Third National Immunoglobulin Database Report (2012)

Medical Data Solutions and Services

mdsas

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NHS

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Executive summary

As the National Immunoglobulin Database approaches completion of its sixth 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. Intravenous immunoglobulin (IVIg) is a fractionated blood product made from pooled human plasma. IVIg is increasingly important in replacement therapy and as an immunomodulatory agent in autoimmune disease. It is the market driver for the plasma industry in the developed world, with an increasing demand internationally.

Pooled human plasma is the starting point for the manufacture of IVIg. Plasma is obtained either by separation of whole blood or by plasmapheresis. Plasmapheresis is a process whereby only plasma is collected at the time of donation and the cellular components of blood are returned to the donor. The procedure is more time consuming for the donor. However, it does enable larger quantities of plasma to be collected more frequently from each donor. Immunoglobulin is obtained by using variations in the concentration of ethanol, salt, temperature and pH, and all licensed manufacturers have incorporated viral reduction procedures into their manufacturing processes. When combined with donor screening and plasma quarantining procedures now in place in all developed countries, these manufacturing procedures result in a close to zero risk of viral transmission to the recipients of plasma products.

The development of the IVIg 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 subsequent to the introduction of a number of significant changes within the National Clinical Guidelines, which included specific selection criteria, tighter definitions of duration of treatment, recommendations on reduction of doses when chronic patients are stable [excluding primary immunodeficiency (PID)] and definition of the outcome measures to be recorded.

General findings

The data presented are for the 12-month period January–December 2012. Neurology remains the highest-using specialism (43% of total volume), with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) accounting for 49.5% of volume. The data suggest that only 14% of prescribing in neurology was for life-threatening symptoms; this suggests that up to 86% of prescribing could 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) if there was a serious and prolonged shortage in the supply of immunoglobulin.

Immunology indications are the second largest user (33%), almost entirely for the treatment of 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 **first recommendation** in the Guidelines is *dose reduction in stable patients* (excluding PID), with the expectation that some patients will be able to reduce and stop therapy. The patterns of prescribing in neurology and secondary immunodeficiency have been examined closely to assess the impact of these new recommendations. In neurology, this appears to have halted the increasing volume of immunoglobulin year on year.

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). The **second recommendation** of the Guidelines is to follow the international management guidelines advice and *initiate treatment at 1 g/kg* for newly diagnosed and acute ITP, halving the initial dose of immunoglobulin that was previously widely used and ought to have reduced immunoglobulin use for this high-volume indication by at least one third. Unfortunately, there is little evidence of this occurring.

The **third recommendation**, in order to reduce the volume of immunoglobulin used, is to consider using *lean-bodyweight (LBW) dosing* and *strict starting and stopping criteria*. We do have examples of good practice this year, namely LBW in all major conditions in neurology and strict starting criteria in one particular category: Guillain–Barré syndrome (GBS).

Unity of effort

The overall number of patients entered into the database as this report goes to press has reached over 30,000. 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, there has been no overall shortage but we do report in Chapter 3 on two shortages of IVIg products that occurred in the periods October 2010–June 2011 and May 2011–October 2011.

Product recall and license suspension

The first shortage was due to a product recall in September 2010 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.

Product supply problems

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 provided 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. Patients, having switched product on the second occasion to one that was infused more quickly, were content to stay on the new product.

The next phase

The DH was the major stakeholder in the development and implementation of the Demand Management Programme for immunoglobulin. From 1st April 2012, the DH stepped back from its role, and responsibility for the database was transferred to the 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. The lead SCG for immunoglobulin has developed Quality Dashboard-related goals linked to achieving quality indicators for immunoglobulin prescribing, set within the CQUIN payment framework. By 1st April 2013, immunoglobulin prescribing will fall in the various definition sets, e.g., neurology, immunology, cancer and paediatrics under the authority of the NHS National Commissioning Board (NHS CB).

The Second Edition Update of the *Clinical Guidelines for Immunoglobulin Use* was published in July 2011 (gateway reference 16290). There is a need to follow this in the near future with a thorough review of these Guidelines, to include new autoimmune neuropathies.

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Abbreviations

AML	Acute myeloid leukaemia
CIDP	Chronic inflammatory demyelinating polyradiculoneuropathy
CLL	Chronic lymphocytic leukaemia
CVID	Common variable immunodeficiency disorder
DH	Department of Health
GAD	Glutamic acid decarboxylase
GBS	Guillain-Barré syndrome
IAP	Immunoglobulin Assessment Panel
IFR	Individual Funding Request
ITP	Immune thrombocytopenia
IVIg	Intravenous immunoglobulin
KPI	Key Performance Indicator
LBW	Lean body weight
MAG	Myelin-associated glycoprotein
MDSAS	Medical Data Solutions and Services
MMN	Multifocal motor neuropathy
NHS CB	NHS National Commissioning Board
NMDA	N-methyl D-aspartic acid receptor
ODSS	Overall disability sum score
ONLS	Overall neuropathy limitations score
PCT	Primary Care Trust
PID	Primary immunodeficiency
SCG	Specialised Commissioning Group
SSNDS	Specialised Services National Definitions Set

CHAPTER 1

Introduction

Denise O'Shaughnessy

1.1 Background

In 2006, precipitated by a severe and prolonged shortage of immunoglobulin, the DH initiated a review that resulted in the first DH publications *Clinical Guidelines for Immunoglobulin Use* and *Demand Management Plan for Immunoglobulin* 2007 (Gateway reference). Revised versions were published in 2008 (Gateway reference 10012 and 10013) and an update was published in 2011 (Gateway reference 16290). These documents can be accessed at www.ivig.nhs.uk.

The National Immunoglobulin Database (Reference No. ROCR/OR/0221) was launched in June 2008, with NHS 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 Bio Products Laboratory (BPL) product shortage, or due to 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 IVIg 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 was the major stakeholder in the Demand Management Programme, chairing the various working groups that researched and wrote the Guidelines and the Demand Management Plan, and developed the database. From 1st April 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 immunoglobulin as one of the subsets of the SSNDS ('Minimum Take') services from April 2012. By 1st April 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 database will play an increasingly important role and is fit for this purpose.

1.3 The Third 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.

The *Second National Database Report (2009–2011)* presented data prior to the update of the Clinical Guidelines introduced in late 2011. This *Third National Database Report (2011–2012)* will examine the implementation of the changes to the Guidelines and, in particular, the recording of outcomes for each disease category.

1.4 Entries in the database

To date (April 2013), over 30,000 patients are registered and 165 NHS Trusts enrolled (156 submitting data) 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 in the volume of immunoglobulin use recorded. The rate of increase in patient numbers for the period of this analysis is shown in Figure 1.4.1. As many of these

patients will have stopped treatment, it is more informative to see monthly registrations and the use per month of immunoglobulin, which are shown in Figures 1.4.2–4.

Total volume of immunoglobulin recorded exceeds 10.7 million grams.

Figure 1.4.1 Patients registered on the database June 2009–March 2013

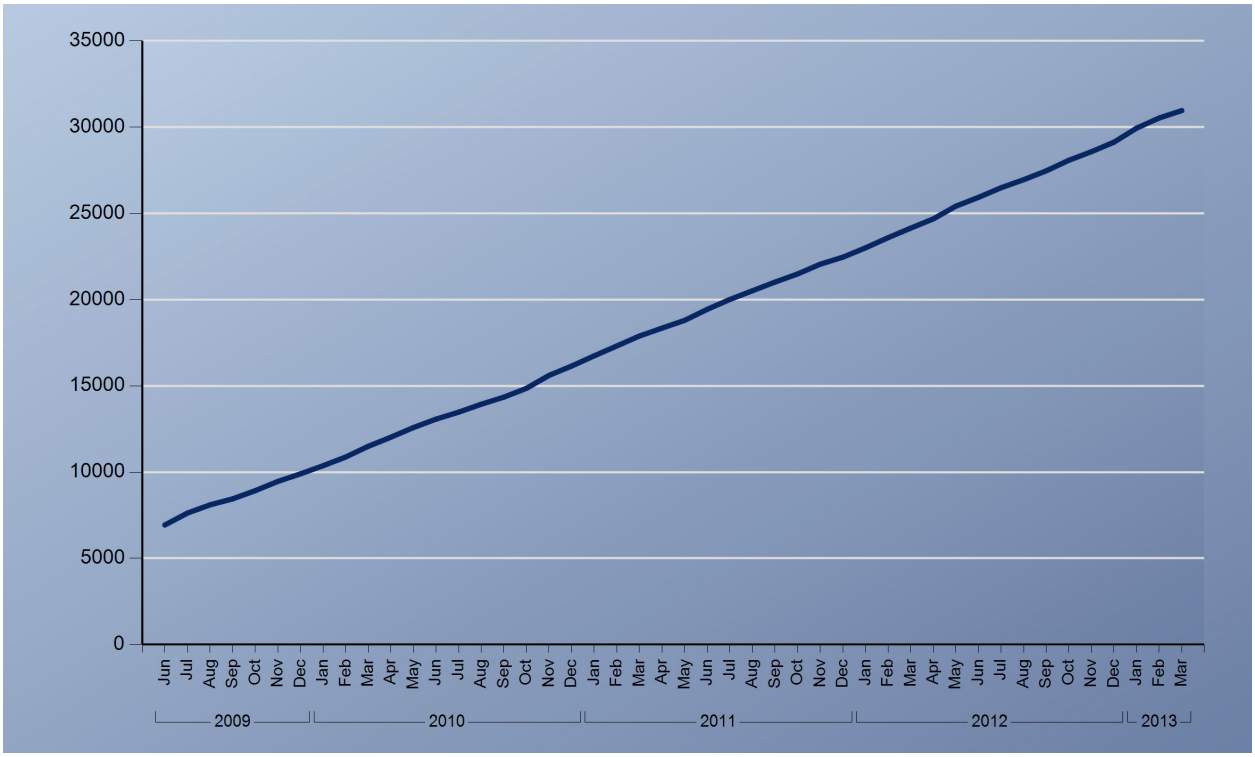
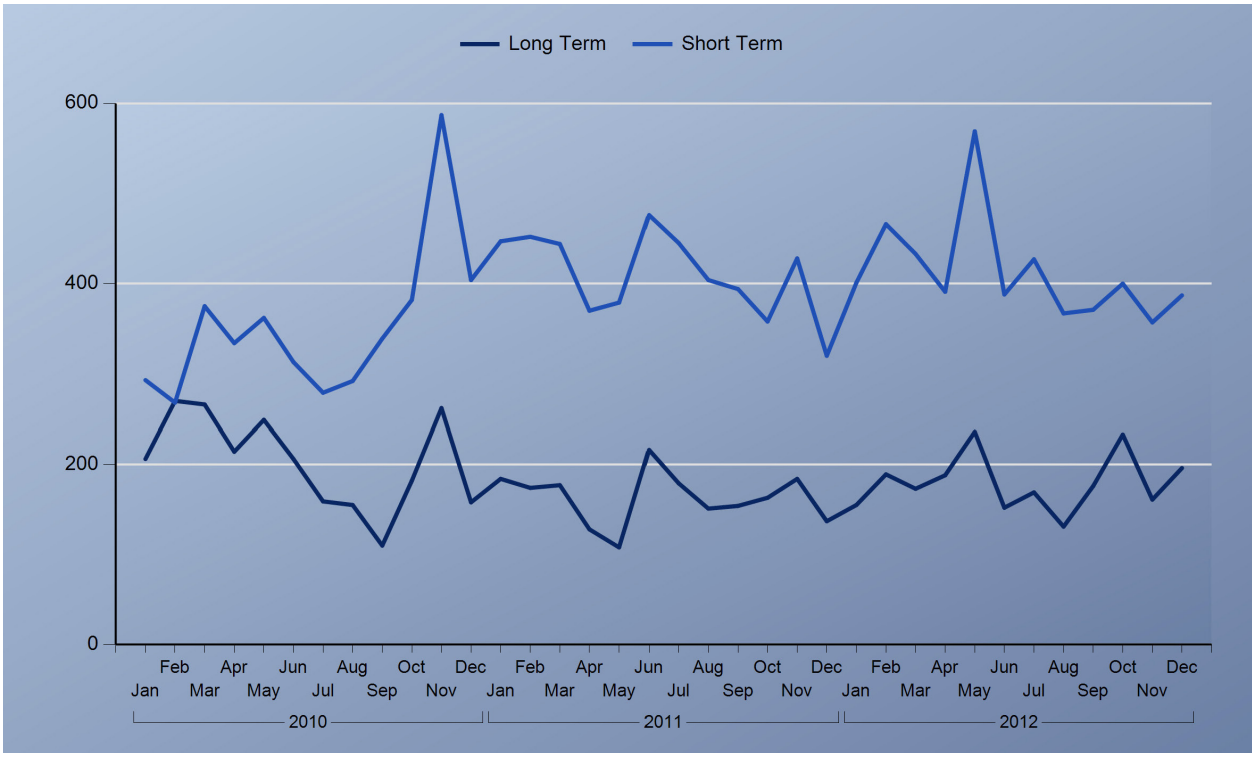


Figure 1.4.2 New patients registered per month in the last 3 years



Since November 2010, there has been a fairly constant level of 180 patients registered per month for long-term conditions, whilst short-term conditions are twice that amount (n=360).

Neurology and immunology account for most of the long-term use. Of that, one third of long-term use (i.e., 11%) is given subcutaneously. Note that this will not take into account all homecare deliveries.

Figure 1.4.3 Monthly patient registrations in the past year January to December 2012

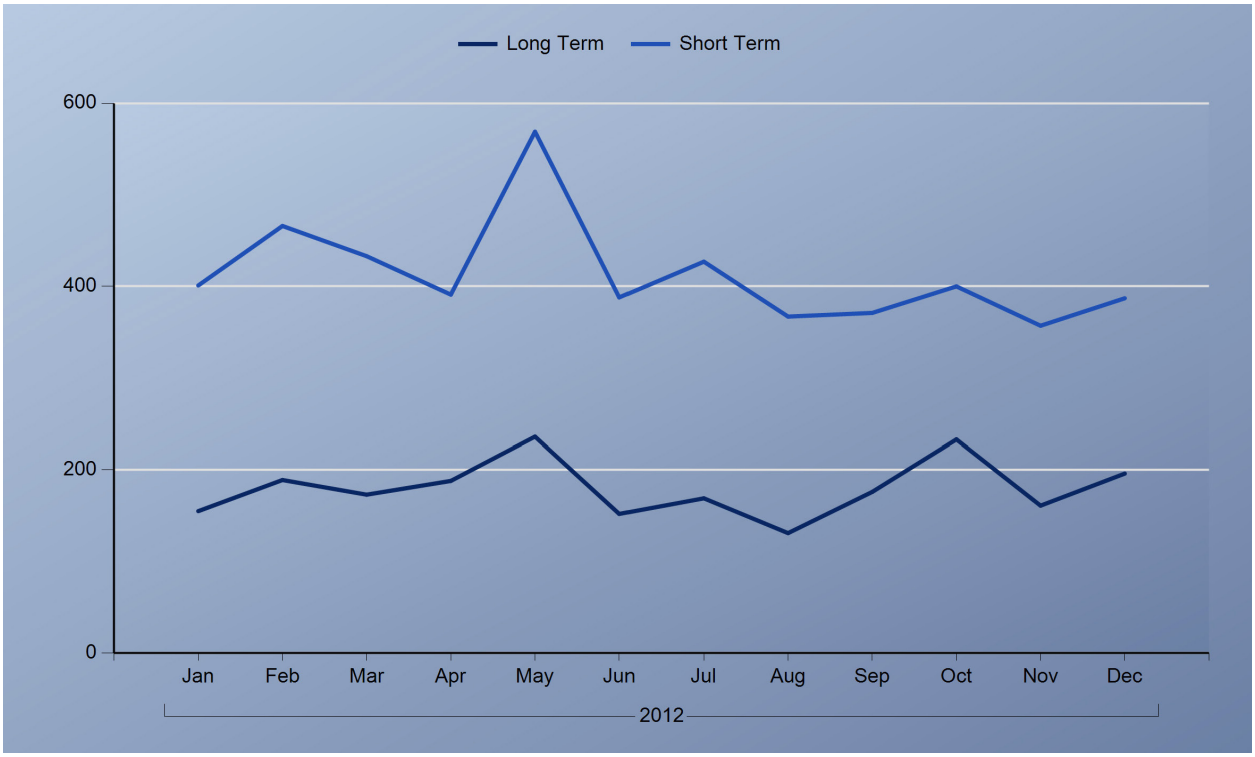
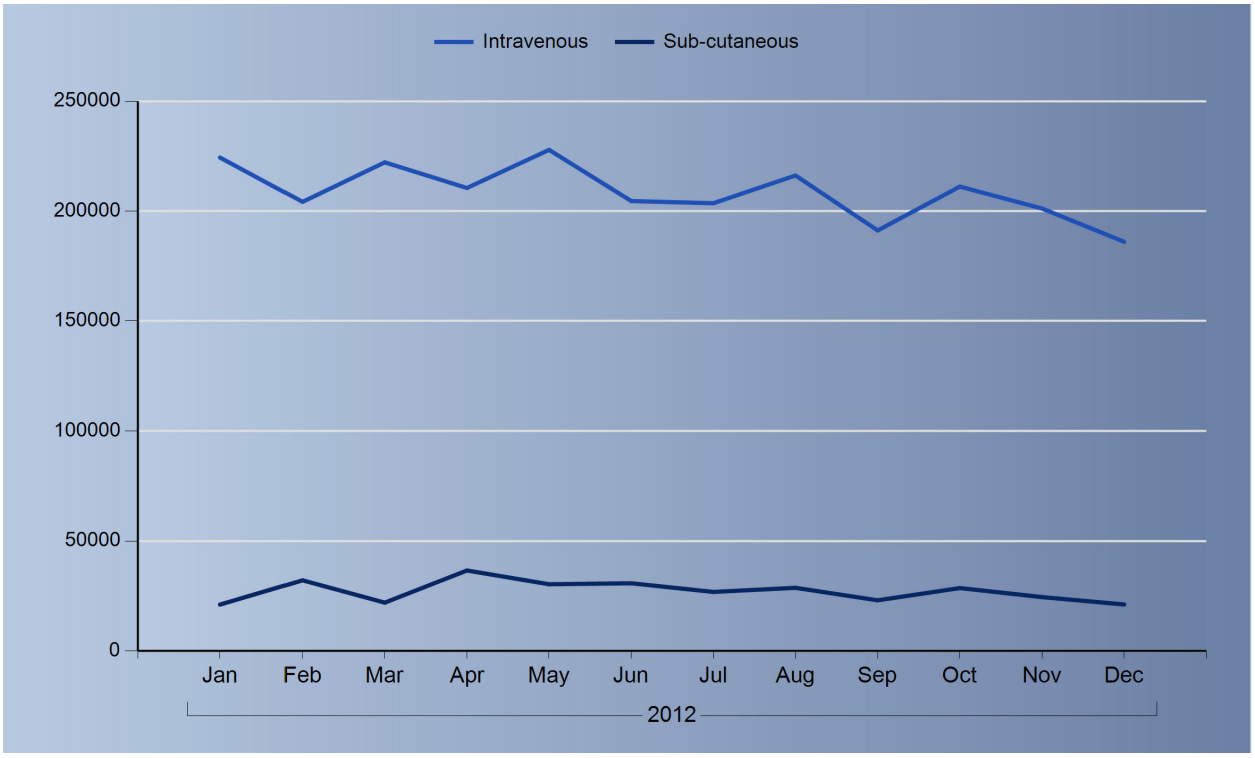


Figure 1.4.4 Monthly use of intravenous and subcutaneous immunoglobulin



Ever since the Demand Management Programme was launched, we have suggested that for patients who were suitable, subcutaneous immunoglobulin should be encouraged. It is clear that much of these products are delivered to the patient and not recorded by the hospital, so the data on subcutaneous use have to be interpreted cautiously.

