Clinical Commissioning Policy for the use of therapeutic immunoglobulin (Ig) England (2025)

Publication date: March 2025 version number: 2.0

Commissioning position

Summary

Therapeutic immunoglobulin is recommended to be available as a routinely commissioned treatment option for the indications within the criteria set out in this document.

Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Executive summary

Plain language summary

About the treatment

Immunoglobulin replacement therapy is a blood-based treatment. Immunoglobulin is made from plasma separated out from donated blood. During manufacture everything except a type of immunoglobulin called immunoglobulin G (IgG) is removed from the plasma. The immunoglobulin contains IgG antibodies that help to fight infection. Therapeutic immunoglobulin is used when the immune system is either not making antibodies, not making enough antibodies or the ones they are making do not work properly. IgG has other effects too, so it is not just used for people with immune deficiency. You might hear about immunoglobulin being used in some people with other immune (autoimmune) problems. Immunoglobulin can be given intravenously (into a vein) or subcutaneously (under the skin).

What we have decided

NHS England has carefully reviewed the evidence to treat the indications within this policy (detailed in appendix A) with therapeutic immunoglobulin. We have concluded that there is enough evidence to make the treatment available at this time.

Indications that have been considered as part of the evidence review and determined to be "not routinely commissioned" are included in Appendix B. This list is not exhaustive and

therefore any indication not explicitly detailed within this policy is considered to be “not routinely commissioned”.

Links and updates to other policies

This document updates and replaces:

- Commissioning Criteria Policy for the use of therapeutic immunoglobulin (Ig) England, 2024
- Commissioning Criteria Policy for the use of therapeutic immunoglobulin (Ig) England, 2021
- Updated Commissioning Criteria for the use of therapeutic immunoglobulin (Ig) in immunology, haematology, neurology and infectious diseases in England November 2019 v1.4
- Department of Health and Social Care. Clinical Guidelines for Immunoglobulin Use (2nd edition update; July 2011): *dh_131107.pdf (publishing.service.gov.uk)*

Committee discussion

The Clinical Priorities Advisory Group reviewed the evidence and recommended the policy proposition cpag-commissioning-criteria-policy-for-therapeutic-immunoglobulin-2021.pdf (england.nhs.uk).

The condition

The policy covers multiple indications, detailed in Appendix A, for immunology, haematology, neurology, infectious diseases and other specialities.

Evidence summary

The updated commissioning criteria for the use of therapeutic immunoglobulin (Ig) 2024 describes all conditions for which Ig is commissioned and provides the detail around the role, dose and place of Ig in the treatment pathway for individual indications alongside possible alternative treatment options for use of Ig in both adults and children. This policy was built on a review of the literature including detailed scoping reviews undertaken by Cochrane Response (2020) updated with a further evidence review, expert opinion and multi-organisational input. The commissioning criteria were developed by the Ig Expert Working Group following wide consultation with specialty experts, relevant scientific societies and the NHS England Specialised Commissioning Clinical Reference Groups (CRGs).

Implementation

The Immunology and Allergy CRG, in conjunction with the Ig Oversight Group, will review this document as per NHS England policy review process or when there is a significant change in evidence. Recommendations on Ig dose and outcomes are based on a combination of available evidence and expert opinion.

Criteria

The following commissioning criteria set out all the indications recognised by NHS England as immunoglobulin responsive based on a systematic literature review. These were previously categorised in a hierarchy of importance in a Demand Management Plan as follows:

- Red indications - conditions for which Ig treatment is considered the highest priority because of a risk to life without treatment
- Blue indications - conditions for which there is a reasonable evidence base for the use of Ig but other treatment options are available
- Grey indications - immune-mediated disorders with limited or little/no evidence
- Indications for which immunoglobulin is not recommended.

With this policy update, the colour coding system is removed and indications are instead categorised as follows:

- Routinely commissioned indications – see Appendix A
- Not routinely commissioned indications - see Appendix B

The Demand Management Plan will be superseded by the Immunoglobulin Management Plan once published.

Application process:
A completed (e-) referral form is required for use of Ig in ALL indications to ensure immunoglobulin stewardship and oversight by the Sub-Regional Immunoglobulin Assessment panels (SRIAP). For the purpose of this document, the term 'panel' refers to SRIAP.

Local policy should be followed for all applications – urgent, non-urgent and out-of-hours. Consideration needs to be given to the requirement of panel approval and oversight as follows:

- Prior panel approval required – NO
  Treatment can proceed without prior panel approval. Submit a completed application form for retrospective review by the panel
- Prior panel approval required – YES
  Treatment should not proceed without prior panel approval. For urgent approvals in hours – a process will need to be in place on the agreed pathway for approval. For those cases that require out of hours approval, panels will have local processes in place, to ensure robust governance for retrospective panel approval. Where local expertise is not available, panels will also be able to advise on dose optimisation and trials of treatment withdrawal. If prior panel approval is not possible, for example in an urgent case, retrospective approval must be sought.

All referrals should be carried out via the Medicine Database Solutions and Services (MDSAS) National Immunoglobulin Database e-referral platform. Immunoglobulin data will be reviewed and findings reported to the Immunoglobulin Oversight Group and relevant CRG to inform any recommendations on changes in policy. If available, MDSAS data will be analysed for ethnic groups to ensure any possible inequality in access is identified.

Indications or clinical scenarios not listed in appendix A of this document are not routinely commissioned and require an Individual Funding Request (IFR) application to be submitted to the NHS England IFR system, should the clinician consider there is an arguable case for the IFR policy criteria to be met. If the IFR is approved, the diagnosis and locally agreed efficacy criteria are recorded on the immunoglobulin database.

More information on IFRs in general is available here: *NHS commissioning » Key documents (england.nhs.uk)*.

Dosing in adult patients:

In keeping with the advice included in previous iterations of these guidelines and to ensure cost-effective use and minimise dose-dependent adverse effects, Ig prescribing will be based

on ideal body weight dosing (IBW)[1,2] with doses subsequently titrated according to clinically meaningful response (immunomodulation) or Ig trough level (immunoreplacement).

For pregnant patients, IBW based on booking weight should be used.

Optimal use of vials:

The following principles should apply:

- Calculate total treatment course and round down to the nearest dose which can be administered using whole vials.
- Note in an adult patient part vials should never be used. Where the dose is split over multiple days, daily dose may differ.

Example:

- Male patient - Height 170cm; Actual Body Weight (ABW) 84kg
- Diagnosed with Guillain-Barre syndrome and meets criteria for IVIg, plan to receive 2g/kg based on IBW to be given over 5 days as per guidelines.

Calculation of IBW (male)	IBW = 50 + (0.91 x [Height(cm) – 152.4]) = 50 + (0.91 x [170-152.4]) = 66kg
Calculation of total dose	2 x 66kg = 132g → rounded down to nearest 5g vial = 130g
Split total dose over 5 days	• Day 1: 30g • Day 2: 20g • Day 3: 30g • Day 4: 20g • Day 5: 30g

Dosing in paediatric patients

In all paediatric patients Ig dosing should be based on IBW. ABW should not be used. In patients whose ABW is < IBW, IBW should still be used to ensure appropriate dosing and preventing underdosing.

The recommended methods suggested by the Royal College of Paediatrics and Child Health (RCPCH) and Neonatal and Paediatric Pharmacy Group (NPPG) to calculate IBW, include the use of the table at the back of the British National Formulary for Children (BNFC)[3] [Approximate Conversions and Units | About | BNFC | NICE] or methods suggested in the

[1] Chow S et al. Transfusion and apheresis science: official journal of the World Apheresis Association : official journal of the European Society for Haemapheresis 2012;46:349-52.
[2] Grindeland JW et al. Ann Pharmacotherapy. 2020;54:205-212
[3] MedicinesComplete. *BNF for Children*. Available from: *British National Formulary for Children | MedicinesComplete*

UKMI document[4]. In the future, the RCPCH and NPPG aim to work on a standardised approach in conjunction with the BNFC.

