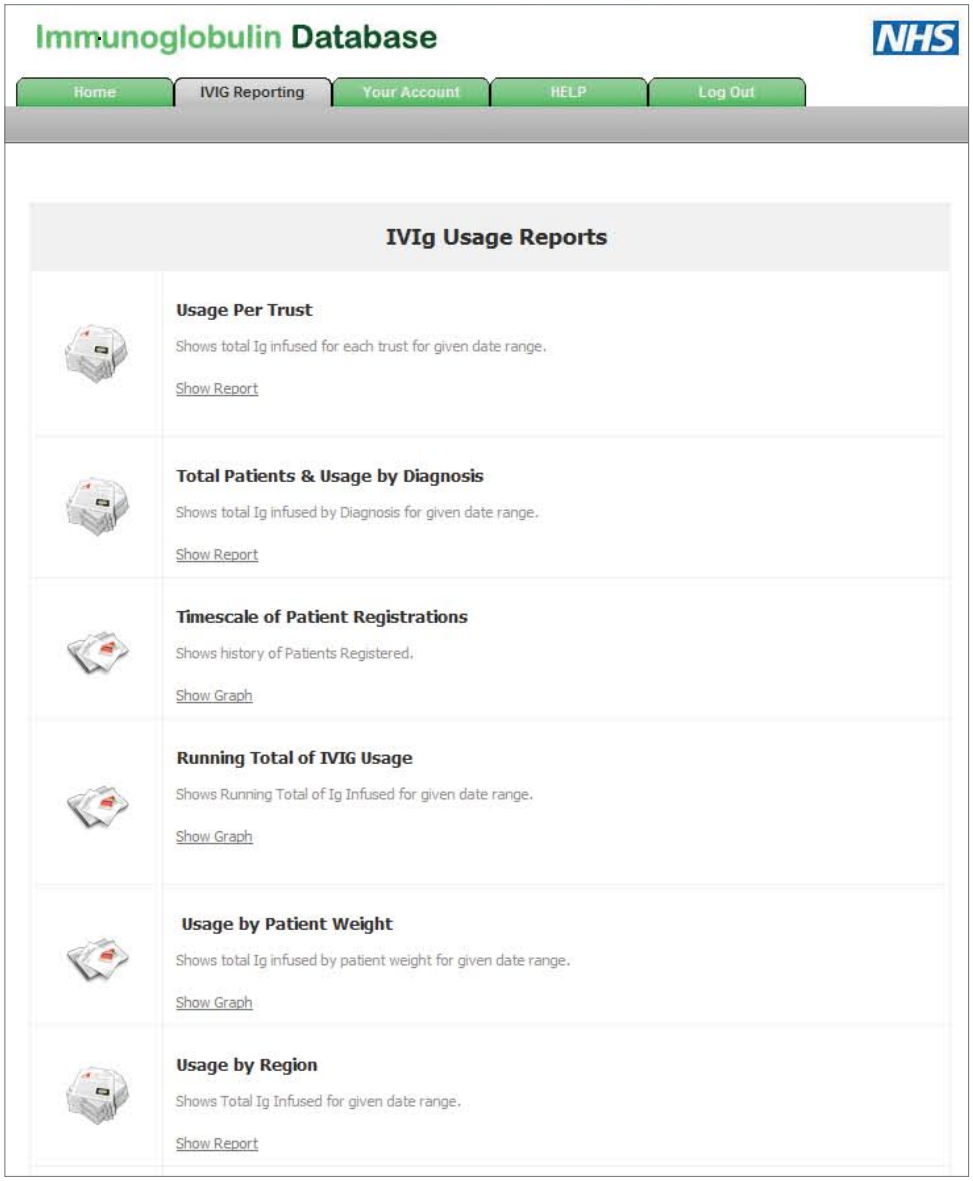
A second system, the National Immunoglobulin Information Service allows real-time online access to summary information. The flexible reports allow filtering of the information, allowing users to view the summary data at a national level, a regional level, and a Trust level. The reports within the information service were originally designed to aide Commissioners and the DH in their planning of immunoglobulin usage and budgeting, and to aide in the management of product shortages. The service is also available for users at Trust level to help share good practice, but the data available through this service is anonymised.

7.7 Summary of changes

The changes that have had to be made are summarised below:

- Merging diagnoses
- Modification/addition of specialities
- Changing of indication colours (from Blue to Red or Grey to Blue)
- Defining outcome measures for each diagnosis (except PID)
- Enforcing short-term/long-term guidance (automated durations of treatment)
- Alignment of all historical data
- Updating the information service to reflect data changes

Figure 7.6 Information Service reports



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