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 (43% by volume), then immunology (33%), haematology (11%) and haemato-oncology (8%).

Table 1.5 Number of patients and volume of immunoglobulin used by each specialism

Diagnosis specialism	Patients	Usage (grams)
Neurology	2983	1,127,952
Immunology	2703	866,860
Haematology	1651	290,732
Haemato-oncology	1200	201,475
Rheumatology	200	44,939
Dermatology	191	29,544
Transplantation	171	17,118
Infectious diseases	141	14,915
Paediatric rheumatology	130	10,869
Paediatrics	88	8672
Total	**9458**	**2,613,076**

Figure 1.5.1 Graphical representation of the volume of immunoglobulin used for each specialism

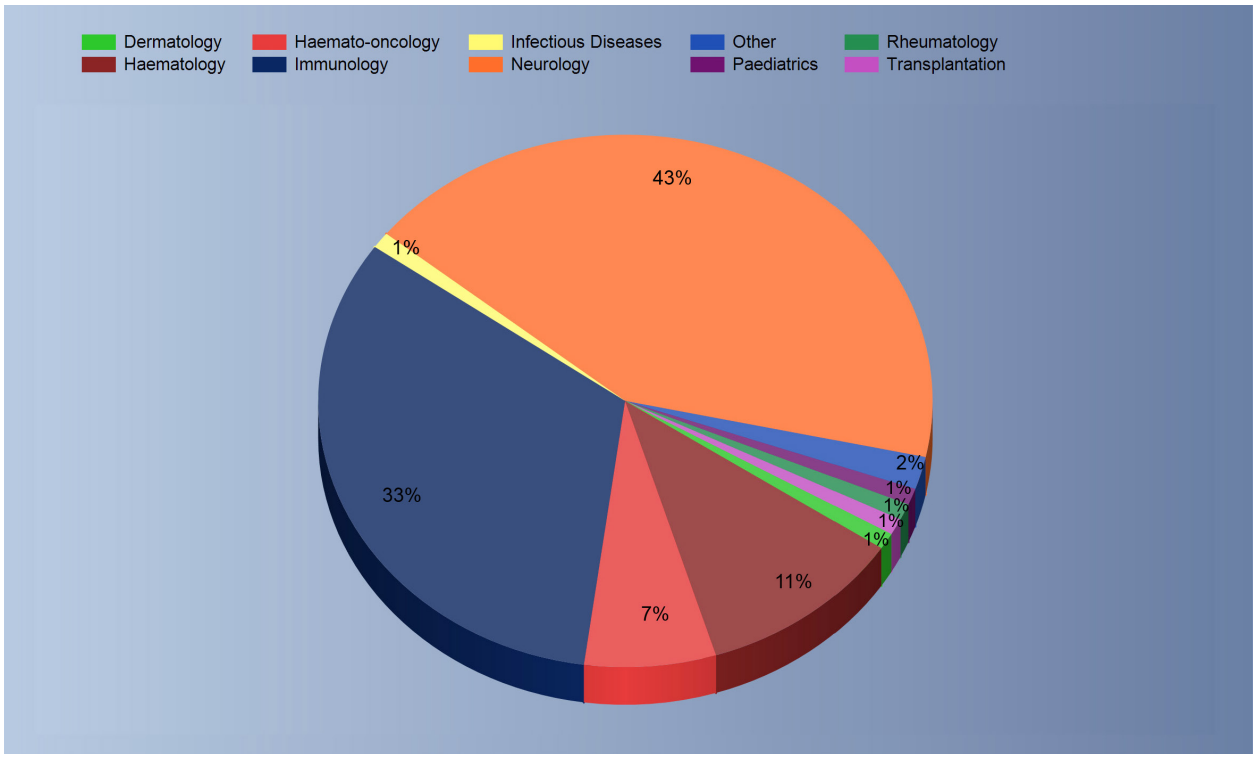


Figure 1.5.2 Cumulative use in each specialism

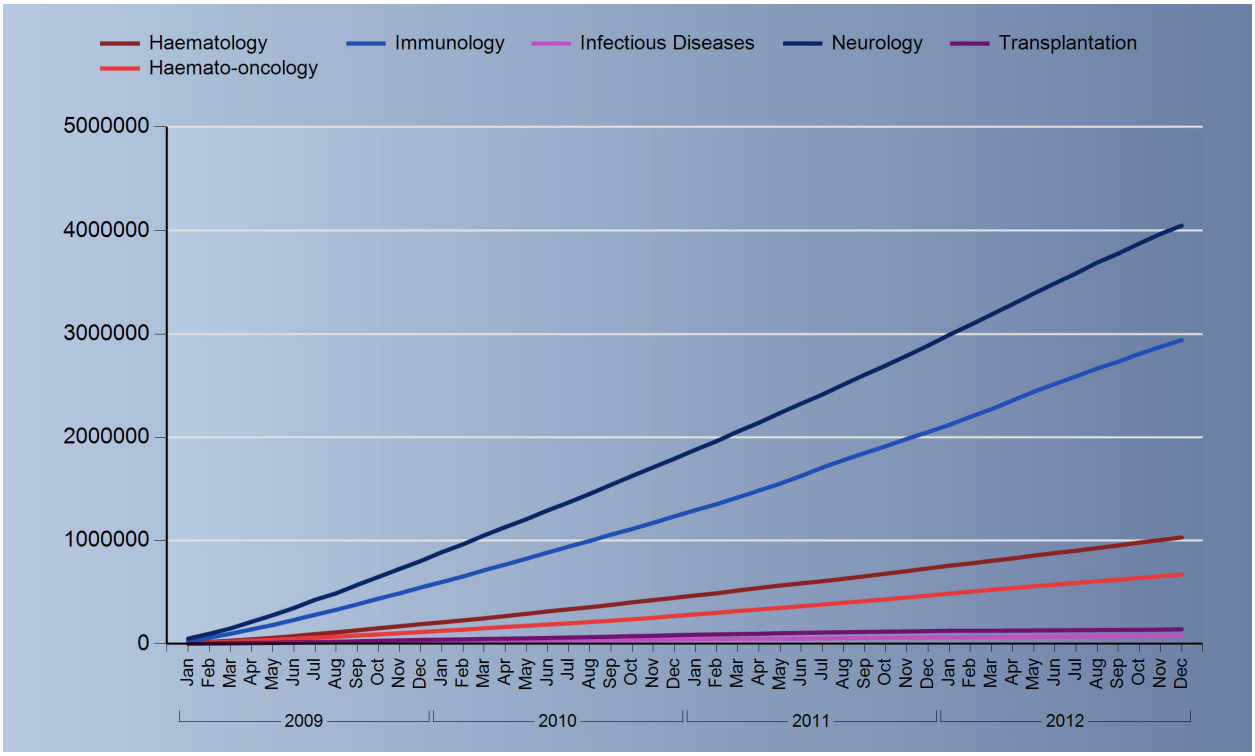
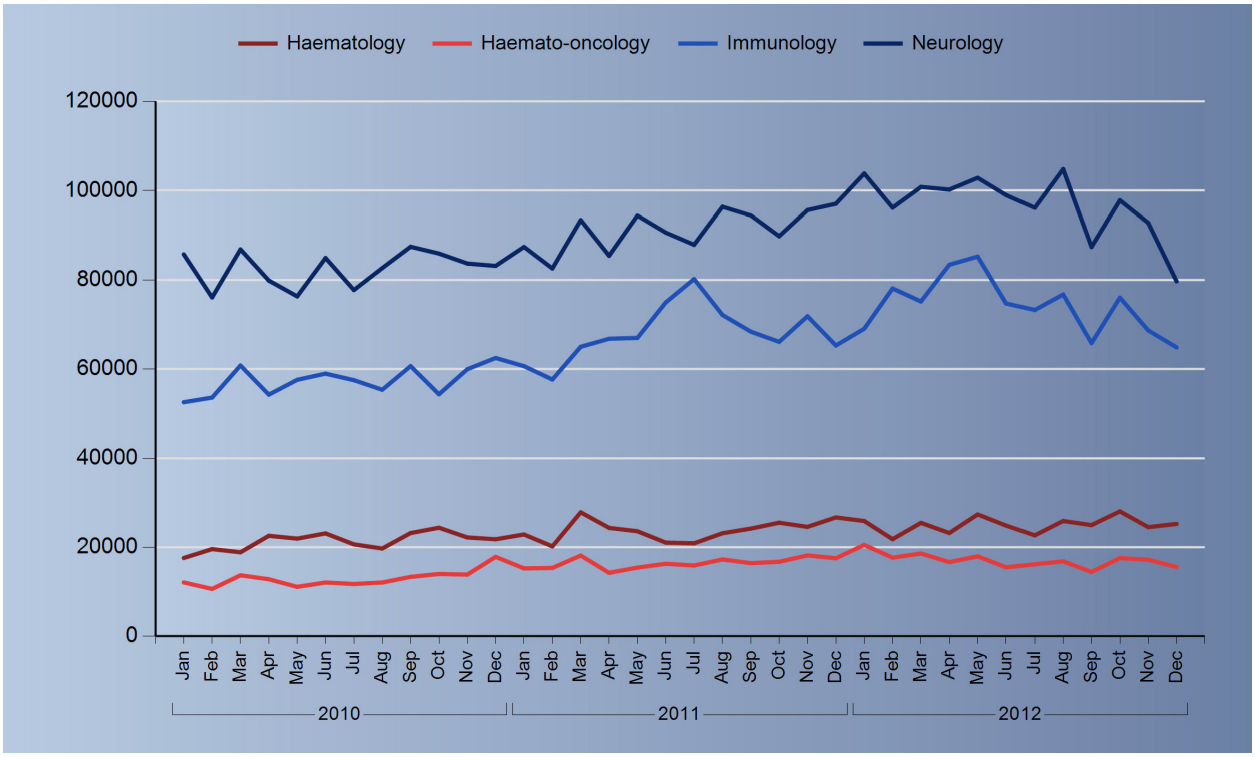


Figure 1.5.3 Monthly usage by specialism from January 2010



It would be more informative to see the trends in monthly usage in the top four categories, which together constitute 90% of all immunoglobulin used. In Figure 1.5.3, neurology use increased from January 2010 to May 2012, when a fall is noted.

1.6 Immunoglobulin use in individual NHS Trusts

The number of patients entered by each Trust, and the volumes used, vary considerably. The largest number of patients treated for the period reported (2012) was at the Royal Free Hospital.

The highest volume user remains University College London Hospitals, which includes the National Hospital for Neurology and Neurosurgery. Interestingly, Barts and the London appears to be the fifth biggest user. Although Imperial has the eighth largest number of registered patients, these obviously have used less immunoglobulin (maybe more short-term usage). The Heart of England and Manchester have made it into the top 10 for the first time. Some Trusts like King's College Hospital are unfortunately failing to record the volumes that they use.

Table 1.6.1 Number of patients registered in top 10 Trusts (1st January 2012 to 31st December 2012)

NHS Trust	Patients
Royal Free Hampstead NHS Trust	343
The Newcastle Upon Tyne Hospitals NHS Foundation Trust	335
Oxford Radcliffe Hospitals NHS Trust	308
Leeds Teaching Hospitals NHS Trust	305
Barts and the London NHS Trust	301
University College London Hospitals NHS Foundation Trust	261
Sheffield Teaching Hospitals NHS Foundation Trust	251
Imperial College Healthcare NHS Trust	239
Central Manchester and Manchester Children's University Hospitals NHS Trust	214
Heart of England NHS Foundation Trust	199
Total	**2756**

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 (34.1%) and the largest volume used. The next highest disease is CIDP.

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.

Table 1.6.2 Volume of immunoglobulin used in top 10 Trusts

NHS Trust	Usage (grams)
University College London Hospitals NHS Foundation Trust	168,679
Oxford Radcliffe Hospitals NHS Trust	142,956
Royal Free Hampstead NHS Trust	135,288
The Newcastle Upon Tyne Hospitals NHS Foundation Trust	114,986
Barts and the London NHS Trust	110,467
Leeds Teaching Hospitals NHS Trust	101,116
Sheffield Teaching Hospitals NHS Foundation Trust	96,487
Salford Royal NHS Foundation Trust	87,593
University Hospitals of Leicester NHS Trust	73,385
Heart of England NHS Foundation Trust	60,576
Total	**1,091,533**

There is considerable variation between Trusts of the diseases they treat with immunoglobulin. University College London Hospitals and Salford Royal treat many patients with CIDP. Sheffield, the Heart of England, Oxford and the Royal Free have many PIDs, whilst Oxford and University College London Hospitals have a large number of MMNs. Imperial stands out from all of these due to IVIg use in solid organ transplantation.

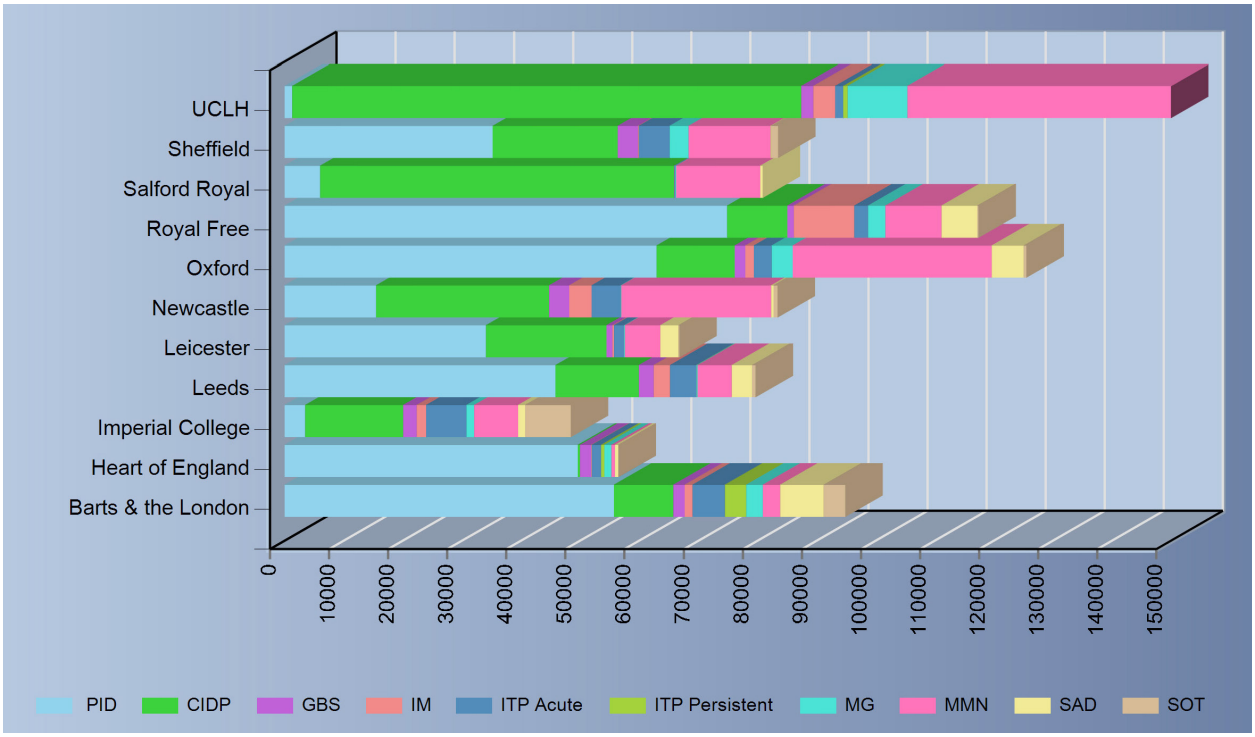
Table 1.7.1 Number of patients for top 10 diagnoses January–December 2012

Diagnosis	Patients
PIDs	2296
CIDP	972
ITP – acute	954
Guillain–Barré syndrome (GBS)	702
Secondary antibody deficiencies (SAD)	430
Multifocal motor neuropathy (MMN)	405
Myasthenia gravis (MG)	381
Kawasaki disease	254
ITP – persistent	173
Transplantation (solid organ)	168
Total	**6735**

Table 1.7.2 Volume of immunoglobulin used for the top 10 diagnoses

Diagnosis	Usage (grams)
PIDs	731,484
CIDP	551,854
MMN	285,300
ITP – acute	149,200
GBS	110,334
MG	82,299
SAD	70,889
Inflammatory myopathies (IM)	46,006
ITP – persistent	35,107
Transplantation (solid organ)	20,464
Total	**2,082,937**

Figure 1.7.1 The use of immunoglobulin in 11 Trusts highlighting use in each of top 10 diagnoses



1.8 Immunoglobulin use in each region

From the beginning of national purchasing, it has not been possible to use the database to correctly forecast volumes of product needed. As illustrated in Table 1.8.1, some regions are excellent, such as East Midlands, East of England, North East and Yorkshire and the Humber. Clearly, these regions understand the concept of payment by result. Unfortunately, in the new supra-regions, West Midlands will be paired with the first group and the North West with the second group. Hopefully peer pressure will improve these results for next year.