Where possible doses should be rounded down to the nearest vial size to prevent wastage.

[4] Specialist Pharmacy Service. *UKMI NPPG - drug dosing in childhood obesity May 2021*. Available from: *How should medicines be dosed in children who are obese? – SPS - Specialist Pharmacy Service – The first stop for professional medicines advice*

Appendix A

Use of Immunoglobulin in Immunology

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database)	Prior panel approval required
Haematopoeitic stem cell transplantation (HSCT) in primary immunodeficiencies (PID) / inborn errors of immunity (IEI) – long term use	PID (IEI) patients undergoing HSCT	None	Ig is the only definitive treatment for antibody deficiency	Initiate at 0.4 – 0.6 g/kg/month; dosing requirements may increase and should be based on clinical outcome. Because of the possibility of B-cell reconstitution, evaluation of immune function (off Ig) is required at 2 years	• Raised trough IgG level compared to baseline	No
Primary immunodeficiencies (PID) / Inborn errors of immunity (IEI) associated with significant antibody defects (excluding specific antibody deficiency) – long term use	A specific PID (IEI) diagnosis must be established by a clinical immunologist In newly diagnosed patients with PID (IEI) with no significant burden of infection, the decision to start Ig replacement should be based on an MDT discussion	None	Ig is the only definitive treatment for antibody deficiency	Initiate at 0.4 – 0.6 g/kg/month; dose requirements may increase and should be based on clinical outcome	• Raised trough IgG level compared to baseline • Reduction in number of infections • Reduction in number of treatment courses of antibiotics • Reduction in number of days in hospital	No
Specific antibody deficiency – long term use	• Diagnosis by a clinical immunologist • Severe, persistent, opportunistic or recurrent bacterial infections despite continuous oral antibiotic therapy for 6 months • Documented failure of serum antibody response to unconjugated pneumococcal or other polysaccharide vaccine challenge	None, but see comments in column of position of Ig	Many patients with specific antibody deficiency will achieve protection from bacterial infections with prolonged antibiotic prophylaxis. Ig is reserved for those patients in whom antibiotic prophylaxis proves to be ineffective	Initiate trial at 0.4 – 0.6 g/kg/month for a period of 6 - 12 months; Long-term maintenance treatment should be based on clear evidence of benefit from this trial and require panel approval. Dose requirements may increase and should be based on clinical outcome	6 monthly reviews (compared to baseline) • Raised trough IgG level • Reduction in number of infections • Reduction in number of treatment courses of antibiotics • Reduction in number of days in hospital	Yes
Secondary antibody deficiency – long term use	• Underlying cause of hypogammaglobinaemia cannot be reversed, or reversal is contraindicated; **OR** Hypogammaglobinaemia associated with drugs including emerging bispecifics, therapeutic monoclonals targeted at B cells and plasma cells (rituximab and other anti-CD20, CD19 agents, daratumumab etc) post-HSCT*, NHL, CLL, MM or other relevant B-cell malignancy confirmed by haematologist **AND** • (a) Recurrent or severe bacterial infection despite continuous oral antibiotic therapy for 6 months	None, but see comments in column of position of Ig	Many patients with secondary antibody deficiency will achieve protection from bacterial infections with prolonged antibiotic prophylaxis. Ig is reserved for those patients in whom antibiotic prophylaxis proves to be ineffective Since infection susceptibility in patients with haematological malignancies is frequently multifactorial, the reduction in overall burden of infections with long term Ig replacement may be variable. For this reason, annual reviews of treatment are	0.4 – 0.6 g/kg/month modified to achieve an IgG trough level of at least the lower limit of the age-specific serum IgG reference range	6 monthly reviews (compared to baseline) • Raised trough IgG level • Reduction in number of infections • Reduction in number of treatment courses of antibiotics • Reduction in number of days in hospital	Yes

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database)	Prior panel approval required
	(b) IgG <4 g/L* (excluding paraprotein) (c) Documented failure of serum antibody response to unconjugated pneumococcal or other polysaccharide vaccine challenge **Note:** It is recognised that vaccine challenge may be of limited value in patients with very low serum IgG (< 3g/L). In these circumstances, vaccine challenge may be omitted if it is considered inappropriate clinically • It is acknowledged that not all of criteria (a) – (c) will need to be fulfilled for an individual patient * IgG < 4g/L – not specific for paediatric patients • In patients developing **hypogammaglobinaemia associated with B-cell aplasia as a consequence of Chimeric Antigen Receptor – T cell therapy (CAR-T cells)** targeted against B cell or plasma cell antigens, the prophylactic use of Ig in the absence of a burden of severe infections and vaccine challenge may be appropriate • Use of **Ig post-CAR-T therapy in B-cell acute lymphoblastic leukaemia (B-ALL)** Because of the severity of B-cell aplasia and the longer time required for reconstitution, it is anticipated that virtually all patients (children and adults) with B-ALL will initially require Ig replacement following CAR-T cell therapy. As with the use of Ig post-CAR-T therapy in B-cell lymphoma, continued use of IVIg should be reviewed at regular intervals based on B-cell recovery, serum immunoglobulins and burden of infection • Use of **Ig post-CAR-T cell therapy in B-cell lymphoma**		recommended. In patients with seasonal preponderance of infections, it may be appropriate to consider temporary cessation of Ig in the summer			

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database)	Prior panel approval required
	The need for Ig replacement in patients receiving CAR-T cell therapy for B-cell lymphoma is variable ranging between 31% to 64% in published studies[5] highlighting faster B-cell recovery in this group in contrast to patients with B-cell acute lymphoblastic leukaemia • Use of Ig at inception of bi-specific antibody treatment in patients with myeloma and B-cell lymphoma Many patients in these disease groups will have a low serum IgG at baseline due to previous chemo-immunotherapy, including CD20 and CD38 depleting agents. The prophylactic use of Ig would be appropriate in patients with a serum IgG of < 4g/l at the time of commencement of a bi-specific antibody. *There is variable practice regarding Ig replacement in adult patients with hypogammaglobinaemia post-HSCT for haematological malignancy. The American Society for Blood and Marrow transplantation and the Canadian Blood and Marrow Transplant group have recently stated as follows: 'Don't routinely give Ig replacement to adult HSCT recipients in the absence of recurrent infections regardless of the IgG level'[6]. It is possible that patients with recurrent sino-pulmonary infections on a background of chronic pulmonary GVHD and hypogammaglobinaemia may benefit if they fulfil the criteria for secondary antibody deficiency.					
Thymoma with immunodeficiency – long term use	• Profound B cell depletion **AND/OR** • significant antibody deficiency	None	Ig is the only definitive treatment for antibody deficiency	Initiate at 0.4 – 0.6 g/kg/month; dose requirements may increase and should be based on clinical outcome	• Raised through IgG level compared to baseline • Reduction in number of infections • Reduction in number of treatment courses of antibiotics • Reduction in number of days in hospital.	No

[5] Locke et al. Lancet Oncol 2020; 20:31-42, Wang et al NEJM 2020;382:1331-42, Schuster et al NEJM 2017;377:2545-54