In total, 2.4 million grams were infused; using an average cost of £36 per gram, the annual bill is about £86 million. The discrepancy from the database amounts to 0.95 million grams (£34 million).

Table 1.8.1 Supra-regional comparison of intravenous immunoglobulin purchased (Commercial Medicines Unit, CMU) with database infusions

Purchased	CMU total sales (grams)	Database infusions (grams)	Discrepancy (grams)	Population
London	**803,914**	**602,000**	**202,000**	**8.2 M**
West Midlands	298,501	136,000	163,000	
East Midlands	170,915	145,000	26,000	
East of England	305,325	215,000	90,000	
Total	**774,741**	**496,000**	**279,000**	**15.9 M**
North East	203,186	198,000	5000	
North West	458,068	217,000	241,000	
Yorkshire and the Humber	324,228	298,000	26,000	
Total	**985,482**	**713,000**	**272,000**	**14.9 M**
South Central	185,642	*252,000	66,000	
South East Coast	261,445	148,000	113,000	
South West	367,420	188,000	179,000	
Total	**814,507**	**588,000**	**226,000**	**13.8 M**

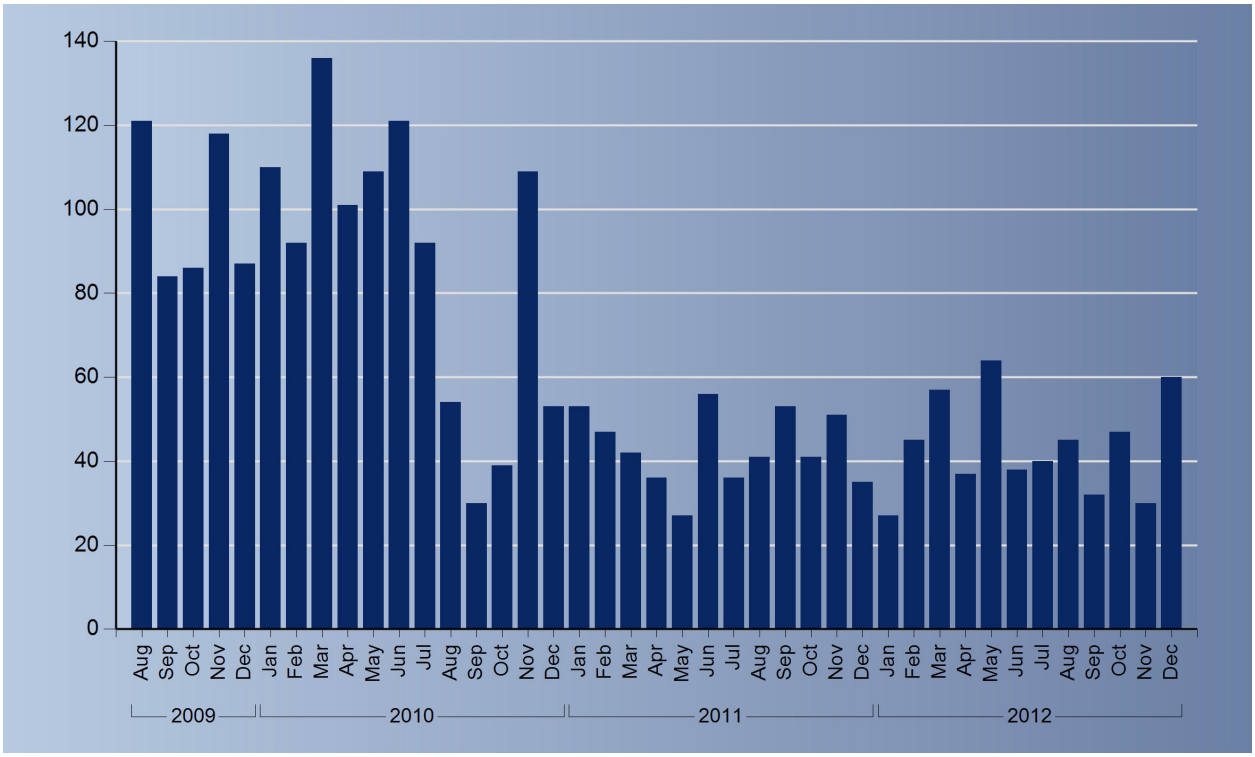
*May include homecare

1.9 Immunoglobulin use for 'other' diagnoses

Considerable volumes of immunoglobulin are still used with no specific condition recorded. Measures to address this were taken by MDSAS, prior to September 2010, 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. 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

Figure 1.9 The number of 'other' diagnoses registered, June 2009–December 2012

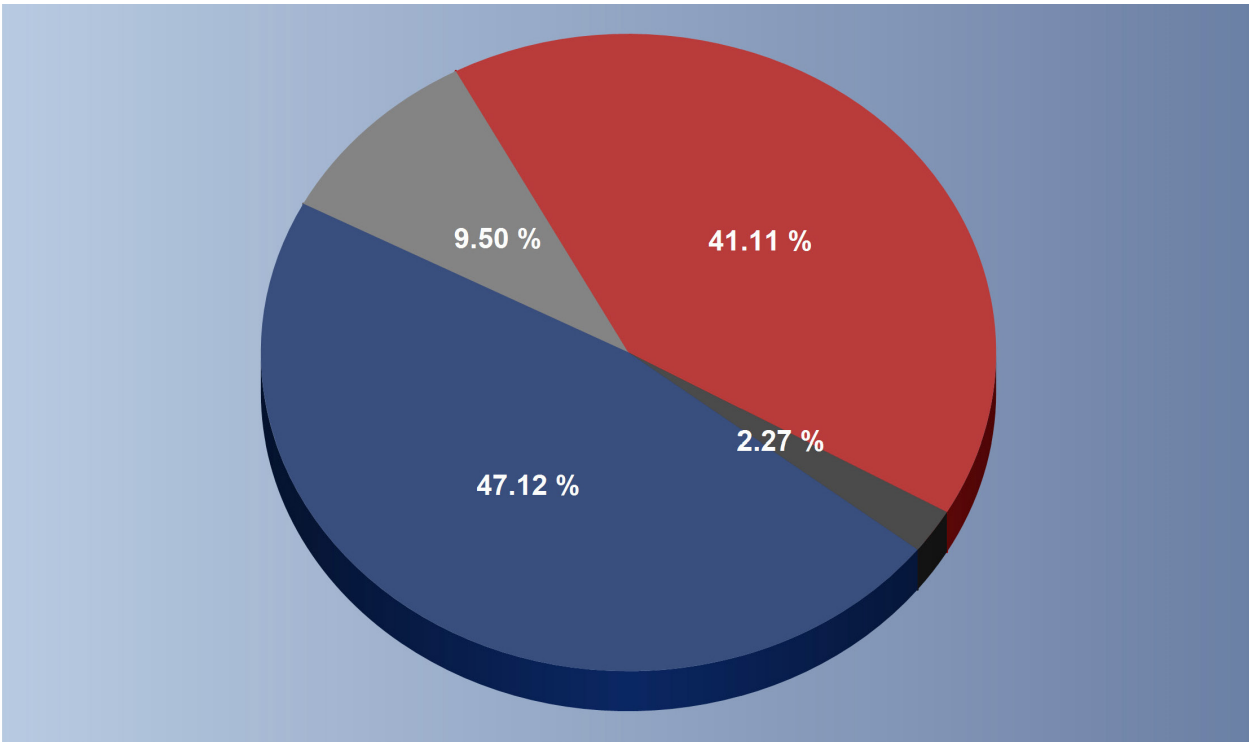


Because 5% of cases (764 patients using 137,296 grams of IVIg) were classed as 'other', a sample month (November 2012) was audited and the 64 cases reviewed. Reasons for treatment are given in Table 1.9. These were assigned to Grey automatically, but review shows most should have been assigned as Red or Blue indications. This occurs when the user does not check to see if the diagnosis is in the drop-down menu and proceeds to registering the patient as 'Other Diagnosis'. Others pertaining to neurology are found in Table 4.3.2.

Table 1.9 Reasons for prescribing intravenous immunoglobulin recorded as 'other' with correct colour prioritisation assigned

Common variable immunodeficiency disorder (CVID; not on list)	Netherton syndrome
CVID (bronchiectasis)	Thrombocytopenia, G1 sepsis, femoral deep vein thrombosis
Variable combined immune deficiency	Tetanus
Neonatal alloimmune thrombocytopenia	Epileptic child unable to have vaccinations in contact with measles
Mantle-cell lymphoma	Tetanus-prone wound
Hodgkin's disease	Contact with measles in an immune-compromised patient
Non-Hodgkin's lymphoma (post stem cell transplant)	Relapsed acute myeloid leukaemia (AML)
Non-Hodgkin's follicular lymphoma with chronic obstructive pulmonary disease	Acute lymphoblastic leukaemia
Chronic parvovirus B19 infection	Macrophage activation syndrome
Congenital parvovirus B19 infection	Neonatal haemochromatosis
Ongoing severe parvovirus (immunosuppressed patient with aplastic anaemia)	Pompe disease
Autoimmune haemolytic anaemia or hyperhaemolysis	Post-radiation plexopathy
Chronic autoimmune pancytopenia with ITP (not listed option)	Immunodysregulation polyendocrinopathy enteropathy X-linked syndrome
Reduced half-life of von Willebrand factor due to paraprotein; gastrointestinal bleed	**Other reasons recorded that would not be funded**
Myocarditis	Unknown
Anti-Rho/Anti-La antibodies causing complete heart block in foetus	Awaiting data from consultant
Clostridium difficile not responsive to treatment – HIV	'Grey' indication not on list
Cytomegalovirus viraemia following HSCT	NEMO
Parvovirus following cardiac transplant	Unsure of diagnosis
Desensitisation for HLA antibodies before living donor renal transplantation	Diagnosis not on list

Figure 1.10 Immunoglobulin usage by colour-coded prioritisation



1.10 Immunoglobulin use by colour-coded prioritisation

The highest usage recorded on the database until April 2012 was 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 were 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 was made to link specific indications to a specific colour, which is then automatically assigned. Note the change from previous figures.**

'Grey' indications, which require referral for Primary Care Trust (PCT) approval, still account for 9% (short and long term) of all usage despite changing the classification of two frequently prescribed 'Grey' conditions to a 'Blue' classification. As mentioned before, most of these remain incorrectly completed and end up classified as 'Other'.

Table 1.10 Immunoglobulin usage by colour-coded prioritisation

Indication	Patients
Red	4908
Blue	3764
Grey	1372
Black	239
Total	**10,283**

1.11 Lean-body-weight-adjusted dosing

Some adverse reactions with IVIg in obese patients have been ascribed to relative overdosing as the distribution of IVIg has been demonstrated to have little distribution in body fat. One Canadian jurisdiction as well as the Western Australia Red Cross have made recommendations to use adjusted-weight-based dosing. This is particularly relevant as recent data continue to demonstrate a 35.5–35.8% prevalence of obesity. Dosing weight, an intermediate between ideal body weight and actual body weight, was developed to more accurately dose IVIg, and, in 2009, the Ontario Regional Blood Coordinating Network created an online tool encouraging physicians to take advantage of a dosing weight calculator. The utilisation of dosing weight for IVIg prescribing can make a significant impact to the amount of IVIg issued.

CHAPTER 2

Commissioning of Immunoglobulin

Malcolm Qualie

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 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 £90 million. Immunoglobulin remains a high-cost drug entirely funded by specialised Commissioners under the auspices of the NHS CB.

2.1 Model Commissioning Policy for immunoglobulin

In 2009, the Model Commissioning Policy was published 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 both clinically effective and cost effective. Although there have been changes from regions to 'supra regions', the policy still requires in-hospital 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, and funding for immunoglobulin is now related to accurate data entry, with some centres having 100% compliance.

A National Immunoglobulin Working Group, which has Commissioner (Head of Pharmacy) and clinician representatives (and in the future pharmacy and patient representation), will continue to provide advice to the NHS CB on further development of the service specification via the National Clinical Reference Group.

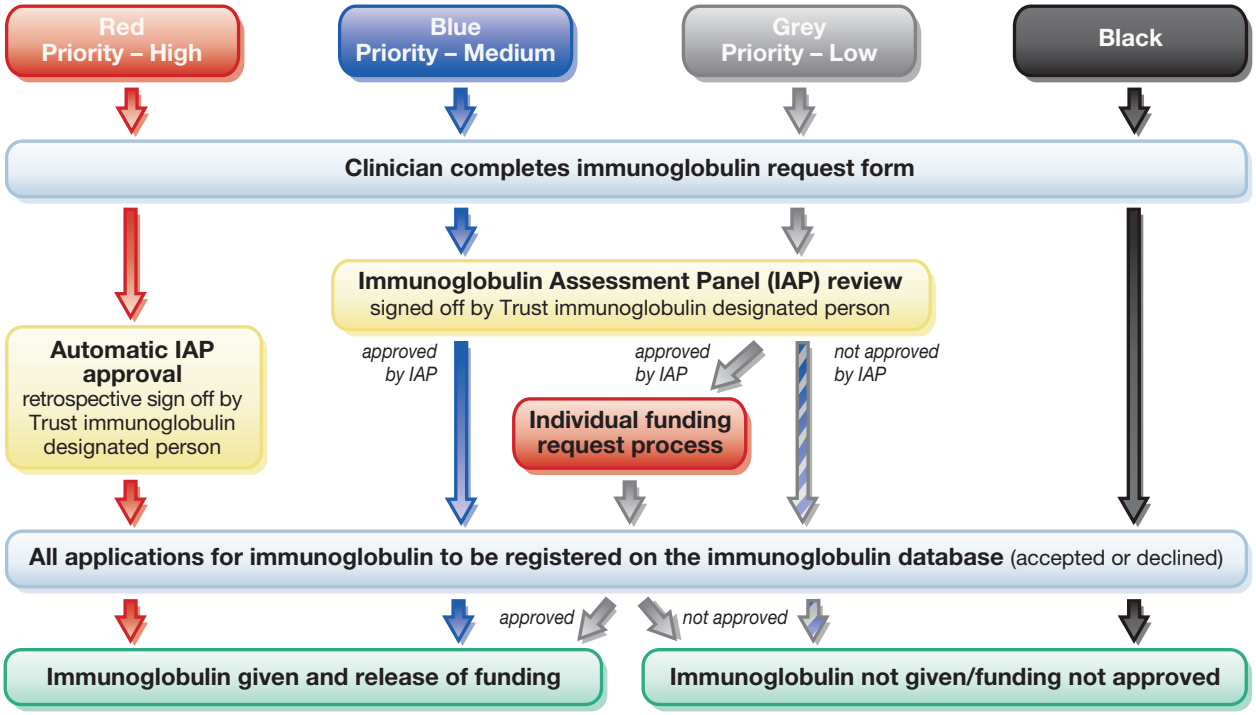
Four Factors determine whether the NHS CB commissions a service as a prescribed specialised service; these are:

1. The number of individuals who require provision of service
2. The cost of providing the service or facility
3. The number of persons able to provide the service or facility
4. The financial implications for Clinical Commissioning Groups if they were required to arrange for the provision of the service or facility themselves

The ambition of the NHS CB is to bring equity and excellence to the provision of specialised care and treatment. This will be achieved through a commissioning process that is patient centred and outcome based, with the patient placed at the centre of planning and delivery. Commissioners, working with providers, must deliver improved outcomes, be fair and consistent throughout the country and ensure that patients have equal access to services regardless of their location.

A national consistent and coherent approach to specialised commissioning is built on universal support. To date, there has been wide variation in how each region discharges its commissioning responsibilities, resulting in inconsistencies in the management of the commissioning cycle such as budget setting, contract negotiation, performance management and the development and application of service specifications, commissioning policies and quality standards. It has also resulted in duplication of some activities and functions. A consistent approach to central planning that is delivered locally will help to tackle these variations and take positive steps towards raising standards of care for all patients receiving treatment for rare and specialised conditions with equity across the country.

Figure 2.1.1 Change to the approval process



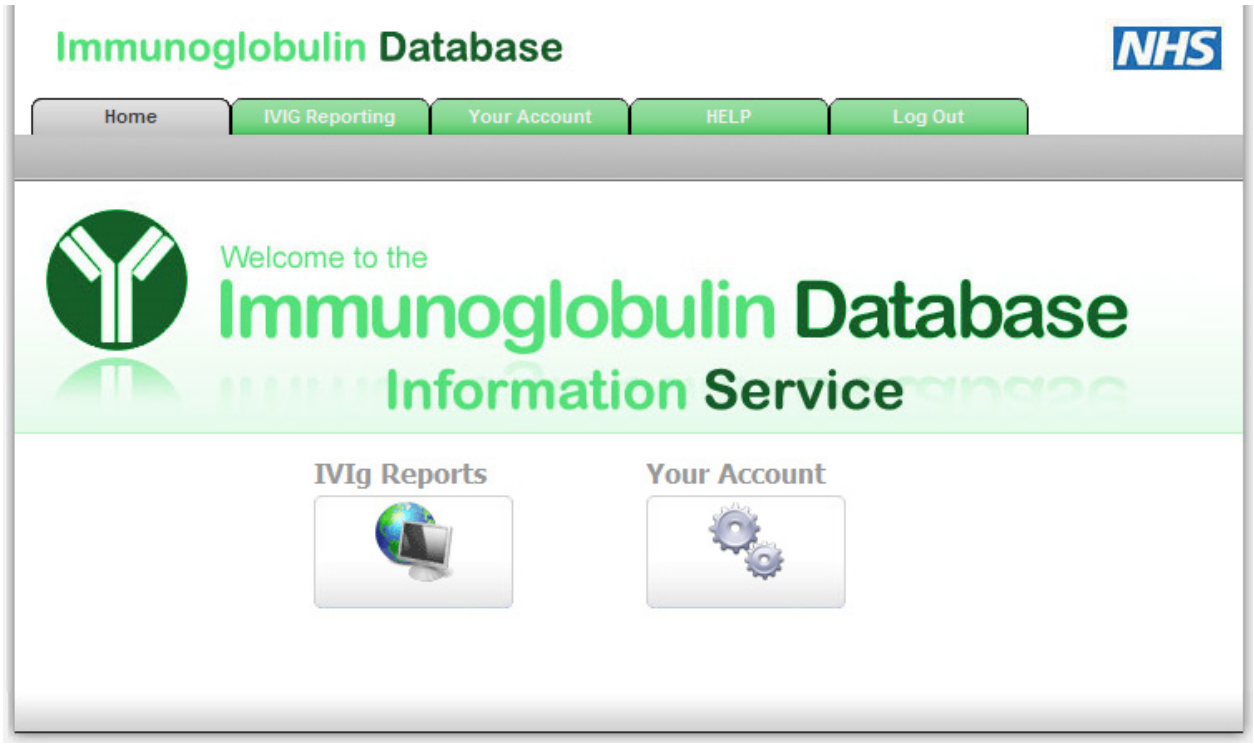
2.1.1 Change to the approval process in 2013

The resulting change to the approval process (Figure 2.1.1) is that Individual Funding Requests (IFRs) will no longer go to PCTs or regional SCGs. Instead there will be one Specialised Commissioner IFR Panel.

2.2 Commissioner's Database Information Service

As part of the database improvements launched in June 2009, the database migrated onto the internal NHS N3 network, which uses industry-standard encryption. One of the key additions was the information service for Commissioners (Figure 2.2.1).

Figure 2.2.1 Commissioners Database Information Service



By activating the IVIg reporting window, a page of useful reports are seen (Figure 2.2.2), which has allowed access to data by region, subdivided by centres, as well as the ability to geographically map patients attending a particular centre (Figure 2.2.3).

Figure 2.2.2 Intravenous immunoglobulin usage reports available on the Information Service

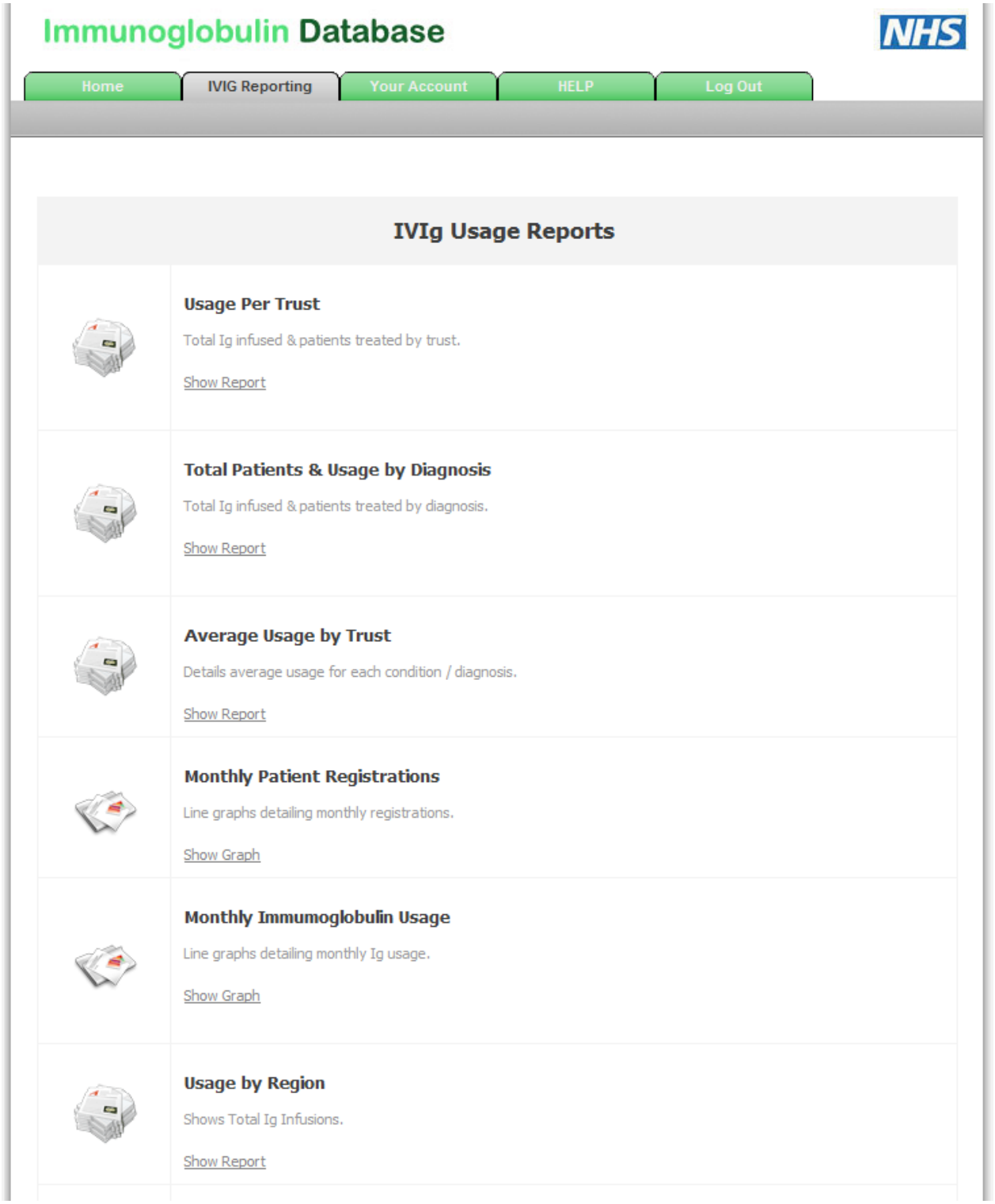
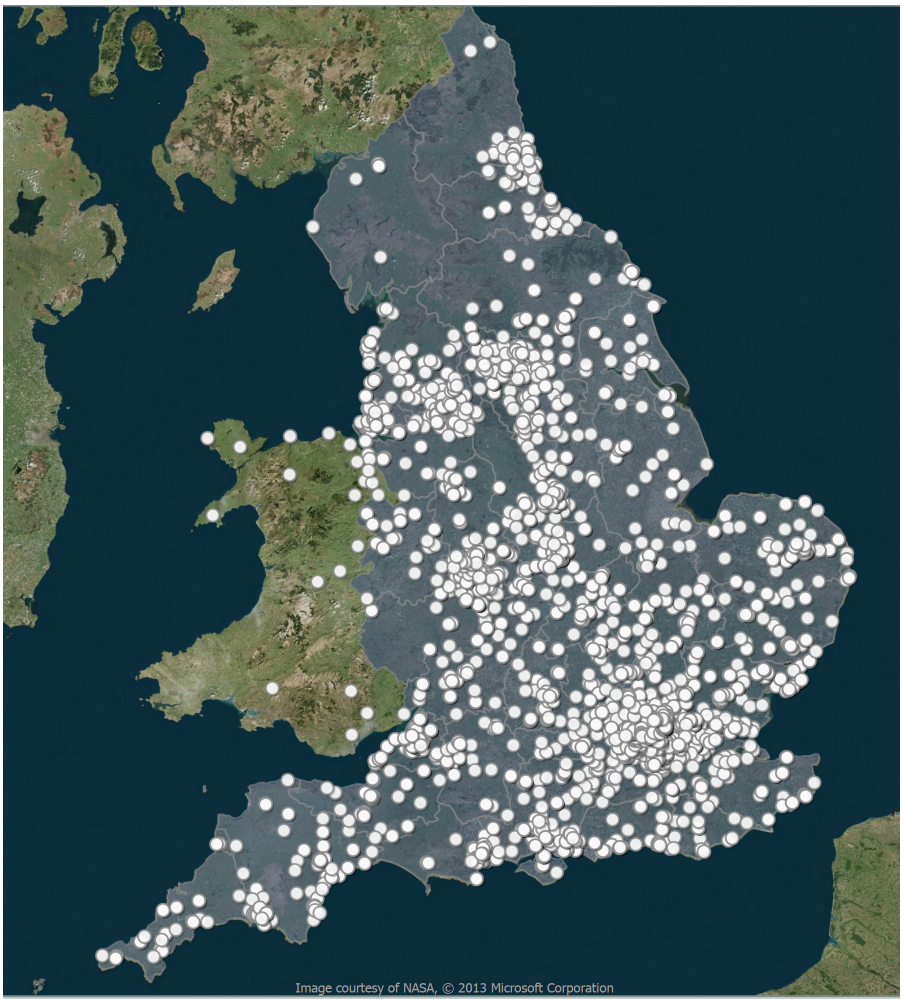


Figure 2.2.3 Location of patients being treated for primary immunodeficiency



This service gives secure, real-time online access to reports and charts so there is now an opportunity to link immunoglobulin use to payment. One example of its use is in the East Midlands, where their SCG had 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 allowing for cost analysis of each product. These data are 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 is now also 'stopping criteria.' These have been automated with email alerts and automatic stopping rules through database locking to prevent inappropriate unsanctioned use. This has made 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"**

Dose reduction

In addition, for patients on long-term immune-modulatory 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 in 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).

Outcomes

The last update now specifies the **outcome(s) measures** but not the degree in improvement of outcome(s) required to constitute treatment success.

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.

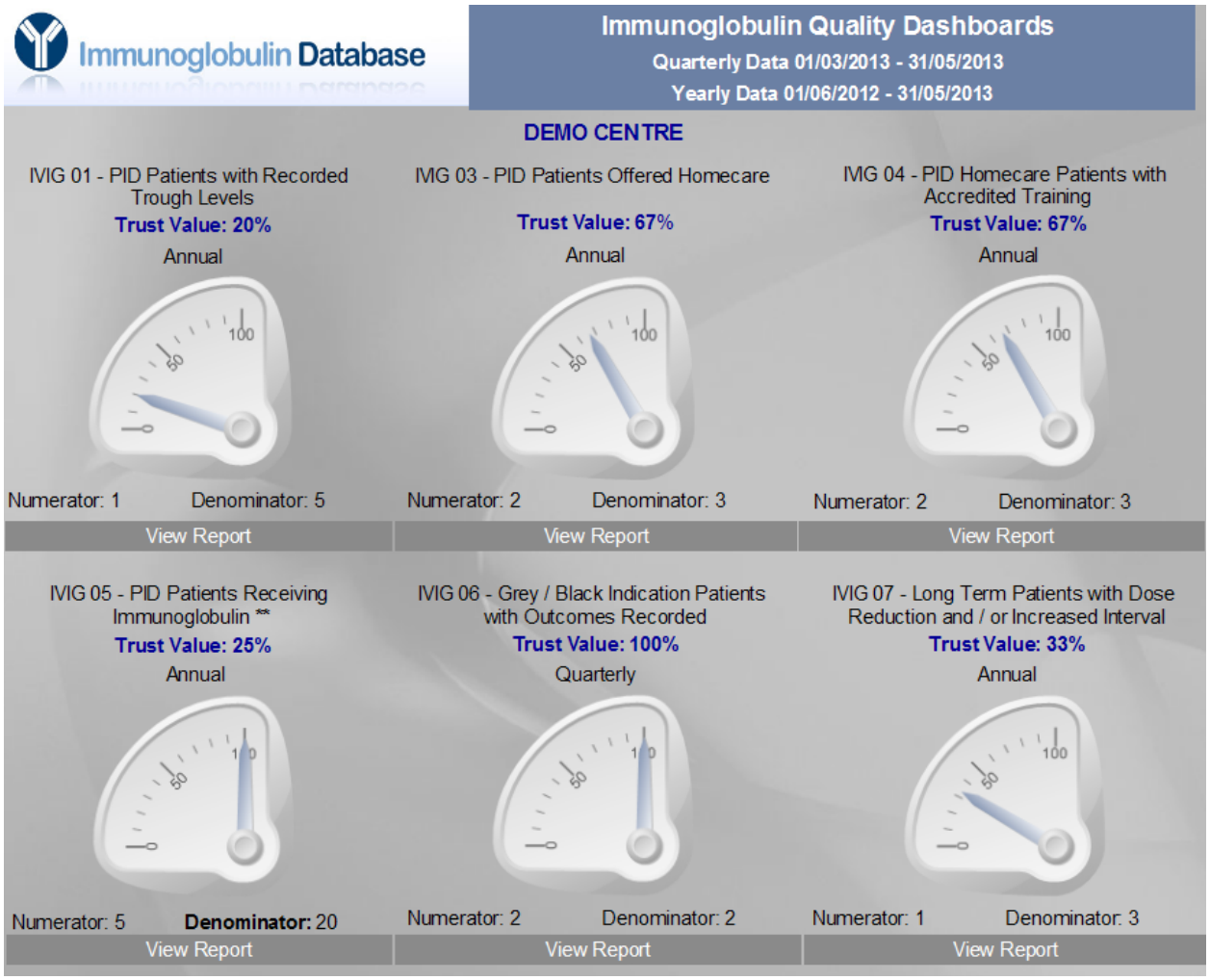
2.4 Immunoglobulin Quality Dashboard

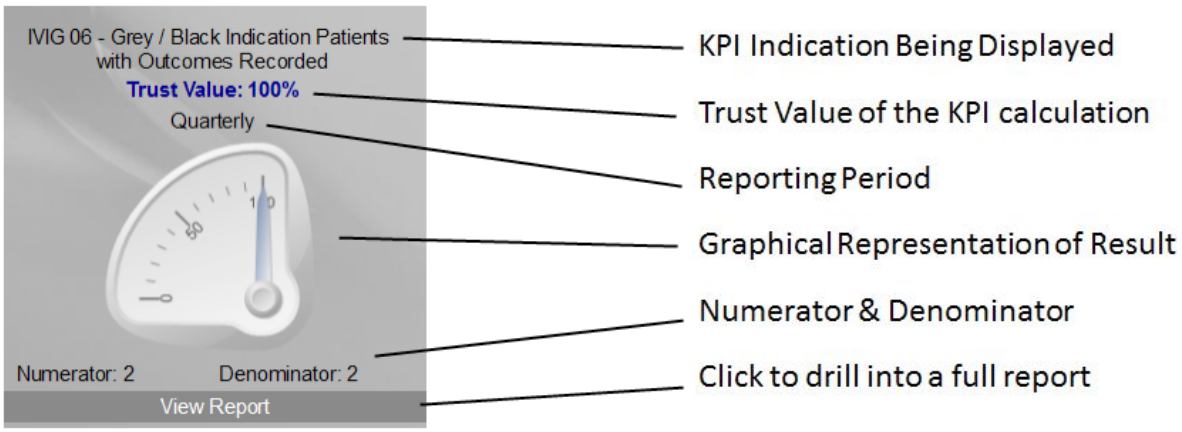
The database has now been updated to capture information for the new Key Performance Indicators (KPIs). The KPIs are presented as a dashboard to enable a quick overview of how the Hospital Trust is performing. A complete guide is available on the IVIg website.

Table 2.4 The new Key Performance Indicators measurements

KPI	Description	Outcome measure
01	No. of PID patients with trough levels recorded	Automatic
03	No. of patients with PID offered treatment by homecare	Yes, No, N/A or unknown
04	No. of PID patients at home who have received training from accredited Home Therapy Centre	Yes, No, N/A or unknown
05	Proportion of PID patients receiving treatment who are registered on the database	Automatic
06	Proportion of 'Grey'/'Black' with outcomes	Automatic
07	No. of long-term treatments with evidence of dose reduction	Dose, new dose and date changed
09	No. of adverse events on database	Automatic
10	No. of short-term treatments re-registered on database	Automatic
11	Short-term 'Red' and 'Blue' conditions with outcomes	Automatic
12	How many 'Grey' indications were approved prior to treatment	Automatic
13	Long-term neurological indications with objective measures of improvement	Automatic
15	Long-term conditions receiving annual review (and GP notified?)	Automatic

Figure 2.4.1 The Immunoglobulin Key Performance Indicators Dashboard





CHAPTER 3

NHS purchasing

David Ford

The aims of the Commercial Medicines Unit (CMU) since 2006 have always been to maintain security of supply of immunoglobulin and ensure value for money for the NHS whilst following EU tendering procedures.