[6] Bhella et al. Biol Blood Marrow Transplant 2018;24:909-13

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database)	Prior panel approval required
Acquired red cell aplasia associated with chronic parvovirus B19 infection – short term use	• Parvovirus B19 infection confirmed by PCR, **AND** • Evidence of high viral load, usually above 10^9 IU/ml In cases of foetal hydrops: Likely to be associated with parvovirus B19	Infection other than parvovirus B19	Ig is an adjunct to transfusion. Chronic parvovirus infection generally occurs on a background of immunosuppressive therapy, primary or HIV-related immunodeficiency and may resolve with a reduction in immunosuppression. Acute parvovirus infection associated with transient aplastic crisis requires urgent transfusion rather than Ig	1.0 – 1.2 g/kg in divided doses. This may be repeated on relapse and for a 2nd relapse	• Rise in haemoglobin • Rise in reticulocyte count • Transfusion independence	Yes
Alloimmune thrombocytopenia (foetal-maternal/neonatal) **Foetal-maternal alloimmune thrombocytopenia (FMAIT)**	**Prevention or treatment of foetal thrombocytopenia or haemorrhage:** • Clinical suspicion of FMAIT in the antenatal setting based on clinical and laboratory features: Unexplained previous foetal death, haemorrhage, hydrocephalus or thrombocytopenia or known affected sibling, **AND** • The presence of maternal platelet-specific alloantibodies directed against current paternal antigens (most commonly HPA-1a or HPA-5b).	None	**Maternal:** Ig is the primary treatment and sometimes combined with steroids	**Maternal:** The dose of Ig and the gestation at which to start treatment should be tailored according to the history of NAIT in earlier pregnancies. A patient with a low-risk obstetric history (where the previous infant had thrombocytopenia but no intracranial haemorrhage) should be commenced on 0.5-1.0 g/kg/week from 20 weeks' gestation. In high-risk pregnancies, treatment should commence from as early as 12 weeks' gestation with a dose of 1 g/kg/week (where the previous foetus or neonate had intracranial haemorrhage after 28 weeks' gestation), or 2 g/kg/week (where the previous foetus or neonate had intracranial haemorrhage before 28 weeks)[7,8,9,10,11] The weight used to calculate the dose will be the mother's weight at booking.	• Successful outcome of pregnancy i.e. no severe haemorrhage such as intracranial haemorrhage • Platelet count above $50x10^9$/L at time of delivery • Increment in neonatal platelet count	Yes – for FMAIT

[7] Pacheco et al. Fetal and neonatal alloimmune thrombocytopenia. Obst & Gyn 2011; 118: 1157-1163
[8] Peterson et al. Neonatal alloimmune thrombocytopenia: pathogenesis, diagnosis and management. Br J Haematol. 2013; 161: 3-14
[9] Regan et al. Prenatal Management of Pregnancies at Risk of Fetal Neonatal Alloimmune Thrombocytopenia (FNAIT). BJOG 2019; 126: 173-185.
[10] Lieberman et al. Fetal and neonatal alloimmune thrombocytopenia: recommendations for evidence-based practice, an international approach. Br J Haematol. 2019; 185: 549-562
[11] Winkelhorst et al. Fetal and neonatal alloimmune thrombocytopenia: evidence based antenatal and postnatal management strategies. Exp Rev Hematol 2017; 10: 729-737

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database)	Prior panel approval required
Neonatal alloimmune thrombocytopenia (NAIT)	**Prevention or treatment of neonatal thrombocytopenia or haemorrhage:** Clinical suspicion of NAIT in the neonatal setting based on clinical features suggestive of bleeding e.g. purpura and/or bruising and/or more serious bleeding and a low platelet count		**Neonatal:** First line treatment is with HPA-1a/5b – negative platelets which covers 95% of HPA incompatibilities responsible for NAIT. Platelet transfusion is effective immediately. In contrast, Ig is a second line treatment and works in approximately 75% of cases. It has a delayed effect over 24 – 48 hours. Ig may be of value if there is prolonged thrombocytopenia with the aim of minimising the need for platelet transfusions	**Neonatal:** 1 g/kg; a 2nd dose may be required if thrombocytopenia persists In the rare event of retreatment after the 2nd dose, approval from SRIAPs should be sought.		No – for NAIT
Autoimmune haemolytic anaemia (AHA, including Evans syndrome) – short term use	• Symptomatic or severe anaemia, except in patients with co-morbidities), **AND** • Refractory to conventional treatment with corticosteroids, **OR** Corticosteroids contra-indicated, **OR** As a temporising measure prior to splenectomy **AHA in pregnancy:** • Pregnant women with warm AHA refractory to corticosteroids **OR** with evidence of foetal anaemia. • Neonates of mothers with AHA who have evidence of haemolysis **AND** rising bilirubin despite intensive phototherapy	None	Ig is reserved for patients unresponsive to steroids or where steroids are contra-indicated	1 - 2 g/kg in 2 to 5 divided doses. This may be repeated on relapse and for a 2nd relapse. The weight used to calculate the dose will be the mother's weight at booking.	• Rise in haemoglobin • Reduction in haemolysis markers (bilirubin, lactate dehydrogenase) • Transfusion independence	No – for treatment of acute episodes Yes – for repeat courses
Coagulation factor inhibitor disorder (alloantibodies and autoantibodies) – Acquired von Willebrand disease (VWD) – short term use	• Life- or limb-threatening haemorrhage, **AND** • Failure to respond to other treatments, **AND/OR** • Prior to invasive procedure Treatment directed by the haemophilia centre at which the patient is registered	Acquired VWD associated with IgM monoclonal gammopathy	Ig is a therapeutic option in acquired VWD, particularly in cases associated with an IgG monoclonal gammopathy alongside other therapies – plasmapheresis, desmopressin, VWF-containing concentrates and recombinant Factor VII	Either 0.4 g/kg for 5 days or 1 g/kg for 2 days	• Rise of factor level • Resolution of bleeding • Reduction in number of bleeding episodes	Yes If prior approval is not possible then treatment should proceed, and retrospective approval should be sought

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database)	Prior panel approval required
Haemolytic disease of the newborn – short term use	Adjunct to continuous multiple phototherapy in cases of Rhesus haemolytic disease, or ABO haemolytic disease: • Rising bilirubin despite intensive phototherapy (see NICE CG98[12]) Prevention of foetal haemolytic disease in women with a previous history of this and confirmed red cell antibodies to current paternal or foetal antigens, to delay the need for intrauterine transfusions	None	Ig is an adjunct to phototherapy See NICE CG98[12]	0.5 g/kg over 4 hours	• Reduction in bilirubin level • Reduced need for exchange transfusion • Long term morbidity	No
Haemophagocytic syndrome (Haemophagocytic lymphohistiocytosis or HLH) – short term use	Diagnosis by a consultant haematologist or rheumatologist based on H-score* including: • pyrexia • organomegaly • multiple lineage cytopenias • triglycerides • fibrinogen • ferritin • serum aspartate aminotransferase • haemophagocytosis on bone marrow biopsy • long-term pharmacological immunosuppression *A score >169 is 93% sensitive and 86% specific for HLH	None	Other therapies include IL-1 receptor inhibition (anakinra) See NHS England Clinical Commissioning Policy[13]	2 g/kg in 2 - 5 divided doses alongside corticosteroids (dexamethasone) as per HLH protocol. This may be repeated on relapse and for a 2nd relapse, where alternative therapies are not indicated or are contraindicated	• Improvement of cytopenias • Improvement of HLH markers – Ferritin/soluble CD25 • Survival	Yes

[12] National Institute for Health and Care Excellence. Jaundice in newborn babies under 28 days. Clinical guideline [CG98]. Available from: https://www.nice.org.uk/guidance/cg98

[13] National Health Service. Clinical Commissioning Policy: Anakinra for Haemophagocytic Lymphohistiocytosis (HLH) for adults and children in all ages [210701P] (1924). Available from: https://www.england.nhs.uk/publication/anakinra-for-haemophagocytic-lymphohistiocytosis-for-adults-and-children-in-all-ages