The CMU, together with pharmacists, Commissioners, clinicians and the database, has been working with suppliers, both within the tender process and ongoing contract management, to ensure:

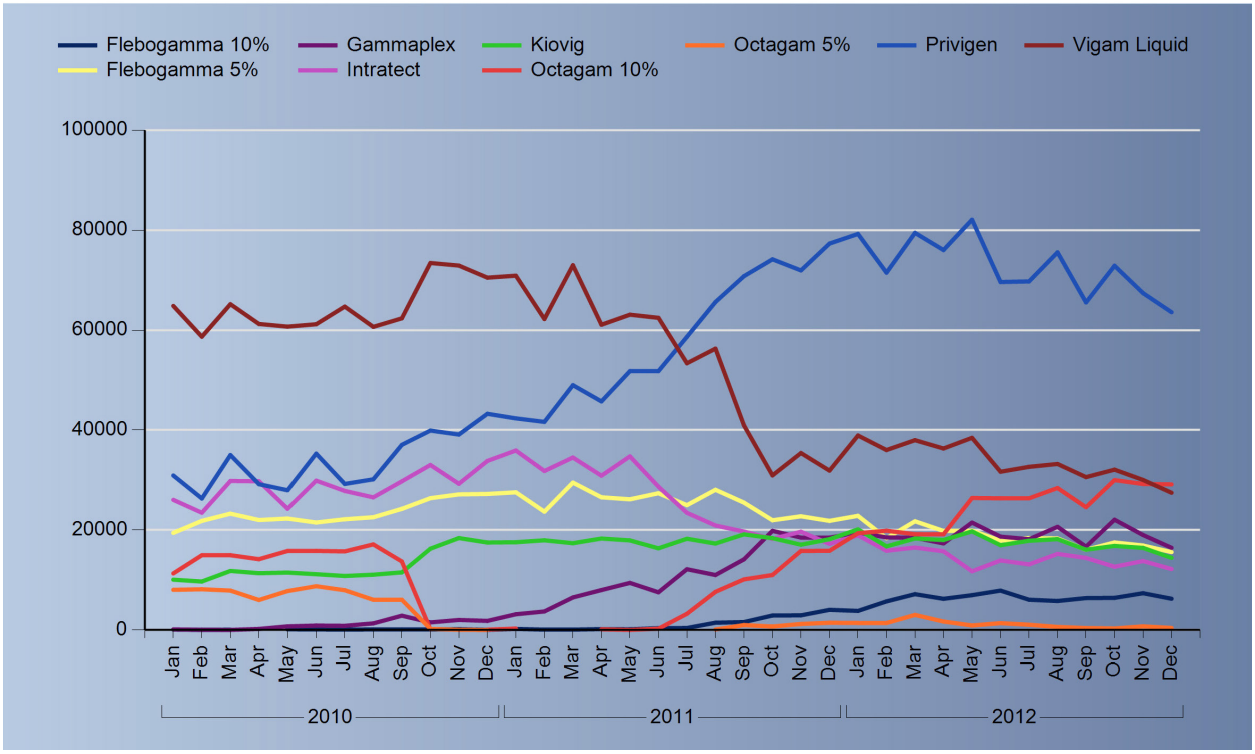
- There are adequate stocks to maintain continuity of supply measured by whether there is extra product availability and contingency planning in both production and delivery should these fail
- There is a procedure for handling patients' complaints as well as a management plan for problems such as recalls
- The packaging is clear and preferably bar-coded to enable hospital staff to upload information more quickly to the database
- Products with shorter infusion times are rewarded as part of the scoring of the tenders (this varies from 1 hour to over 4.5 hours based on a 30 gram dosage)
- Products with longer shelf life at room temperature are rewarded as part of the scoring of the tenders. This information is also provided within the tender briefing document

Further information regarding any aspect of the tender process can be obtained from the Specialised Pharma team at the CMU specialisedpharma@cmu.nhs.uk or Tel. 01928 794 635.

3.1 Managing shortages

There have been two periods of product unavailability. These were managed by endeavouring to use the same product for those long-term patients with diagnoses colour coded Red. All the others patients were started on a different product so that overall immunoglobulin supply was maintained.

Figure 3.1 Use of immunoglobulin in the past 2 years



CHAPTER 4

Neurology

Michael Lunn

Before the institution of the National Immunoglobulin Database, neurology was known to be a heavy user of immunoglobulin, and there was concern at the DH about the proliferation of usage for large numbers of rare and unusual diagnoses, where the evidence base for efficacy was not strong or was 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 specialist 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 randomised controlled trial evidence, which for CIDP, GBS and MMN is of high quality.

The information in the database (see Table 4.1.2) illustrates that only 12% is for life-threatening conditions and 88% of use is for reducing impairment and improving abilities. Many might respond, in a shortage situation, to an alternative treatment or a delay in treatment that may not lead to harm. It is worth noting that IVIg gives a response in a shorter period of time than steroids or oral immunosuppressants, and plasma exchange may not be available.

Table 4.1.1 Number of patients treated and volumes of intravenous immunoglobulin used in neurology

Diagnosis	Usage (grams)	Patient (n)
CIDP	565,683	972
MMN	290,771	717
GBS	113,308	404
MG	85,454	388
IM	46,601	145
Paraprotein-associated demyelinating neuropathy (IgG or IgA)	20,361	44
Stiff person syndrome	17,635	40
Rasmussen syndrome	4018	13
Total	**1,143,831**	**2723**

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

Diagnosis	Red (short-term; grams)	Blue (long-term; grams)	Blue (short-term; grams)
CIDP	41,628	527,770	–
GBS	106,691	–	–
MMN	–	285,082	4,444
MG	–	28,553	50,169

Volumes used by neurology are the highest of all the conditions. Figure 4.1.1 gives the monthly usage of immunoglobulin since the database started and demonstrates a steady climb from January 2010 until May 2012. This is in spite of the partial shortages of immunoglobulin June–October 2011 and October 2010–May 2011.

We can postulate that the downward trend of IVIg usage from May 2012 onwards might be because clinicians are adhering to one of the three requirements of the Commissioners: that, in stable long-term conditions, *attempts should be made to reduce the dose* either by increasing the dosing interval or reducing the dose, excluding PID.

Figure 4.1.1 Monthly usage by specialism (volume)

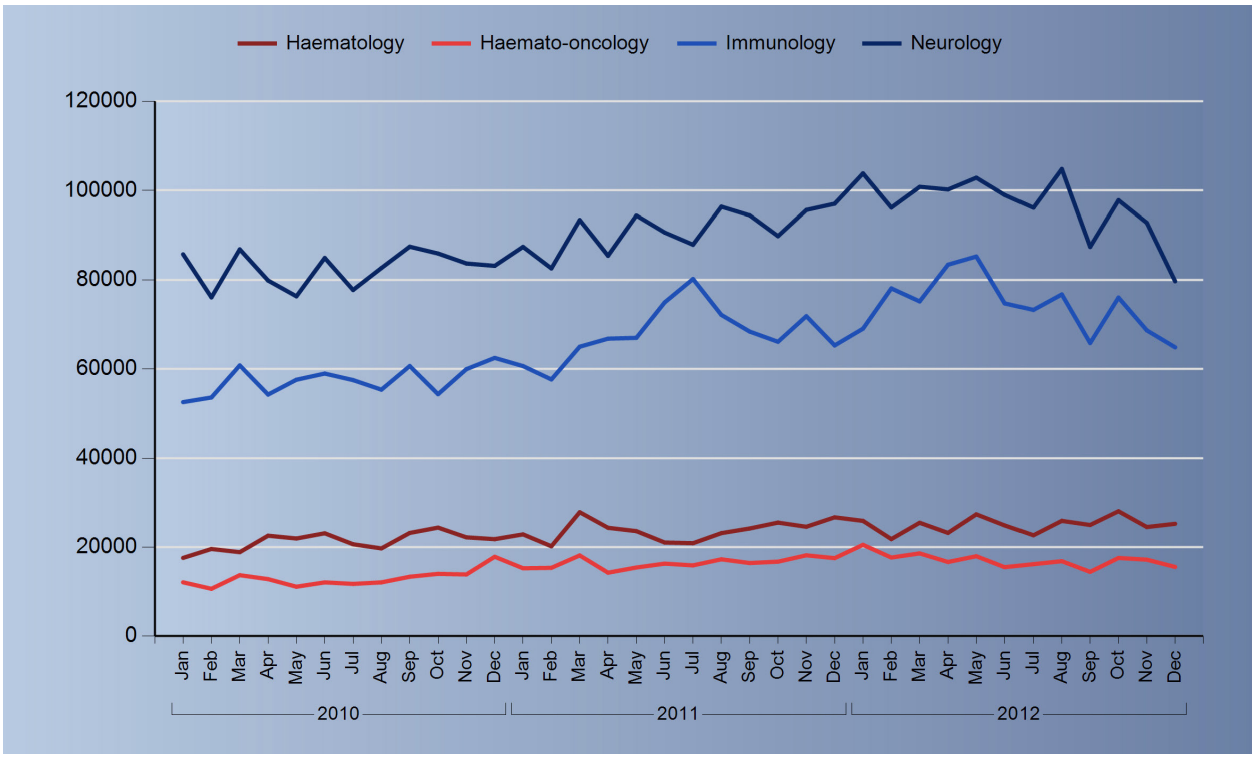
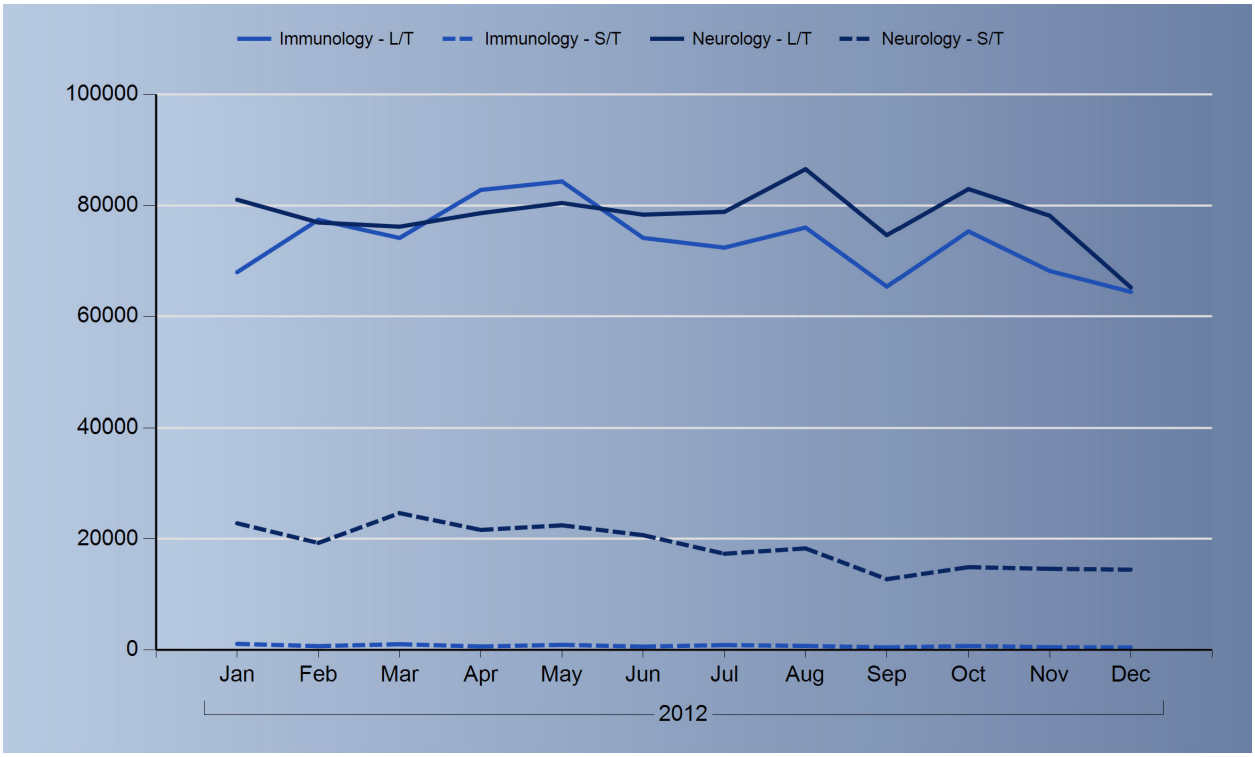


Figure 4.1.2 Monthly usage in 2012 showing short-term and long-term volumes



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 2012, there were 404 GBS patients in the database, suggesting case ascertainment between 75% and 94%.

4.3 Updates in neurology

The Second Edition Update of the *Clinical Guidelines for Immunoglobulin Use* did not review and revise all of the content of the Second Edition, but limited itself to three key areas:

1. Defining selection criteria for appropriate use
2. Efficacy outcomes to assess treatment success
3. Reassignment of existing indications /inclusion of new indications (e.g. polymyositis was grouped with dermatomyositis as **Myositis**).

Table 4.3.1 Selection criteria for top four conditions with required outcome criteria

Neurology					
Condition	**S**	**L**	**Selection criteria**	**Outcomes for review**	**Dosing**
Chronic inflammatory demyelinating polyradiculoneuropathy	●	●	Probable or definite diagnosis of CIDP by a neurologist according to the EFNS/International Peripheral Nerve Society Guidelines; AND Significant functional impairment inhibiting normal daily activities	Improvement in any of the following prespecified measures (record 3 of 5) • MRC score (7 pairs of muscles in upper and lower limb scored 0–5, maximum 70) • INCAT sensory sum score • The ONLS • Up and go 10-m walk (in secs) • Other validated disability measure	2 doses of IVIg (2 g/kg given over several days) 6 weeks apart; restarted at relapse and repeated using the 'time to relapse' as the interval between courses (i.e. if a patient relapses after 6 weeks, 2 g/kg is given over several days every 6 weeks)
Guillain-Barré syndrome (includes Bickerstaff's brain stem encephalitis)	●		Diagnosis of GBS (or variant) in hospital; AND Significant disability (Hughes Grade 4); OR Disease progression	Record the disability grade at diagnosis	2 g/kg usually given over 5 days (shorter time frame not recommended because of potential fluid overload and autonomic problems); second dose may be considered at 14 days for non-responsive or late deteriorating patients
Myasthenia gravis [includes Lambert-Eaton myasthenic syndrome (LEMS)]	●		Diagnosis of MG or LEMS by a neurologist; OR Acute exacerbation (myasthenic crisis); OR Other immunosuppressive treatments are ineffective/ inappropriate; OR Weakness requires hospital admission; OR Prior to surgery and/or thymectomy	Improvement in fatigability and weakness using any pre-specified measure: • Forward arm abduction time (up to 5 min) • Quantitative Myasthenia Gravis Score (Duke) • Respiratory function, e.g. forced vital capacity • Variation of a myasthenic muscular score	2 g/kg given over 2–5 days
Multifocal motor neuropathy		●	Diagnosis by a neurologist of multifocal motor neuropathy with or without persistent conduction block; AND Significant functional impairment inhibiting normal daily activities	Improvement in pre-specified measures: • Power score from 10 pre-defined pairs of muscles including six most affected muscles neuro-physiologically • The ONLS • Up and go 10-m walk (in secs) • Other validated disability measure	2 doses of IVIg (2 g/kg given over several days) 6 weeks apart; restarted at relapse and repeated using the 'time to relapse' as the interval between courses (often may be 4 weeks, but doses required may be less than CIDP)

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

1. Immune-mediated disorders with limited evidence of immunoglobulin efficacy
2. Presumed immune-mediated disorders with little or no evidence of efficacy

Any entries to the database as 'other' would automatically be classified as Grey, which are then supposed to go to the Independent Funding Panel for approval. An audit carried out recently of neurological diagnoses in the text box found most of these fell in the "likely to be funded" category as the entered diagnoses were frequently specific sub-forms of another diagnosis or misnomers.

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)	Diabetic proximal neuropathy (likely to be vascular)
*Autoimmune encephalitis (including NMDA and VGKC antibodies, among others)	*Paraneoplastic disorders (that are not clearly autoimmune)
Catastrophic antiphospholipid syndrome	Chronic facial pain
Cerebral infarction with antiphospholipid antibodies	Vasculitic neuropathy
Intractable childhood epilepsy	Acute idiopathic dysautonomia
Neuromyotonia	PANDAS
Systemic vasculitides and anti-neutrophil cytoplasmic antibody disorders	POEMS
*Opsoclonus myoclonus	

*These will probably be 'Blue' in the next guidelines

Table 4.3.3 Neurological disorders recorded as 'Other'

Demyelinating neuropathy	Anti NMDA (see above)
Inflammatory sensory ataxia	Autoimmune encephalitis (see above)
Facial-onset sensory and motor neuropathy	Limbic encephalitis (VGKC antibodies) (see above)
Multifocal acquired demyelinating sensory and motor neuropathy/Lewis Sumner syndrome (CIDP variant)	Autoimmune encephalitis (see above)
Devic's syndrome (neuromyelitis optica antibodies) optic neuritis and spastic paraparesis	Anti-myelin-associated glycoprotein (MAG) peripheral neuropathy
Susac's syndrome (retinocochleocerebral vasculopathy) *If steroids fail*	Axonal neuropathy likely inflammatory (MAG-like)
Anti-glutamic acid decarboxylase (GAD) (autoimmune) cerebellar ataxia	Autoimmune cerebellar ataxia (GAD-like)

In this table, there are CIDP cases ('Blue'), Devic's and Susac's syndromes (likely to be 'Blue' in the next guidelines), and all of the rest are 'Grey', but likely to be funded.