<table>
<tr><th>Indications</th><th>Eligibility criteria</th><th>Exclusion criteria</th><th>Position of immunoglobulin, taking into account alternative therapies</th><th>Recommended dose</th><th>Outcome measures (to be recorded on the national immunoglobulin database)</th><th>Prior panel approval required</th></tr>
<tr>
<td>Immune Thrombocytopenic Purpura (ITP)
- short term use</td>
<td>Ig generally used in only 4 situations in ITP:
1) Life-threatening bleeding
2) Where an immediate increase in platelet count is required e.g. before emergency surgery or other procedure (see table for target platelet counts)
3) Where the patient is refractory to all other treatment to maintain the platelet count at a level to prevent haemorrhage. It may need to be given every 2-3 weeks during a period where other second line treatments are being tried
4) Moderate severity bleeding in patient at higher risk of subsequent severe bleed. Patients with mucosal bleeding or bleeding from multiple sites or a previous history of severe bleeding are at higher risk of a subsequent severe bleed

These eligibility criteria are also applicable when considering the short term use of Ig in patients with chronic ITP experiencing acute bleeding or requiring invasive procedures.

Bleeding severity as defined by the “Updated international consensus report on the investigation and management of primary immune thrombocytopenia 2019”[14]

Target platelet counts for surgery*
<table>
<tr><th>Procedure</th><th>Platelet count</th></tr>
<tr><td>Dentistry</td><td>>20</td></tr>
<tr><td>Simple dental extraction</td><td>>30</td></tr>
<tr><td>Complex dental extraction</td><td>>50</td></tr>
<tr><td>Regional dental block</td><td>>30</td></tr>
<tr><td>Minor surgery</td><td>>50</td></tr>
<tr><td>Major surgery</td><td>>80</td></tr>
<tr><td>Major neurosurgery</td><td>>100</td></tr>
</table>
</td>
<td>None</td>
<td>Thrombopoietin mimetics may be useful substitutes in some patients (in situation 3) or as an adjunct in the other situations</td>
<td>Adults: 1 g/kg as a single infusion.
A 2nd dose may be required after 24 – 48 hours, if severe or life-threatening bleeding:
e.g. intracranial bleed or pulmonary haemorrhage.
Otherwise, if a haemostatically adequate platelet count is not achieved a 2nd dose (1 g/kg) may be considered at day 5- 7

Children: 0.8 – 1.0 g/kg as a single infusion.
A 2nd dose may be required after 24 – 48 hours, if severe or life-threatening bleeding, such as an intracranial bleed or pulmonary haemorrhage.
Otherwise, if a haemostatically adequate platelet count is not achieved a 2nd dose (1 g/kg) may be considered at day 5 - 7</td>
<td>• Increase in platelet count
• Resolution of bleeding
• Reduction in number of bleeding complications</td>
<td>No - for acute ITP; the use of a 2nd dose should be discussed with the designated panel lead.

Yes – for maintenance treatment</td>
</tr>
</table>

[14] Provan et al. Blood Adv (2019) 3 (22): 3780–3817

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database)	Prior panel approval required
	ITP in pregnancy: Maintenance treatment with Ig may be required antenatally to maintain platelets above $20x10^9$/l and/or to increase platelets to over 50 $x10^9$/l for delivery in women with symptomatic persistent or chronic ITP where other treatments have failed *There is controversy regarding the target platelet count for epidural anaesthesia[15]. There are no data to support a minimum platelet count and each case must be carefully considered. In the absence of bruising, bleeding history, and anticoagulation and if the INR, APTT and fibrinogen levels are normal, a small consensus of obstetric anaesthetists agree no changes to normal practice are needed until the platelet count drops below 50.					
Covid vaccine-induced thrombosis and thrombocytopenia (VITT) or a syndrome of anti-PF4 (platelet factor 4) associated immune-mediated thrombosis and thrombocytopenia	Confirmed/Probable diagnosis of VITT made by a haematologist conforming to up to date guidance from the Expert Haematology Panel - See British Society for Haematology website for details.	Isolated thrombocytopenia or thrombosis: • Reduced platelet count without thrombosis with D-dimer at or near normal and normal fibrinogen. • Thrombosis with normal platelet count and D dimer	Treatment with intravenous Ig irrespective of the degree of thrombocytopenia is urgent as this is the treatment most likely to influence the disease process. A repeat course of IVIg may be required depending on clinical course	1 g/kg (divided over 2 days if required)[16]	• Increase in platelet count	No
Post-transfusion hyperhaemolysis – short term use	Treatment of acute post-transfusion hyperhaemolysis	None	In combination with steroids, Ig is used as 1st line treatment	2 g/kg (usually over 2 days) given with IV methylprednisolone	• Rise in haemoglobin • Reduction in haemolysis markers (bilirubin, lactate dehydrogenase) • Transfusion independence • No haemolysis • Maintenance of post-transfusion Hb at 1 – 3 weeks • Avoidance of need for repeated transfusion	No
Prevention of haemolysis in	Symptomatic or severe anaemia (Hb <60g/L, with evidence of on-going			1 - 2 g/kg over 2 - 5 days given with steroids		

[15] Provan et al. Blood 2010;115:168-186
[16] Misbah et al J Clin Path 2023;76:143-144

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database)	Prior panel approval required
patients with a history of transfusion-associated hyperhaemolysis **Prevention of delayed haemolytic transfusion reaction**	intravascular haemolysis due to a delayed haemolytic transfusion/hyperhaemolysis). It is recognised that some patients with an Hb 60 g/l may require treatment. Patients who have had previous delayed haemolytic transfusion reactions/post-transfusion hyperhaemolysis or who have single or multiple allo-antibodies **AND** who may require a blood transfusion		Eculizumab is commissioned as a 2nd line treatment where 1st line treatment has failed; Rituximab is recommended as a 3rd line treatment[17].	1 – 2 g/kg over 2 - 5 days, given with IV methylprednisolone		
Post-transfusion purpura – short term use	• Sudden severe thrombocytopenia 5 to 10 days post-transfusion of blood products, **AND** • Active bleeding (typically occurs in Caucasian HPA-1a antigen negative females previously exposed to HPA-1a antigen in pregnancy or transfusion)	None	There are now very few cases in UK following the implementation of universal leucocyte-reduction of blood components in 1999	1 – 2 g/kg in divided doses over 2 - 5 days	• Increase in platelet count • Resolution of bleeding • Number of bleeding complications	No

[17] National Health Service. Clinical Commissioning Policy; Rituximab and eculizumab for the prevention and management of delayed haemolytic transfusion reactions and hyperhaemolysis in patients with haemoglobinopathies [URN 1821] [200602P]. Available from: *NHS England » Rituximab and eculizumab for the prevention and management of delayed haemolytic transfusion reactions and hyperhaemolysis in patients with haemoglobinopathies*

Use of Immunoglobulin in Neurology

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database)	Prior panel approval required
Acute idiopathic/ autoimmune dysautonomia/ ganglionopathy	• Acute onset autonomic failure with presence of ganglionic (alpha3) acetylcholine receptor antibodies **OR** Acute onset autonomic failure with clinical pattern consistent with above including pupillary involvement but without identifiable antibodies **AND** • Authorised by specialist autonomic unit	Non-immune causes of autonomic failure (for example primary autonomic failure [PAF] without pupillary involvement, multisystem atrophy [MSA], diabetes mellitus)	Ig may be required to obtain rapid control, but may be substituted by prednisolone, mycophenolate mofetil, plasma exchange or other immunosuppressants which are preferable in the longer term	2 g/kg over 5 days initially repeated at 6 weeks then titrated to optimal interval and minimum dose to achieve stability Annual reassessment with Ig suspension as necessary	• Postural BP drop - reduction with improved activities of daily living • Increase in time to significant postural BP drop • Reduction in numbers of syncopal and pre-syncopal episodes • Reduced oral dryness score • Reduced diarrhoea and constipation frequency	Yes
Autoimmune encephalitides (AIE) - antibody associated	• Non-infective encephalitis, with or without underlying teratoma or malignancy with known encephalitis associated antibody (e.g. LGI1, Caspr2, NMDAR, GAD, DPPX, AMPA, GABAb and others) **AND** • Functional disability caused by seizures, encephalopathy, stiffness, cognitive dysfunction or other relevant neurological sequelae	Infective encephalitis or other non-inflammatory cause of encephalopathy or seizures	Search for underlying malignancy and treat as appropriate Prednisolone/ methylprednisolone is 1st line, with or without plasma exchange (where this is available) Ongoing treatment with Ig may be necessary where long-term oral immunosuppression, tumour removal and definitive strategies to reduce antibody levels (e.g. cyclophosphamide/rituximab) are ineffective or contra-indicated NB: Please note the Enceph-IG study is available[18]. Consider recruitment within the trial for suitable patients.	2 g/kg over 5 days initially repeated at 3 - 6 weeks. Repeat course 3 times if necessary. If repeated courses are required, consider institution of alternative longer-term strategy immediately	• Decrease in antibody titre • Improvement in Modified Rankin Score • Decrease in seizure numbers • Improvement on one or more validated tests of memory or executive tasks • Resolution of MRI signal change (where present) • Resolution of hyponatraemia where present	Yes
Autoimmune encephalitides (AIE) - no known antibody defined	• Non-infective encephalitis, with or without underlying teratoma or malignancy without known encephalitis associated antibody	Infective encephalitis or other non-inflammatory cause of	Search for underlying malignancy and treat as appropriate. Prednisolone is 1st line, with or without	2 g/kg over 5 days initially repeated at 3 - 6 weeks. Repeat course 3 times if necessary	• Improvement in Modified Rankin Score • Decrease in seizure numbers • Improvement on one or more validated tests of memory or executive tasks	Yes

[18] University of Liverpool. Enceph-IG Study - Institute of Infection, Veterinary and Ecological Sciences. Available from: *Enceph-IG Study - Institute of Infection, Veterinary and Ecological Sciences - University of Liverpool*

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database)	Prior panel approval required
	AND • Functional disability caused by seizures, encephalopathy, stiffness, cognitive dysfunction or other relevant neurological sequelae **AND** • Evidence of inflammatory CNS disorder including active CSF, EEG defined seizures, MRI imaging changes consistent with AIE, known antibodies etc in the absence of infection	encephalopathy or seizures	plasma exchange (where this is available) Ongoing treatment with Ig may be necessary where long-term oral immunosuppression, tumour removal and definitive strategies to reduce antibody levels (e.g. cyclophosphamide/ rituximab) are ineffective or contra-indicated NB: Please note the Enceph-IG study is available[18]. Consider recruitment within the trial for suitable patients.	If repeated courses are required, consider institution of alternative longer-term strategy immediately	• Resolution of MRI signal change (where present) • Resolution of hyponatraemia where present	
Chronic inflammatory demyelinating polyneuropathy (CIDP) - including IgG or IgA associated paraprotein associated demyelinating neuropathy	• Probable or definite diagnosis of CIDP by a neurologist according to the EAN/PNS Criteria[19] **AND** • Significant functional impairment inhibiting normal daily activities. All patients should have an initial documented assessment after induction dosing and a further assessment after 2-3 doses to demonstrate meaningful functional improvement. Annual withdrawal/clinical reviews should be performed to document on-going need.	No specific exclusion criteria but see General notes regarding prothrombotic risks of Ig	Ig should not always be considered 1st line treatment for CIDP, although it may be where steroids are contra-indicated and plasma exchange is not available. Where steroids, Ig and plasma exchange are all available Ig would be considered preferable in patients with motor predominant CIDP, rapidly progressive disease where rapid response is required (particularly patients requiring admission to hospital) or where steroids or plasma exchange are contra-indicated. Strong consideration should be given to the early use of steroids or	An initiation regimen of a maximum 4 g/kg divided into at least two courses of 1 - 2 g/kg each and given over a 4 - 8-week period, with assessment at the end of the period. Regimens to establish response might include: • 2 g/kg given over 2 - 5 days and repeated after 6 weeks[20]. • 2 g/kg initially followed by 1 g/kg after 3 weeks and a further 1 g/kg 3 weeks later[21] **Refer to dose optimisation section below for maintenance**	Efficacy outcomes should be used to measure response after the chosen initial regimen and thereafter when assessing for dose optimisation Clinically meaningful improvement in any three of the following prespecified measures: • MRC score • INCAT sensory sum score • ONLS • Hand dynamometry • Inflammatory RODS score • 10-m walk (in seconds) • Up and go 10m walk (in seconds) • Berg Balance scale • Other validated disability score	Short-term initiation treatment to assess Ig responsiveness – No Long-term treatment - Yes

[19] European Academy of Neurology/Peripheral Nerve Society Guideline on diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy: Report of a joint Task Force — Second Revision. June 2021. Journal of the Peripheral Nervous System 26(2)
[20] Lunn M et al. J Peripher Nerv Syst. 2016 Mar;21(1):33-7.
[21] Hughes R et al. Expert Rev Neurother. 2009 Jun;9(6):789-95.

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database)	Prior panel approval required
			plasma exchange in other circumstances			
Guillain-Barre syndrome (GBS) **(includes Bickerstaff's brain stem encephalitis and other GBS variants)**	• Diagnosis of GBS (or variant) in hospital, **AND** • Significant disability (Hughes Grade 4) **OR** Disease progression towards intubation and ventilation **OR** mEGRIS score ≥ 3 **OR** Poor prognosis mEGOS ≥ 4	Patients with mild and/or non-progressive disease not requiring intubation	Patients with Miller-Fisher Syndrome do not usually require Ig and unless associated with GBS overlap with weakness will recover normally Plasma exchange is equally efficacious as Ig in GBS and should be preferentially considered where it is clinically appropriate and easily accessible For those disease indications in children and young adults where IVIg and plasma exchange (PLEX) are equally efficacious, IVIg may be preferentially considered if poor peripheral venou s access or challenges in service delivery preclude the use of PLEX	2 g/kg as soon as possible after the diagnosis is confirmed, given over 5 days. Administration over a shorter time frame not recommended because of fluid and protein overload and pro-coagulant effects. Ig is unlikely to be effective if given more than 4 weeks after the onset of symptoms[22]. Second doses of Ig are not effective in the treatment of GBS and may be associated with real potential harm[23].	None	No
IgM Paraprotein-associated demyelinating neuropathy	• Diagnosis by a neurologist, **AND** • Significant functional impairment inhibiting normal daily activities. **AND** • Other therapies have failed, are contra-indicated or undesirable	Mild disease with non-progressive sensory loss and imbalance does not require treatment	Ig is seldom significantly effective, and response should be reviewed at least every 6 months if there is initial functional improvement. Alternative underlying haematological diagnoses should be considered which may direct treatment, or other therapies such as single agent rituximab (or biosimilars) should be considered. Rituximab is recommended in IgM	An initiation regimen of a maximum 4 g/kg divided into at least 2 courses of 1-2 g/kg each and given over a 4- 8-week period, with assessment at the end of the period. Regimens to establish response might include: • 2 g/kg given over 2 - 5 days and repeated after 6 weeks[20]. • 2 g/kg initially followed by 1 g/kg after 3 weeks and a further 1 g/kg 3 weeks later[213]. **Refer to dose optimisation section below for maintenance**	Efficacy outcomes should be used to measure response after the chosen initial regimen and thereafter when assessing for dose optimisation Clinically meaningful improvement in any three of the following prespecified measures • MRC score • INCAT sensory sum score • ONLS • Hand dynamometry • Inflammatory RODS score • 10-m walk (in seconds) • Up and go 10m walk (in seconds) • Berg Balance scale • Other validated disability score	Yes

[22] Hughes R et al. Cochrane Database Syst Rev. 2014 Sep 19;2014(9):CD002063
[23] Lunn M et al. Lancet Neurol. 2021 Apr;20(4):249-251.