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 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 where this is feasible.

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 or MMN who fulfil the diagnostic criteria, Trusts are now expected to record three outcome scores from five:

- MRC score – seven pairs of muscles in upper and lower limbs scored from 0 to 5
- Sensory sum score
- Overall neuropathy limitations score (ONLS)
- 10-m walk
- Any other validated disability measure

CIDP, as the name implies, is a long-term autoimmune condition with inflammation of nerve and nerve roots that leads to demyelination (loss of insulation). It presents as progressive sensory loss and weakness of the limbs. Bulbar function (speech or swallowing) and respiratory function may be affected in severe cases. *MMN* is a condition affecting only motor nerves in which inflammatory demyelination results in blocking of conduction in individual nerves resulting in patchy progressive weakness. It usually presents as asymmetric weakness such as finger drops or wrist extension weakness, but can progress to foot drop and leg weakness. Respiratory and swallowing nerves are not affected but the weakness may be severe and very disabling. It may be associated with antibodies to ganglioside GM1.

Outcomes may be measured at a number of levels; impairments, abilities, functions or quality of life. Measures of ability are most applicable to patients as these reflect day-to-day functioning. The *overall disability sum score (ODSS)* and the *ONLS* capture the abilities of patients with inflammatory neuropathies and have been validated. They are *ordinal scales* based on classical test theory and suffer from "floor and ceiling" effects, limiting their responsiveness.

Impairment scores (MRC sum score and *INCAT sensory sum score*) are more traditionally captured by clinicians. They may not accurately reflect change in conditions where the distribution of weakness can be highly variable, as in MMN with conduction block, and suffer from some fundamental statistical flaws, making summation and comparisons invalid.

A recently validated *Rasch-built overall disability scale* more successfully captures abilities over the whole range of functioning. Modifications based on Rasch statistics have been proposed but are yet to be widely accepted.

Strength impairments measured with dynamometry are quantitative and reliable, but dynamometers are not widely available and their use is limited to a small number of movements.

4.4.1 November audit of outcomes for selected neurology indications

Outcomes of 28 patients with CIDP treated with immunoglobulin are presented in Table 4.4.1.

An audit of outcomes in 10 patients with MMN are presented in Table 4.4.2. These data illustrate that the scores used are largely in the impairment domain measuring muscle strength.

Table 4.4.1 Chronic inflammatory demyelinating polyradiculoneuropathy outcomes recorded in 28 patients

Date	Outcome	Outcome result	Date	Outcome	Outcome result
07/11/2012	MRC score	69 s	22/10/2012	50-m walk	30 s
07/11/2012	Up-and-go 10-m walk	7.5 s	22/10/2012	Hand dynamometer	rt 31 kg; lt 37 s
07/11/2012	MRC score	69	22/10/2012	Nine-hole peg test	rt 23 s; lt 25 s
07/11/2012	Up-and-go 10-m walk	8.5 s	12/11/2012	50-m walk	28 s
16/11/2012	Clinical improvement on assessment	Yes	12/11/2012	Hand dynamometer	rt 30 kg; lt 34 kg
21/11/2012	ONLS	7	19/11/2012	50-m walk	27 s
16/01/2012	Nine-hole peg test	rt 120 s; lt 84 s	19/11/2012	Nine-hole peg test	rt 22 s; lt 20 s
20/02/2012	Nine-hole peg test	rt 87 s; lt 100 s	19/11/2012	Grip	rt 34 kg; lt 35 kg
11/04/2012	Hand dynamometer	rt 13 kg; lt 10 kg	19/11/2012	Romberg test	60 s
11/04/2012	Nine-hole peg test	rt 87 s; lt 135 s	18/12/2012	50-m walk	26 s
21/05/2012	Hand dynamometer	rt 10 kg; lt 18 kg	18/12/2012	Nine-hole peg test	rt 26 s; lt 24 s
21/05/2012	Nine-hole peg test	rt 92 s; lt 114 s	18/12/2012	Grip	rt 39 kg; lt 39 kg
21/05/2012	pinch gauge	rt 1 kg; lt 1 kg	22/01/2013	50-m walk	27 s
15/10/2012	Hand dynamometer	rt 9 kg; lt 14 kg	22/01/2013	Nine-hole peg test	rt 23 s; lt 21 s
15/10/2012	Nine-hole peg test	rt 93 s lt 138 s	22/01/2013	Grip	rt 27 kg; lt 35 kg
26/11/2012	ONLS	10	19/02/2013	50-m walk	27 s
28/01/2013	Hand dynamometer	rt 10 kg; lt 16 kg	19/02/2013	Nine-hole peg	rt 23 s; lt 19 s
28/01/2013	Nine-hole peg test	rt 133 s; lt 154 s	19/02/2013	Grip	rt 30 kg; lt 36 kg
19/11/2012	ONLS	4	02/10/2012	Nine-hole peg test	20.9 s
08/02/2012	Nine-hole peg test	rt 35 s; lt 41 s	02/10/2012	Nine-hole peg test	22.43 s
19/11/2012	ONLS	3	02/10/2012	Muscle power (0–5)	12
28/01/2013	Hand dynamometer	rt 27 kg; lt 20 kg	02/10/2012	Muscle power (0–5)	19
28/01/2013	Nine-hole peg test	rt 28 s; lt 45 s	02/10/2012	Stairs ascent	13.42 s
26/11/2012	ONLS	5	02/10/2012	Stairs descent	12.37 s
19/11/2012	ONLS	0	02/10/2012	Up-and-go 10-m walk	14.7 s
20/11/2012	MRC score	69	16/11/2012	Nine-hole peg test	17.92 s
20/11/2012	Up-and-go 10-m walk	8.2 s	16/11/2012	Nine-hole peg test	19.04 s
19/10/2012	Hand dynamometer	rt 59 kg; lt 25 kg	16/11/2012	Muscle power (0–5)	24
16/11/2012	Clinical improvement on assessment	Yes	16/11/2012	Muscle Power (0-5)	27
16/11/2012	MRC score	64	16/11/2012	Stairs ascent	7.82 s
08/11/2012	Hughes score	2	16/11/2012	Stairs descent	7.04 s

rt = right; lt = left; s = seconds
Shading separates outcomes for individual patients

Table 4.4.1 Continued Chronic inflammatory demyelinating polyradiculoneuropathy outcomes recorded in 28 patients

Date	Outcome	Outcome result	Date	Outcome	Outcome result
08/11/2012	MRC score	4/5 ankle dorsiflexion, 5-/5 ankle eversion; else 5/5	16/11/2012	Up-and-go 10-m walk	9.75 s
08/11/2012	Patient own functional score	Shows improvement after each infusion – starts to drop off before next infusion due	19/11/2012	MRC score	48
19/11/2012	ONLS	0	09/11/2012	Sensory changes	Vibration reduced to knee in lower limbs
20/11/2012	ONLS	3	09/11/2012	Sensory changes	Vibration reduced to the knee in lower limbs
08/01/2013	Berg balance	52/52	09/11/2012	Sensory examination landmarks	Pin prick reduced to the upper thighs
18/06/2012	MRC score	60	13/11/2012	General review	Patient on ICU ventilator dependent, weak bulbar function
12/11/2012	MRC score	60	26/11/2012	MRC grade of power in upper and lower limbs	Sh ab 10, El fl 8, Wr ex 7, Hi fl 8, Kn Ex 9, Ankle df 10; MRC sum score 52/60
14/11/2012	Up-and-go 10-m walk	11.7 s	20/11/2012	Sensory changes	Clinical sensory examination – reduced vibration sense both lower limbs
19/11/2012	MRC score	68	28/11/2012	MRC score	-
20/11/2012	ONLS	5	21/11/2012	Clinical improvement on assessment	Yes
27/11/2012	Patient strength and performance status	Weakness of left leg			

rt = right; lt = left; s = seconds
Shading separates outcomes for individual patients

GBS is an acute, post-infectious radiculoneuropathy. Ascending paralysis, (with weakness beginning in the feet and lower legs, followed by the hands and migrating towards the trunk), is the most typical presenting symptom. It can cause life-threatening complications, in particular if the respiratory muscles are affected or if there is autonomic nervous system involvement. Subtypes are Fisher syndrome (ophthalmoplegia, ataxia and areflexia – often associated with anti-GQ1b antibodies), acute motor axonal neuropathy (often anti-GD1a antibodies), acute motor sensory axonal neuropathy, acute pandysautonomia (rare) and Bickerstaff's brainstem encephalitis.

Table 4.4.2 Outcomes recorded in 10 patients with multifocal motor neuropathy

Patient	Date	Outcome	Outcome result
1	12/11/2011	MRC muscle assessment	59
	26/11/2012	MRC muscle assessment	67
2	21/11/2012	50-m timed walk	37 s
	21/11/2012	Grip	18 kg
	21/11/2012	Nine-hole peg test	rt 12 s; lt 21 s
3	29/11/2011	Clinical improvement	Yes
	11/11/2012	Power score from 10 predefined pairs of muscles including six most affected muscles neurophysiologically	5
4	21/05/2012	Hand dynamometer	rt 34 kg; lt 36 kg
	21/05/2012	Pinch gauge	rt 5 kg; lt 5 kg
	20/11/2012	ONLS	0
	21/01/2013	Hand dynamometer	rt 34 kg; lt 34 kg
	21/01/2013	Nine-hole peg test	rt 17 s; lt 17s
5	23/11/2012	Upper limb function	Improvement
6	26/11/2012	Hand dynamometer	rt 38 kg; L 34 kg
	26/11/2012	ONLS	1
	21/01/2013	Hand dynamometer	rt 38 kg; lt 34 kg
7	19/11/2012	ONLS	1
8	24/04/2012	Grip	29.33 kg
	24/04/2012	Grip	7.66 kg
	24/04/2012	Grip left	29.33 kg
	24/04/2012	Key pinch right	0.65 kg
	06/06/2012	Grip	33 kg
	06/06/2012	Grip	37 kg
	06/06/2012	Grip left	37 kg
	06/06/2012	Key pinch right	0.91 kg
	01/11/2012	Nine-hole peg test	16.07 s
	01/11/2012	Nine-hole peg test	18.4 s
	06/12/2012	Nine-hole peg test	11.66 s
	06/12/2012	Nine-hole peg test	14.22 s
	06/12/2012	Up-and-go 10-m walk	8.43 s
9	05/11/2012	MRC muscle assessment	97
10	19/11/2012	Functional measures	Difficulties walking upstairs

rt = right; lt = left; s = seconds
Shading separates outcomes for individual patients

GBS is an acute monophasic disease that seldom recurs but may leave the affected patient with severe disability. Treatment shortens time to recovery, reducing complications from ventilation, immobility or ITU stays, which may be severe and potentially fatal. 'Outcomes' recorded are therefore somewhat different, reflecting patients likely to benefit from IVIg. With GBS, only those with severe disease should be treated. They have to have been diagnosed by a neurologist, be Hughes grade 4 or have rapid disease progression. This means that they are confined to chair or bed (4), ventilated (5) and/or not able to walk. This appears to have been correctly reported for 12 of the 15 patients treated in November 2012 (Table 4.4.3).

Going forward, the ongoing Peripheral Neuropathy Outcome Measures Standardisation (PeriNomS) study, which finished recruiting in January 2012, may provide better and more rigorous scientific outcomes to track deterioration or improvement.

The **PeriNomS** study compared tests (strength measurements, sensory tests), instruments and questionnaires using international guidelines, ultimately to improve future research and daily clinical practice by constructing and selecting the best outcome measures. The PeriNomS study took 7 years to complete from its initial conceptualisation and was performed in patients with inflammatory neuropathies (GBS, CIDP, MMN, gammopathy-related neuropathy).

4.5 Conclusions

This is a very exciting time when research into the various different peripheral neuropathies is revealing the antibody that is presumed to be causal and gives a reason for a response to IVIg. In the audit of November 2012, there were 53 outcomes recorded (28 CIDP, 15 GB and 10 MMN) Just as it is now recognised that outcome measures in cancer are critical, so too should resources be available for those on expensive long-term treatment.

Table 4.4.3 Outcomes recorded for Guillain–Barré syndrome in November 2012

Patient	Date	Outcome	Outcome result
1	28/11/2012	Disability grade at diagnosis	5
2	02/11/2012	Disability grade at diagnosis	4
3	30/11/2012	Patient survived	Yes
4	20/11/2012	Resolving muscle weakness	Improve
5	20/11/2012	Clinical symptoms	Poor respiratory function
	20/11/2012	Disability grade at diagnosis	5
	20/11/2012	Physical strength	Weak ++
	03/12/2012	Disability grade post first treatment review	5
6	22/11/2012	Patient survived	Yes
7	20/11/2012	Disability grade at diagnosis	4
8	22/11/2012	Modified Rankin scale	4
9	22/11/2012	Modified Rankin scale	–
10	16/11/2012	Hughes rating scale	4
11	23/11/2012	Disability grade at diagnosis	4
12	19/11/2012	Disability grade at diagnosis	4
13	8/11/2012	Stop progression, functional performance on discharge	readmitted after initial diagnosis with worsening facial weakness, dysarthria
14	08/11/2012	Clinical response	Yes
15	11/11/2012	Disability grade at diagnosis	4

CHAPTER 5

Haematology

Jennie Wimperis

5.1 Use of immunoglobulin in haematology

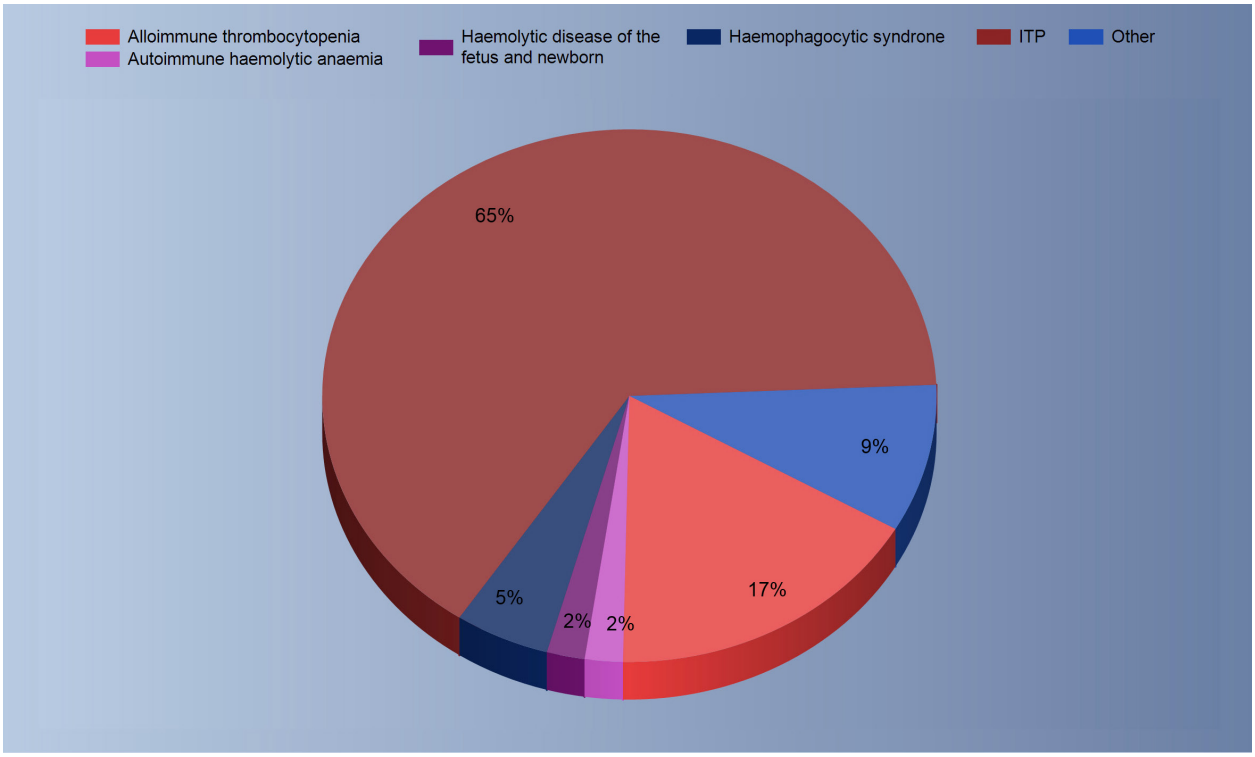
The very first survey in 2006 estimated that 18% of immunoglobulin use in the UK was for the treatment of haematological diseases (both malignant and non-malignant), thus identifying haematology as a major immunoglobulin-using specialism. The National Immunoglobulin Database shows that in 2012 non-malignant haematology indications accounted for 10.5% of the total use of immunoglobulin by volume, of which 65% was used by patients with a diagnosis of ITP.

There are three red indications for use of IVIg in haematology: short-term use for ITP, haemolytic disease of the newborn and neonatal alloimmune thrombocytopenia.