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database)	Prior panel approval required
			paraproteinaemic demyelinating peripheral neuropathy in adults, in line with NHS England clinical commissioning policy[24].			
Inflammatory Myopathies - Dermatomyositis (DM), Juvenile dermatomyositis (JDM), Polymyositis (PM), Other inflammatory myopathies*	• Diagnosis of myositis by a neurologist, rheumatologist, dermatologist or immunologist **AND** • Patients who have significant muscle weakness; **OR** Dysphagia and have not responded to corticosteroids and other immunosuppressive agents; **OR** DM with refractory skin involvement.	No specific exclusion criteria but see General notes regarding prothrombotic risks of Ig *Inclusion body myositis is not routinely commissioned	Where progression is not rapid and in the absence of contra-indications, **steroids** should be considered first. In adult patients (and post-pubescent children through the NHS England Medicines for Children policy[25]) with refractory disease associated with myositis-specific antibodies, **rituximab** (or biosimilar) has been approved as a 2nd line treatment by NHS England[26]. **Abatacept** is recommended in refractory idiopathic inflammatory myopathies (adults and children aged 2 and over), in line with NHS England Clinical Commissioning Policy as a 3rd line treatment[27]. **Ig** would be the 4th line treatment line. Ig is seldom effective in isolation and is best used as an adjunct to immunosuppressive therapy.	An initiation course of a maximum 4 g/kg divided into at least two courses of 1 - 2 g/kg each and given over a 4 - 8-week period, with assessment after dosing. Regimens to establish response might include: • 2 g/kg given over 2 - 5 days and repeated after 6 weeks[202] **Refer to dose optimisation section below for maintenance** The need for maintenance treatment in **resistant juvenile dermatomyositis** should be determined on an individual basis	Efficacy outcomes should be recorded after the initiation course and regularly reassessed and recorded thereafter Clinically meaningful improvement in any three of the following prespecified measures: **DM:** functional/disability scores (ADLs): • semi-quantitative muscle scores (MRC score) • other quantitative muscle strength (e.g. MMT8) • up and go 10-m walk (in secs) • CDASI • CAT or DAS • FVC • CHAQ to include the childhood score **PM/other inflammatory myopathies:** functional/disability scores (ADLs): • semi-quantitative muscle scores (MRC sumscore) • other quantitative muscle strength (e.g. MMT8) • up and go 10-m walk (in secs) • HAQ • FVC **Dermatomyositis (juvenile – JDM):** • MMT-8 • CMAS score • CK for baseline and assess how a patient has improved after each infusion or at least after 3 infusions. • PGALs is used to assess how many inflamed or swollen joints a patient has.	Yes

[24] National Health Service. Clinical Commissioning Policy: Rituximab for the treatment of IgM paraproteinaemic demyelinating peripheral neuropathy in adults. Available from: *NHS England » Rituximab for the treatment of IgM paraproteinaemic demyelinating peripheral neuropathy in adults*

[25] National Health Service. Commissioning Medicines for Children in Specialised Services. Available from*:* *NHS England » Commissioning Medicines for Children in Specialised Services*

[26] National Health Service. Clinical Commissioning Policy: Rituximab for the treatment of dermatomyositis and polymyositis (adults). Available from: *Rituximab-for-the-treatment-of-dermatomyositis-and-polymyositis-adults.pdf (england.nhs.uk)*

[27] National Health Service. Clinical Commissioning Policy: Abatacept for refractory idiopathic inflammatory myopathies (adults and children aged 2 and over). Available from: *NHS England » Abatacept for refractory idiopathic inflammatory myopathies (adults and children aged 2 years and over)*

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database)	Prior panel approval required
			Maintenance treatment with Ig for a prolonged period (usually less than 12 months) may be required in a small minority of patients with inflammatory myositis, as a 3rd line treatment after consideration of rituximab (see comments above). In these cases, every effort should be made to establish the minimum clinically effective dose by either reduction of dose or lengthening the intervals between infusions. Cessation trials should be attempted at least annually to establish on-going need for treatment.			
Multifocal Motor Neuropathy (MMN)	• Diagnosis by a neurologist of multifocal motor neuropathy with or without persistent conduction block; **AND** • Significant functional impairment inhibiting normal daily activities	No specific exclusion criteria but see General notes regarding prothrombotic risks of Ig	No alternative treatments known	An initiation regimen of a maximum 4 g/kg divided into at least two courses of 1 - 2 g/kg each, and given over a 4 - 8 week period, with assessment at the end of the period. Regimens to establish response might include: • 2 g/kg given over 2 - 5 days and repeated after 6 weeks[202]. • 2 g/kg initially followed by 1 g/kg after 3 weeks and a further 1 g/kg 3 weeks later[213] **Refer to dose optimisation section below for maintenance** If no significant measurable and functionally meaningful improved in abilities has been achieved after 3 doses Ig should be stopped	Clinically meaningful improvement in any 3 of the following prespecified measures • MRC score • Power score from 7 pre-defined pairs of muscles including 4 most affected muscle groups neuro-physiologically • RODS for MMN • Hand dynamometry • ONLS • 10-m walk (in secs) • Any other validated MMN disability measure	Short-term treatment to assess Ig responsiveness – No Long-term treatment - Yes

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database)	Prior panel approval required
Myasthenia Gravis (MG), includes Lambert-Eaton Myasthenic Syndrome (LEMS)	• Diagnosis of MG or LEMS by a neurologist **AND** • Acute exacerbation (myasthenic crisis) **OR** Weakness requires hospital admission **OR** Prior to surgery and/or thymectomy	No specific exclusion criteria but see General notes regarding prothrombotic risks of Ig	All patients requiring urgent in-patient treatment should receive plasma exchange first if available, including considering transfer to an appropriate neuroscience centre. Ig could follow plasma exchange if required. Where plasma exchange is not available, Ig may be appropriate. In rare circumstances where a patient has failed all standard treatments (including steroids and immunosuppression) and where authorised by a specialist in MG from a centre with a specialist neuromuscular service, maintenance therapy may be considered. A rituximab biosimilar agent is likely to be an equally effective alternative therapy and has been approved by NHS England[28] for this group of patients with resistant myasthenia	In acute exacerbation use plasma exchange first where available. Patients admitted to hospital should receive 1 g/kg in the first instance, only receiving a further 1 g/kg if there is further deterioration or no response. Patients with life threatening disease (ITU with respiratory and/ or bulbar failure) should receive 2 g/kg over 2 - 5 days. **Refer to dose optimisation section below for maintenance**	Clinically meaningful improvement in variation of myasthenic muscular strength and fatigue measures by the QMGS MG composite score. Additional efficacy may be monitored using: • Forward arm abduction time (up to 5 min) • Quantitative Myasthenia Gravis Score (Duke) • Respiratory function, e.g. forced vital capacity • Variation of another myasthenic muscular score • Dysphagia score • Dysarthria 1-50 counting • Diplopia or ptosis measurement	Myasthenic crisis – No Long-term treatment - Yes
Neuromyotonia (Isaacs syndrome)	• Neuromyotonia from peripheral nerve hyperexcitability associated with significant disability **AND** • Supported by diagnostic electrophysiological changes with or without antibodies to the VGKCh complex (Caspr) and resistant to alternative agents	Non autoimmune myotonia syndromes	Anticonvulsants should be tried first from phenytoin, carbamazepine, sodium valproate and lamotrigine. Immunomodulation: Prednisolone +/- azathioprine or oral immunosuppressant Plasma exchange	2 g/kg over 5 days initially repeated at 6 weeks then titrated to optimal interval and minimum dose to stability	Clinically meaningful improvement in • Timed up and go walk • Functional measure: e.g. Myotonia Behaviour Scale (MBS), Rivermead Mobility Index, or Brief Pain Inventory • Neurophysiological myotonia assessment	Yes

[28] National Health Service. Clinical Commissioning Policy Statement: Rituximab bio-similar for the treatment of myasthenia gravis (adults). Available from: *Rituximab-biosimilar-for-the-treatment-of-myasthenia-gravis-adults-v2.pdf (england.nhs.uk)*

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database)	Prior panel approval required
Non-MS CNS inflammatory disease covering the clinical phenotype of Aquaporin-4 antibodies (AQP4 ab) disease, Neuromyelitis Optica Spectrum Disorder (NMOSD), Acute Disseminated Encephalomyelitis (ADEM) (with or without encephalopathy, including brainstem attacks), Myelin Oligodendrocyte Antibody Disease (MOGAD), Transverse Myelitis (TM), Optic Neuritis (ON)						
Acute disease: Short term use **Chronic relapse prevention:**	• Acute disease attack* not responding to IV methylprednisolone (5 – 7 g or equivalent in children) and plasma exchange. When plasma exchange is not available or delayed or contraindicated, Ig can be used before plasma exchange **AND** • Evidence of ongoing inflammation **AND** • Within 6 weeks unless evidence of active inflammation	Mild relapses without: new neurological signs OR reduced activities of daily living OR other inflammatory disease diagnoses (e.g. MS Sarcoid, Behcets etc)	Refractory to IV methylprednisolone OR plasma exchange not available or contraindicated OR refractory to plasma exchange in cases of severe disability and ongoing inflammation (usually within 6 weeks)	2 g/kg over 2 - 5 days	Clinically meaningful improvement in disease features including 3 of: • Modified Rankin score • 10m walk • 9-hole peg test • Validated neuropsychometric testing • Other relevant validated scale • Objective relevant imaging **Optic neuritis** Clinically meaningful improvement in visual acuity **Transverse myelitis** Clinically meaningful improvement in • EDMUS **OR** • ASIA	No
MOGAD	Refractory to (relapse* breakthrough) at least two treatments; one must be prednisolone and an immunosuppressant (any of mycophenolate mofetil/rituximab/azathioprine/methotrexate) **OR** Serious side effects with prednisolone (adequate dose and length of time)	Pseudo-relapse **OR** MS (may have low positive MOGAbs)	Failed 2 first line therapies	1 g/kg daily over 2 days then 1 g/kg monthly for first year (titrate to 2 g/kg if relapses occur despite steroids and standard 1 g/kg monthly dosing) Annual assessments required for dose optimisation and ongoing therapy	Suppression of further relapses* Treatment failure – defined as objective evidence of true relapse* on treatment	Yes
AQP4 NMOSD	Failed or intolerant to 3 or more 'usual treatments' resulting in relapse*, including at least prednisolone (unless severe prednisolone side effects from adequate dose and time) and immunosuppressant(azathioprine/rituximab/mycophenolate mofetil/methotrexate/ciclosporin or tacrolimus/plasma exchange or new randomised controlled trial treatment if available)	Pseudo-relapse	As per selection criteria	1 g/kg daily over 2 days then 1 g/kg monthly for first year (titrate to 2 g/kg if relapses occur despite steroids and standard 1 g/kg monthly dosing) Annual assessments required for dose optimisation and ongoing therapy	Suppression of further relapses* Treatment failure – defined as objective evidence of true relapse* on treatment	Yes
Ab negative phenotypes	Failed or intolerant to 3 or more 'usual treatments' resulting in relapse* including at least prednisolone (unless severe prednisolone side effects from	Pseudo-relapse **OR** other inflammatory disease diagnoses (e.g.	As per selection criteria	1 g/kg daily over 2 days then 1 g/kg monthly for first year (titrate to 2 g/kg if relapses occur despite steroids and	Suppression of further relapses* Treatment failure – defined as objective evidence of true relapse* on treatment	Yes

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database)	Prior panel approval required
	adequate dose and time) and immunosuppressant (azathioprine/rituximab/mycophenolate mofetil/methotrexate/ciclosporin or tacrolimus/plasma exchange or new randomised controlled trial treatment if available	MS Sarcoid, Behcets etc)		standard 1 g/kg monthly dosing) Annual assessments required for dose optimisation and ongoing therapy		

*Attack or relapse is a new or extended neurological symptom with signs that reflect the anatomical location of the inflammatory lesion (note a minority of MOGAD TM may be difficult to visualise) that is not a fluctuating residual symptom of an old lesion and that usually persists for at least one week. However, acute treatment should not be delayed. Contrast enhancement is present in the majority during the acute phase.

Opsoclonus-myoclonus syndrome (OMS)- paediatric or adult non-paraneoplastic	• Paediatric OMS diagnosed by a paediatric neurologist **OR** • OMS in an adult with no evidence of neoplasm, anti-neuronal antibodies, or focal structural or inflammatory alternative diagnosis	Structural disease. Multiple sclerosis or other inflammatory lesions associated with defined diagnoses where the primary treatment of that disease is not Ig	Corticosteroids should be tried first Consider other anti-inflammatory strategies including oral immunosuppressants, rituximab or cyclophosphamide as appropriate	2 g/kg over 5 days initially repeated at 6 weeks then titrated to optimal interval and minimum dose to achieve stability	Improvement in OMS score	Yes
Paraneoplastic neurological syndromes (PNS) without evidence of autoantibodies	• Defined paraneoplastic syndrome (for example limbic encephalitis, sensory ganglionopathy, cerebellar degeneration etc) **AND** • Evidence of a PNS associated tumour (e.g. small cell lung, ovarian or testicular, breast, thymoma etc)	See eligibility criteria	Treatment of primary tumour Consider steroids and plasma exchange	2 g/kg over 5 days initially repeated at 6 weeks. If beneficial then titrated to optimal interval and minimum dose to achieve stability. Discontinue If not objectively effective after 2 doses.	Clinically meaningful improvement in • Modified Rankin Scale • 10m walk • Any validated relevant disability measure appropriate to the condition	Yes
Rasmussen's Encephalitis	• When other therapies (such as steroids) have failed	No specific exclusion criteria but see General notes regarding pro-thrombotic risks of Ig	Ig is reserved for patients unresponsive to steroids and other therapies.	2g/kg given over 2 -- 5 days and repeated monthly for three months for initial trial	Seizure frequency with expected reduction of 30% to continue therapy	Yes