Table 5.1 Immunoglobulin use in haematology

Diagnosis	Usage (grams)
ITP – newly diagnosed (acute)	150,145
ITP – persistent	35,287
Alloimmune thrombocytopenia	10,950
Coagulation factor inhibitors	8430
Haemophagocytic syndrome	7679
Acquired red cell aplasia	2741
Haemolytic disease of the foetus and newborn	1331
Post-transfusion purpura	1308
Autoimmune haemolytic anaemia	1143
Total	**219,014**

Figure 5.1 Immunoglobulin use for individual diagnoses: volume of immunoglobulin change



5.2 Immune thrombocytopenia

Short-term treatment of ITP is one of the haematological disorders 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 controlled trials confirming response rates comparable to those with corticosteroids but with the advantage of immunoglobulin having a shorter time to response.

5.2.1 Terminology of immune thrombocytopenia

An International Expert Working Group published a consensus document in 2009 recommending standardisation of the terminology for ITP. The term *'idiopathic'* was avoided, preferring *'immune'*, to emphasise the immune-mediated mechanism of the disease, and *'primary'*, to indicate the absence of any obvious initiating and/or underlying cause. *Secondary* ITP was proposed to broadly include all forms of immune-mediated thrombocytopenias except primary ITP, i.e., those that are due to an underlying disease or to drug exposure.

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.

A *platelet count <100 × 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.

Definitions of ITP severity were 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".

Definition of the different phases and severity of ITP were updated

The term **'newly diagnosed ITP'** (equivalent to acute 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 reserved for patients with ITP lasting for >12 months.

5.2.2 Goals of treatment of immune thrombocytopenia

The major goal of treatment of ITP is to provide a safe platelet count (i.e., one that prevents major bleeding) rather than correcting the platelet count to normal levels. Treatment of *newly diagnosed* patients is aimed at rapidly obtaining a safe platelet count to prevent or stop haemorrhage. The goal of treatment for *persistent or chronic* ITP is less well defined and the use of IVIg is usually reserved for "on-demand' treatment at the time or in anticipation of high-risk bleeding situations or surgical procedures.

5.2.3 Immunoglobulin use according to colour-coded prioritisation in immune thrombocytopenia

Short-term treatment of ITP is prioritised by the Demand Management plan as Red for the management of acute bleeding in all groups and to raise the platelet count in those with persistent or chronic ITP for procedures likely to cause bleeding (when corticosteroids are contraindicated or ITP is unresponsive to corticosteroids and a more rapid response is required).

Longer term treatment over 3 months (persistent/ chronic ITP) is usually reserved for pregnancy.

Any other longer term treatment e.g., **chronic ITP** without bleeding, is colour coded **Grey**, purely so that the Assessment Panels can inform the Commissioners that the patient has failed all other alternative treatments such as rituximab, thrombopoietin receptor agonists and including splenectomy.

5.3 Immunoglobulin use according to colour-coded prioritisation for other haematology diseases

Most of the other haematology diseases are **short-term 'Blue'**. These are acquired red cell aplasia (B19 parvovirus), autoimmune haemolytic anaemia, haemophagocytic syndrome and post-transfusion purpura. This now also includes hyperhaemolysis and acquired Von Willebrand's disease. These were considered after the first Annual Database Report and appear as a recommendation in the Second Annual Report 2011. This information was presented at the National Database Workshop 2010 and this categorisation is recommended in the Second Edition Update to the *Clinical Guidelines for Immunoglobulin Use* 2011 (gateway reference 16290). Alloimmune thrombocytopenia and haemolytic disease of the foetus and newborn are both colour coded Red.

5.4 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. The National Clinical Guidelines now make recommendations on outcomes to be recorded using the best currently available. For ITP, the outcome measures are 'resolution of bleeding' and 'increment in platelet count'.

5.4.1 Audit of outcomes for acute immune thrombocytopenia

The total number of ITP patients recorded in 2012 was 1127. Of these, 954 were newly diagnosed ITP (and must include short courses of IVIg to raise platelet counts prior to surgical procedures, so we need to examine this further). For the November audit, we expected to see about 95 cases with no outcomes yet (just started on treatment) and a further 95–190 cases under active follow-up. Interestingly, 65 of the expected 95–190 patients had one or both outcome criteria recorded (See Table 5.4.1 for details of 43 of these cases). In the future, the new Quality Dashboard KPI 11 will automatically record the percentage of short-term conditions with outcomes.

5.4.2 Response of immune thrombocytopenia to treatment with intravenous immunoglobulin

Six patients had no increment in platelet count, of whom three patients had neither an increment in count nor resolution of bleeding. Two patients had an increment of platelet count that was insufficient to resolve bleeding. Patient 33 (highlighted in the table) had a series of platelet counts recorded and the platelet count normalised after 5 weeks.

5.4.3 Estimates of doses used in immune thrombocytopenia

The recommended dosing regimen was updated in the Second Edition Update to the Clinical Guidelines 2011.

Use 1 g/kg (0.8–1 g/kg for children) as a single infusion, to be repeated at a later date if platelet count has not responded

Examining the doses given in 307 cases that had infusions recorded in 2012, we identified that all of the 10 children had 0.8 g/kg as a single infusion. However, of the remaining 297 cases (all adults) only 30 had a single infusion of 1.0 g/kg. The rest had had 2 g/kg (to the nearest 0.5 g). Could it be that the prescribers are unaware of the new recommendations, or are the suggested doses actually inadequate?

Between January and December 2012, 232 patients were recorded in the database weighing 90 kg or more. 65 haematology patients with ITP weighed 90 kg or more, of whom only nine were dosed using LBW.

5.5 Conclusions

Haematology, and in particular ITP, accounts for a lot of the use of IVIg. We have few outcome data, but they are powerful in their message.

- Firstly, there is confusion over the definitions (acute, chronic, persistent)
- Then, confusion over dosing
  - Only 30 patients had the recommended 1 g/kg
  - Only six of 60 ITP patients >89 kg were dosed by LBW

The response rate of 85.5% is encouraging; we will further examine all 30 individuals who had the recommended dose to confirm that halving the historical dose has the same response rate.

Table 5.4.1 Outcomes recorded for acute immune thrombocytopenia

Patient	Date in 2012	Increment in platelet count	Resolution of bleeding	Platelet count ($x10^3$ per mm^3)
1	20/11	Yes	-	
2	08/11	No	-	
3	13/11	Yes	Yes	
4	30/11	Yes	-	
5	15/11	Yes	-	
6	06/11	Yes	Yes	
7	27/11	Yes	-	
8	01/11	Yes	No	
9	30/11	-	Yes	
10	19/11; 28/11	Yes	-	
11	06/11	Yes	Yes	
12	26/11	Yes	-	
13	20/11	Yes	-	
14	22/11	Yes	Yes	
15	27/11	-	-	8
16	14/11	Yes	Yes	
17	20/11	No	-	
18	27/11	No	No	
19	06/11	Yes	Yes	
20	07/11	-	-	<50
21	12/11	Yes	Yes	
22	12/11	Yes	No	
23	12/11	-	-	23
24	26/11	No	No	
25	27/11	Yes	Yes	
26	28/11	Yes	Yes	
27	27/11	Yes	-	
28	29/11	Yes	Yes	
29	21/11	Yes	Yes	
30	13/11	Yes	-	
31	10/11	Yes	-	
32	05/11	Yes	-	
33	26/11; 30/11; 04;12; 07/01	Yes	-	2; 5; 54; 262
34	20/11/2012	Yes	-	
35	28/11/2012	Yes	-	
36	16/11/2012	Yes	-	
37	19/11/2012	Yes	-	
38	16/11/2012	No	-	
39	14/11/2012	-	Yes	
40	09/11/2012	-	Yes	
41	16/11/2012	Yes	Yes	
42	10/11/2012	No	No	
43	16/11/2012	Yes	-	

CHAPTER 6

Immunology

Jennie Wimperis and Denise O'Shaughnessy

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).

6.1 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

Table 6.1 Use of immunoglobulin in immunology January–December 2012

Diagnosis	Usage (grams)
PIDs	732,113
Secondary antibody deficiencies	71,307
Specific antibody deficiency	11,846
Thymoma with immunodeficiency	815
HSCT in PIDs	785
Total	**816,866**

Figure 6.1 Selection criteria for primary immunodeficiency

Primary and secondary antibody deficiency states

Condition	S	L	Selection criteria	Outcomes for review	Dosing
Primary immunodeficiencies (associated with significant antibody defects)		●	A specific PID diagnosis must be established by a clinical immunologist	Outcome measures are not required	Initiate at 0.4–0.6 g/kg/month; dose requirements may increase and should be based on clinical outcome
Thymoma with immunodeficiency		●	Profound B cell depletion and/or significant antibody deficiency	Outcome measures are not required	Initiate at 0.4–0.6 g/kg/month; dose requirements may increase and should be based on clinical outcome
HSCT in primary immunodeficiencies		●	PID patients undergoing HSCT	Outcome measures are not required	Initiate at 0.4–0.6 g/kg/month; dose requirements may increase and should be based on clinical outcome
Specific antibody deficiency		●	Approval by a clinical immunologist, AND Severe, persistent, opportunistic or recurrent bacterial infections despite continuous oral antibiotic therapy for 3 months, AND Documented failure of serum antibody response to unconjugated pneumococcal or other poly-saccharide vaccine challenge	Outcome measures are not required	Initiate at 0.4–0.6 g/kg/month; dose requirements may increase and should be based on clinical outcome

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 31% of total use by volume, with PID collectively accounting for at least 89% of this. The efficacy of immunoglobulin in established PID is supported by a strong evidence base provided by retrospective surveys and controlled studies; it is therefore prioritised as Red by the National Demand Management Programme and in almost all cases treatment is lifelong.

6.2 Secondary immunodeficiency

Secondary antibody defects are found in a wide range of circumstances (in association with, malignant disease, chronic infections, protein-losing states, systemic inflammatory diseases, trauma and iatrogenic factors such as drugs including immunotherapy and splenectomy). However, significant infections associated with low antibody levels appear to be relatively uncommon in secondary deficiencies, with the exceptions of hypogammaglobulinaemia linked with haematological malignant diseases, e.g., chronic lymphocytic leukaemia (CLL), multiple myeloma and non-Hodgkin's lymphoma usually worsened by drug therapy with purine analogues and immunotherapy.

The selection criteria for secondary antibody deficiency

Underlying cause of hypogammaglobulinaemia cannot be reversed or reversal is contraindicated; OR Hypogammaglobulinaemia associated with NHL, CLL, 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

The *selection criteria* for IVIg to treat hypogammaglobulinaemia linked to haematological malignancy include the requirement **to document the failure of serum antibody response to pneumococcal 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 IVIg 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 years previously, it would be reasonable to re-vaccinate and assess the functional antibody response before immunoglobulin was prescribed.

6.2.1 Recommended dosing for secondary immunodeficiency

Use 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. Thus, for a 70-kg person, the monthly dose would be 28 grams per month or 7 grams weekly, which could be given subcutaneously (also .Ssee also Section 1.11 on dosing according to ideal body weight).

6.2.3 Outcomes for secondary immunodeficiencies in haematology and immunology

Chronic lymphocytic leukaemia

CLL is a malignancy of lymphocytes that often results in a deficiency in the production of immunoglobulin. This, together with disordered lymphocyte subtypes, may lead to an increased infection risk.

Table 6.2.3.1 Outcomes in chronic lymphocytic leukaemia (14 patients)

Patient	Date	Outcome	Outcome result (g/L)
1	16/05; 07/11	IgG	10.5; 12.5
2	16/11; 22/11	IgG	11.6; 10.2
3	29/06; 23/11	IgG	8.08; 8.78
4	05/06/2012	IgG	2.9
	19/11/2012	Reduction in infection	Yes
	03/12/2012	IgG	5.7
	05/12/2012	Admissions from infections	No
	05/12/2012	IgG	7.5
	05/12/2012	Reduction in infection	Yes
5	21/05/2012	IgG	2.7
	18/06/2012	IgG	2.7
	26/11/2012	IgG	<2.7
6	29/11/2012	IgG	8.2
	29/11/2012	Reduction in infection	None since IVIg started
7	27/11/2012	Condition – stabilised	No
8	27/11/2012	Condition – stabilised	No
9	07/11/2012	Reduction in number and/or severity of infective episodes	Recurrent infections
10	07/11/2012	Reduction in number and/or severity of infective episodes	Recurrent infections
11	02/11/2012	IgG	3.9
12	19/11/2012	Frequency of infections	Frequent
13	30/11/2012	Frequency of infections	Recurrent
14	21/11/2012	Increased IgG levels	No results required

From the November 2012 audit it can be noted that in the case of patient 4 the concept of measuring immunoglobulin levels and answering *Yes* to *a fall in infections* but *No* to *admission* is understandable, however, not identifying the number of infections will make future comparison difficult.

Multiple myeloma

Multiple myeloma is a cancer in which plasma cells produce abnormal amounts of one immunoglobulin (called paraprotein). Later in the disease or after chemotherapy the rest of the immunoglobulin proteins are reduced in number. In November 2012, only five outcomes were reported, two state "no results".

Table 6.2.3.2 Outcomes in multiple myeloma (four patients) November 2012

Date	Outcome	Outcome result
05/11/2012	Frequency of recurrent infections	No results required
06/11/2012	IgG levels	27**
27/11/2012	Reduction of infection	No
18/04/2012	Value at treatment onset	Frequent chest infections despite prophylaxis
13/11/2012	Marrow transplant	No results required

**Caution should be given to giving IVIg in multiple myeloma as the paraprotein increases the viscosity of the blood and this could be increased further, causing a stroke or ischaemic event in the heart.

Table 6.2.3.3 Outcomes of other secondary antibody deficiencies

Patient	Date	Outcome	Result (g/L)
1	30/08/2012	IgG	7.7
	06/11/2012	IgG	9.3
2	30/08/2012	IgG	9.8
	30/11/2012	IgG	10.3
3	25/01/2012	IgG	12.6
	14/11/2012	IgG	11.4
4	11/09/2012	IgG	6.0
	06/11/2012	IgG	7.3
	18/12/2012	IgG	7.5
5	30/08/2012	IgG	6.1
	26/11/2012	IgG	7.0
6	12/11/2012	IgG	7.60
7	17/08/2012	IgG	8.4
	08/11/2012	IgG	8.8
8	27/11/2012	Infections	Recurrent
9	13/06/2012	IgG	0.6
	25/07/2012	IgG	6.0
	24/09/2012	IgG	9.3
	01/11/2012	Number of days in hospital	0
	01/11/2012	Number of infections	0
	17/12/2012	IgG	9.5
10	03/01/2013	IgG level	7.0
	03/01/2013	Number of days in hospital	0
	03/01/2013	Number of infections	0
	12/02/2013	IgG level	6.0
11	06/07/2012	IgG	10.8
	02/11/2012	IgG	14.0
12	22/11/2012	IgG	1.4
13	03/10/2012	IgG	8.6
	28/11/2012	IgG	10.5
	09/11/2012	IgG	9.0
14	03/02/2012	Number of days in hospital	14
	03/02/2012	Number of infections	7
	16/03/2012	IgG	1.51
	09/11/2012	IgG	9.03
15	10/11/2012	IgG	5.5 g/L
16	27/11/2012	Infections	Reduced number
17	27/11/2012	Infections	Reduced number
18	27/11/2012	Infections	Reduced number
19	27/11/2012	Infections	Reduced number
20	31/10/2012	Number of infections	8
	09/11/2012	IgG	2.16
	21/11/2012	IgG	5.62
21	14/11/2012	IgG	1.1
	02/01/2013	IgG	5.9
22	02/11/2012	IgG	3.3
	12/02/2013	IgG	6.9
23	14/11/2012	Resolution of infection	NONE
24	19/11/2012	IgG	0.38
25	29/11/2012	Number of days in hospital	5
26	19/09/2012	IgG	12.1
	14/11/2012	IgG	11.7
27	23/11/2012	IgG	2.4
28	23/07/2012	IgG	9.3
	12/10/2012	IgG	10.0
	30/11/2012	IgG	13.3

Criticisms of these results are that number of infections pre- and post-treatment as well as obvious pre-treatment IVIg levels are not being recorded.

Secondary antibody deficiencies other than multiple myeloma and chronic lymphocytic leukaemia

Secondary antibody deficiencies may also occur in other haematological malignancies, usually as a result of treatment with chemotherapy, immunotherapy or following HSC. Such patients should fulfill the selection criteria and have outcomes recorded.

6.3 Dosing in haematology and haemato-oncology

Between January and December 2012, 232 patients weighing 90 kg or more were recorded in the database. In *immuno-haematology*, three patients with myeloma were not dosed correctly. Firstly, LBW was not used and the incorrect dose, namely 2 g/kg, was used. This could be hazardous if there was also a significant paraprotein causing hyperviscosity, leading to stroke or heart problems. CLL and secondary immunodeficiencies were dosed at 0.4 g/kg/month, as recommended.

6.4 Conclusions

The dataset on the database will need some re-modelling to ensure appropriate information is collected. However, the data we have do not convincingly show a positive response rate (compared with the data in ITP). The information that we have seen indicates, certainly in myeloma, that inappropriate and possibly hazardous prescribing is taking place. It seems that it was probably wrong to have changed the prioritisation from Grey to Blue, and this will be revisited in the next revision of the Clinical Guidelines.

CHAPTER 7

The National Database

Mark Foster

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. Over time, support has been given to procurement in order to support commissioning and enable batch tracking and other safety-related issues such as recalls.

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 thrombotic thrombocytopenic purpura, and within 28 countries in Europe they manage a Haemophilia Adverse Events Surveillance System, which is now being tried in Canada and Australia. Their Haemophilia Clinical System has recently been installed in various sites across Iran.

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, including SQL Server (2008 R2 version), Reporting Services and ASP.NET. The database has both a data entry portal and an information service portal.

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, Panels' decisions, diagnosis and indication of each treatment episode.

7.2.1 Infusion entries

Patient infusions record batch number, allowing the system to be used for patient safety (batch tracking). There are now New Infusion and Infusion Returns Tabs with the ability to add multiple batches per infusion and an option to differentiate product issues and actual infusions.

7.2.2 Short-term treatment episode

It is now possible to copy a previous treatment episode or to copy data from a previous episode into a new treatment episode, which eliminates the need for repeated data entry.

7.2.3 Efficacy measures

Previously, one had to search for efficacy measurement to be used, but now there is the ability to directly enter a new measure, which reduces data entry time.

7.2.4 User interface developments

In response to user comments there are some developments such as a session timeout icon, which warns when the system is about to log-out and offers the ability to continue the session.

There are also calendars for dates with the ability to select dates from a pop-up calendar, thus reducing the chance of data entry errors and speeding up data entry.

7.2.5 Quality Dashboard measures

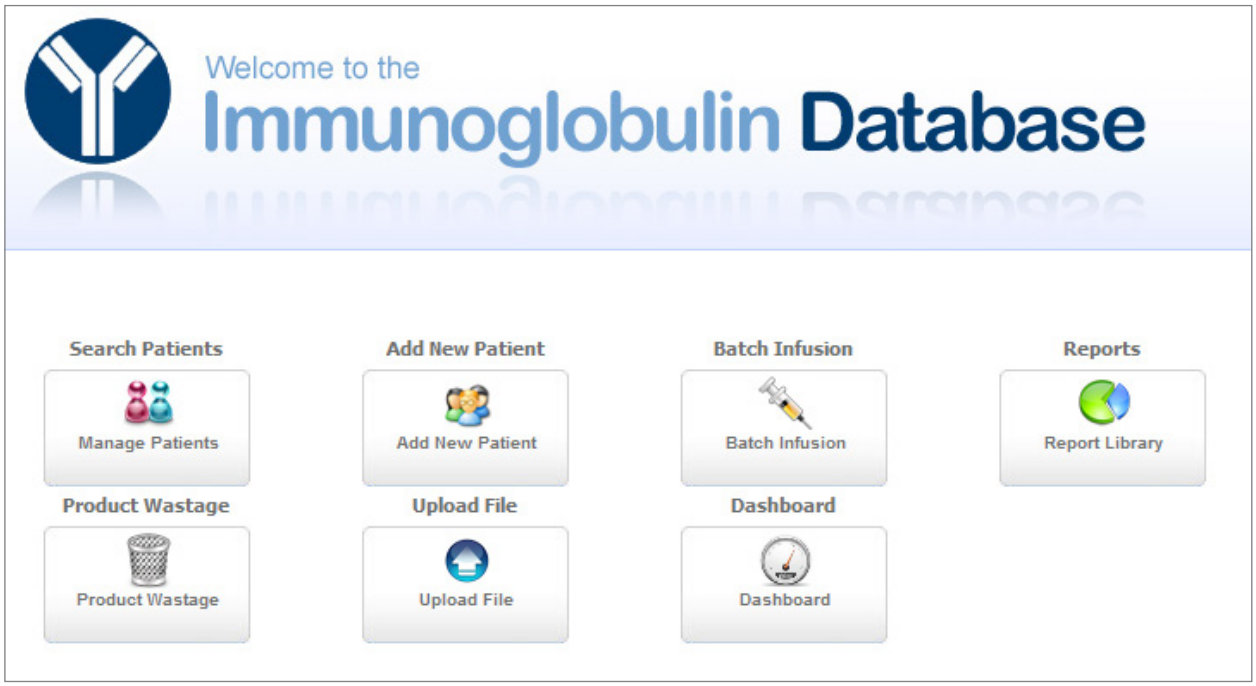
To assist in the delivery of information, additional data items have been added to the database:

Outcome measures have been defined with a written Quality Dashboard guide (available on www.ivig.nhs.uk). Trust-based training on the dashboards is also available.

7.2.6 Automation of upload forms

Immunoglobulin request, infusion entries and follow-up forms.

Figure 7.2.6.1 Request form



Select the upload button and the upload page will appear along with instructions.

Figure 7.2.6.2 The intravenous immunoglobulin upload page

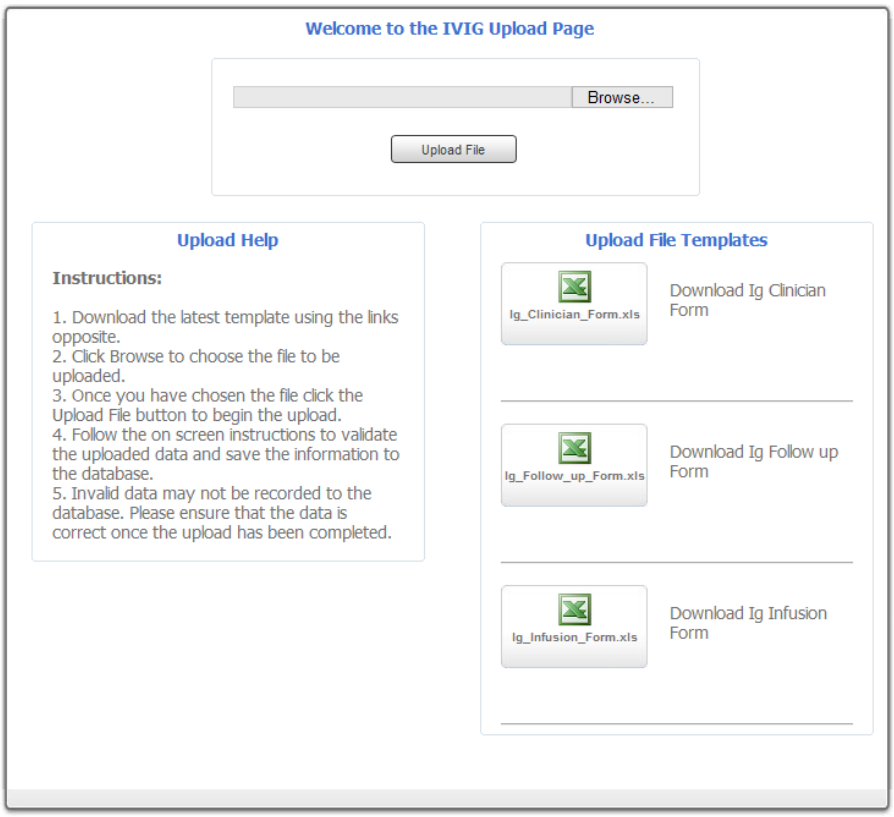


Figure 7.2.6.3 Patient data need to be validated before they are recorded on the database

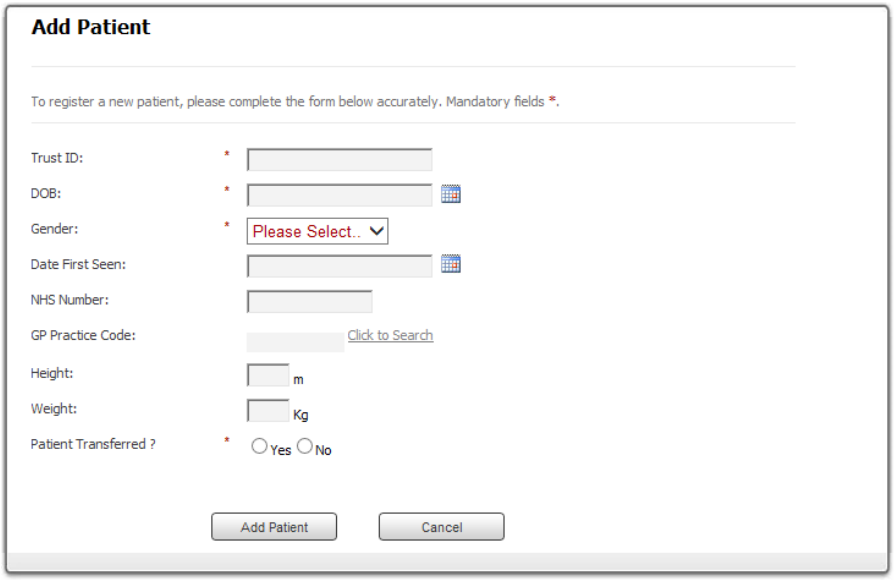
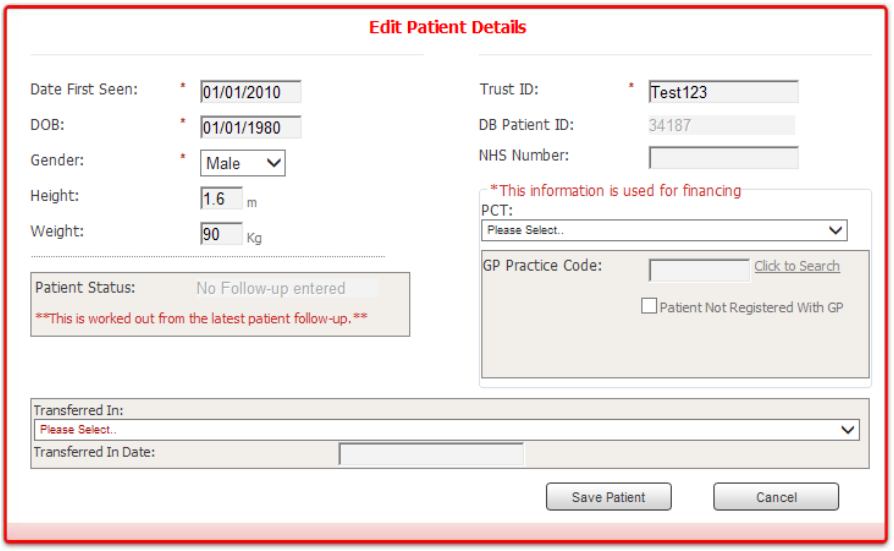


Figure 7.2.6.4 Patient details can be edited



7.2.7 Help desk

MDSAS offer IT support and have the ability to remotely connect to the user's PC. They can also receive suggestions to improve the database functionality and gather suggestions for the Demand Management Plan. MDSAS also offer training on the database; training can take place at their offices in Manchester, onsite at the user's location or via a remote web session using WebEx technology. They also deal with any shortage or recall issues. Contact details: support@mdsas.com, Tel. 0161 277 7917.

7.3 Data held

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

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

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.

7.4 The database architecture

The real benefit of the database is that the SQL server (2008 R2 version) 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.

Figure 7.3 Data entry

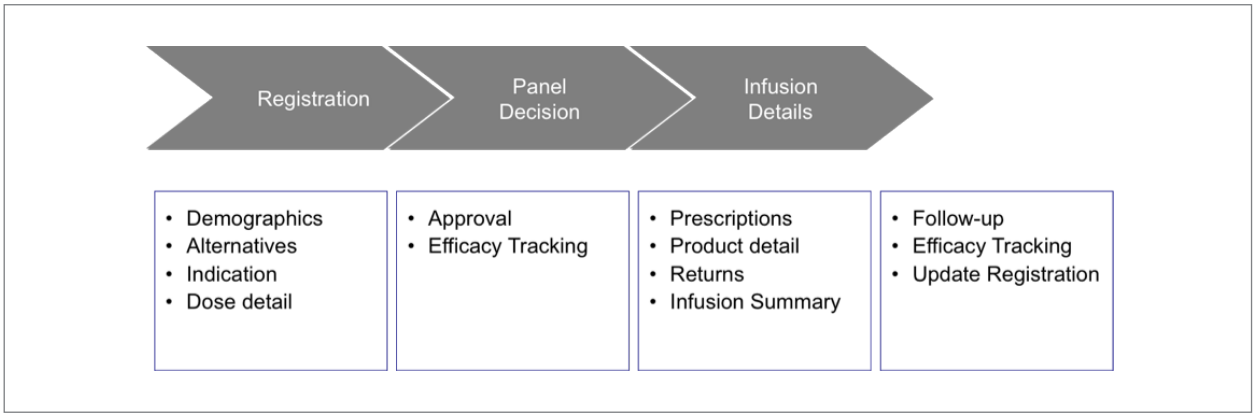


Figure 7.4 Architecture of the database

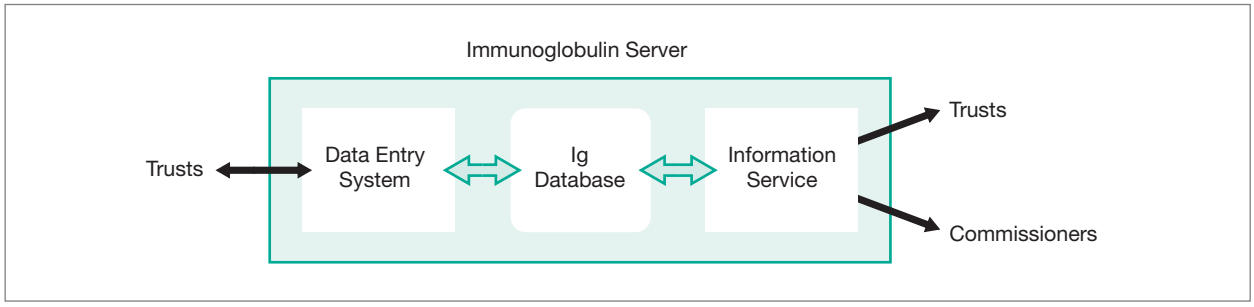


Figure 7.5 Database reports for local Trusts

7.5 Reports available

Many of the reports required by Trusts over the past few years have become automatic. Currently, there are 14 automatic reports available to Trusts (see Figure 7.5). Reports are provided for each centre specifically to analyse their data and aid in the management of their patients. Reports include 'Monthly net usage', List of treated patients', and 'Manage follow-ups'.

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 at 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. The data available through this service are anonymised, real time, single access with the ability to export data locally for analysis (Excel and PDF).

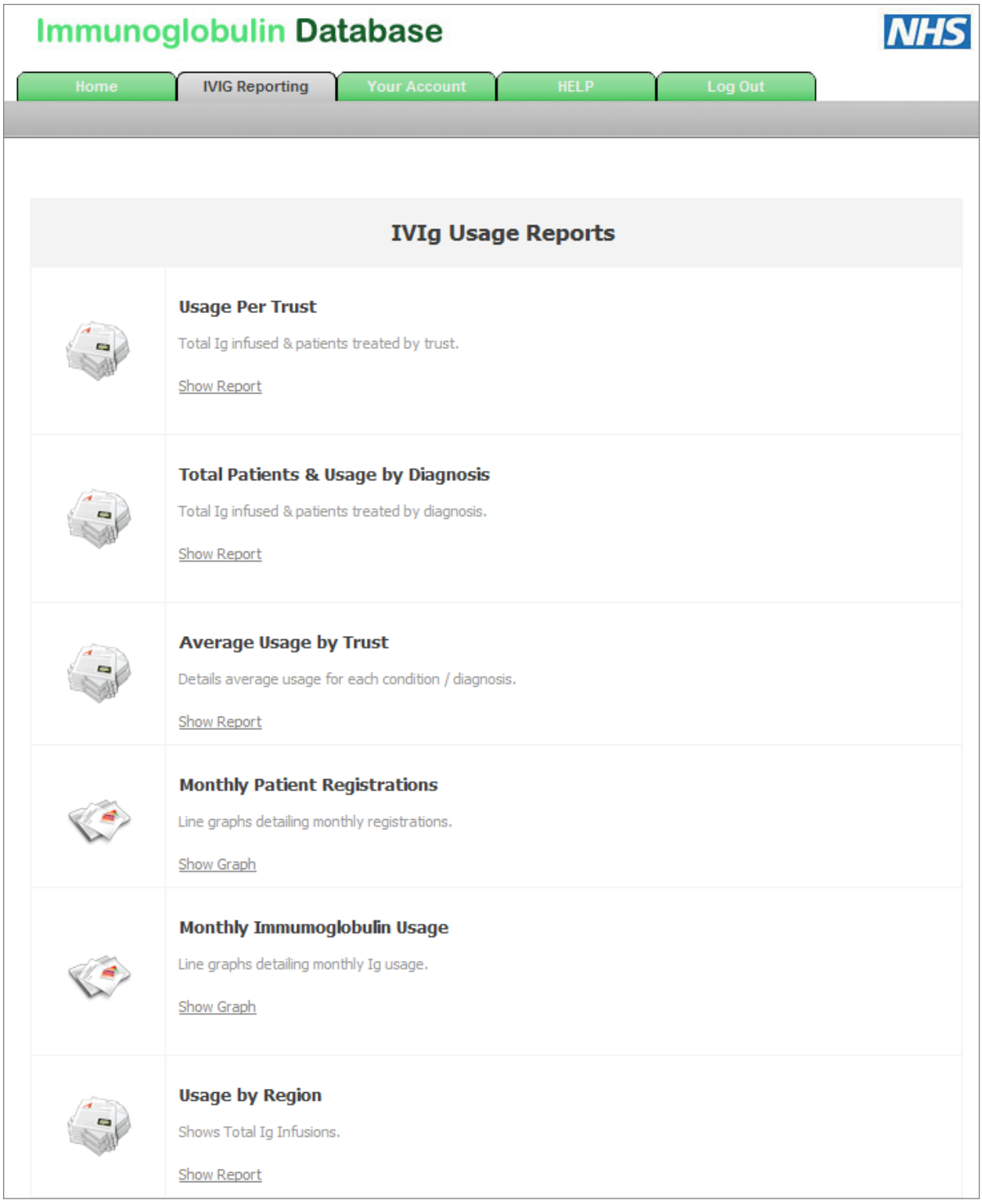
See www.mdsas.nhs.uk/Iginfo (only on the NHS network)

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-/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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