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database)	Prior panel approval required
Stiff person syndrome (SPS) or variant	Diagnosis of SPS or a variant (stiff limb, progressive encephalomyelitis with rigidity and myoclonus [PERM], etc) by a consultant neurologist Supportive criteria: • Demonstration of auto-antibodies to GAD, DPPX, amphyphysin, gephyrin or other stiff person associated antibodies **AND/OR** • Continuous motor unit activity at rest on EMG testing in paraspinal or affected limb musculature	No specific exclusion criteria but see General notes regarding pro-thrombotic risks of Ig	Consider plasma exchange as initial treatment Rituximab is likely to be equally effective but is not commissioned for this indication	An initiation regimen of a maximum 4 g/kg divided into at least two courses of 1 – 2 g/kg each and given over a 4 - 8 week period, with assessment at the end of the period. Regimens to establish response might include: • 2 g/kg given over 2 - 5 days and repeated after 6 weeks.[22]. • 2 g/kg initially followed by 1 g/kg after 3 weeks and a further 1 g/kg 3 weeks later[213] For maintenance dose optimisation see general note below. If no significant measurable and functionally meaningful improvement in abilities has been achieved after 3 doses Ig should be stopped.	Clinically meaningful improvement in at least two of the measures below: • Stiffness • Up and go 10-m walk (in secs) • BRIT score • Number of spasms per day • Validation measure of functional abilities	Yes

For many disorders where rituximab is a potential longer-term alternative to IVIg, the speed of response should be considered in determining treatment choice.
IVIg can provide more rapid but temporary control and is likely to be the preferred option in emergency situations where an immediate response is required, for example in dysphagia and/or difficulty in breathing in inflammatory myositis.

Use of Immunoglobulin in Infectious Diseases

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database)	Prior panel approval required
Hepatitis A	Ig is recommended in addition to hepatitis A vaccine for contacts of hepatitis A who are less able to respond to vaccine • those aged 60 or over, **OR** • those with immunosuppression and those with a CD4 count <200 cell per microlitre, **OR** • those at risk of severe complications (those with chronic liver disease including chronic hepatitis B or C infection)	See eligibility criteria	Hepatitis A vaccine is recommended in addition to Ig Vaccine should be administered within 2 weeks of exposure	Subgam: <10 years 500mg >10 years 1000mg To be given by intramuscular injection *(*Please note SPC currently indicates subcutaneous route of administration only [although previously indicated both s/c and im routes], UKHSA guidance recommends intramuscular administration for post-exposure prophylaxis with Subgam) Given with vaccine in those at high risk, within 2 weeks of exposure (those over 60 years, immunosuppression, CD4 count <200 cell per microliter) and those at risk of severe complications. For those exposed between 2 - 4 weeks ago, Ig may also be offered to modify disease in those at risk of severe complications (i.e. chronic liver disease including chronic hepatitis B or C infection).	Outcome measures not routinely recorded on surveillance databases Ig is issued nationally and locally; records are held of who Ig was issued for with respect to exposure to the hepatitis A virus.	Prior approval is via discussion with UKHSA health protection team Find your local protection team here: https://www.gov.uk/health-protection-team
Measles (immunosuppressed individuals)	Immunosuppressed individuals (Group A and Group B based on level of immunosuppression[29]) who have had a significant exposure to measles and are known to be susceptible (based on vaccine history and/or IgG testing).	See eligibility criteria	For immunosuppressed contacts Ig is the mainstay of management	0.15 g/kg of IVIg recommended ideally within 72 hours of exposure although can be given up to 6 days. Where exposure recognised late or found to be antibody negative between 6 and 18 days after exposure, IVIg may be considered following discussion with specialist clinician.	Prevention of measles	Prior approval is via discussion with UKHSA health protection team *Find your local protection team here: https://www.gov.uk/health-protection-team

[29] UK Health Security Agency. National measles guidelines. Available from: *National measles guidelines July 2024*

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database)	Prior panel approval required
Measles (pregnant women and infants)	Pregnant women who have identified as susceptible based on vaccine history and /or antibody testing who have had a significant exposure to measles. Infants under 9 months of age with a significant exposure to measles. Advice is available at: National measles guidelines - GOV.UK	See eligibility criteria	For pregnant contacts, Ig is mainstay management for post-exposure prophylaxis For infants below 6 months Ig is mainstay treatment; For infants aged between 6 - 8 months, MMR vaccine can be offered if exposure occurred outside household setting AND ideally should be given within 72 hours	• For pregnant contacts, approximately 3000mg of human normal Ig (HNIG) • Infants 0.6 ml/kg up to a maximum of 1000mg of HNIG HNIG to be given within 6 days of exposure in pregnant women and infants. The National Measles Guidance (referenced in column 2), Section 2.3.2 recommends these doses are administered IM, using the SC formulations, as long as use via this route is acknowledged to be off-label.	Prevention of measles	Prior approval is via discussion with UKHSA health protection team Find your local protection team here: https://www.gov.uk/health-protection-team
Polio	To prevent or attenuate an attack: • An immunocompromised person inadvertently given live polio vaccine, **OR** • An immunocompromised person whose contacts are inadvertently given live polio vaccine	See eligibility criteria	Ig represents 1st line treatment	<1 year: 250mg 1 – 2 years: 500mg >3 years: 750mg Stool samples from the immunosuppressed individual must be obtained one week apart. If poliovirus is grown from either sample, repeat Ig at 3 weeks. Continue weekly stool collection and administration of Ig 3- weekly until immunocompromised individual's stool is negative for poliovirus on two occasions	Prevention or resolution of infection	Prior approval is via discussion with UKHSA health protection team Find your local protection team here: https://www.gov.uk/health-protection-team
Severe or recurrent Clostridium difficile infection (CDI) colitis - short term use	• Severe cases (WCC >15 and/or acutely rising creatinine and/or signs/symptoms of colitis) not responding to routine 1st line vancomycin and metronidazole • If multiple recurrences, especially with evidence of malnutrition	See comments under position of Ig	For fulminant or recurrent CDI unresponsive to appropriate antibiotics (see under selection criteria) consider IV tigecycline or Ig[30]. Faecal microbiota transplantation is approved by NICE for patients with recurrent CDI unresponsive to antibiotics and is likely	0.4 g/kg, one dose, and consider repeating once	• Clearance of C. diff. • Duration of hospital in-patient stay	Yes

[30] McDonald et al. Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) Clin Infect Dis 2018;66:e1-e48

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database)	Prior panel approval required
			to be an effective alternative[31].			
Staphylococcal (including PVL-associated sepsis) or streptococcal toxic shock syndrome (TSS) - short term use	• Diagnosis of streptococcal or staphylococcal TSS, preferably with isolation of organism, **AND** • Failure to achieve rapid improvement with antibiotic therapy and other supportive measures, **AND** • Life-threatening	See comments under position of Ig	Ig is reserved for patients with life-threatening disease who fail to achieve rapid improvement with antibiotic therapy. However, for **streptococcal TSS**, it should be noted that there has been significant controversy regarding the benefits of Ig treatment prompting the Infectious Diseases Society of America (IDSA) not to recommend its use in patients with necrotising Group A streptococcal infections.[32] Since then a systematic review and meta-analysis of Ig in clindamycin-treated patients with streptococcal TSS suggests a reduction in mortality from 33.7% to 15.7%, though this finding may be confounded by differences in baseline characteristics between patients receiving IVIg and those who did not.[33] Based on the results of this meta-analysis, the use of IVIg as adjunctive therapy is	Total dose of 2 g/kg, because of uncertainty regarding the timing and optimal dose of Ig, it is recommended that patients are reviewed after an initial dose of 1 g/kg. Should there be no evidence of improvement at 24 hours, a further 1 g/kg may be considered.	• Improvement of FBC, ALK, CPK and acute phase markers • Reduction in hospital inpatient stay • Survival	Yes If prior approval is not possible, then treatment should proceed, and retrospective approval should be sought.

[31] National Institute for Health and Care Excellence. Faecal microbiota transplant for recurrent Clostridium difficile infection. Interventional procedures guidance [IPG485]. Available from: *Overview | Faecal microbiota transplant for recurrent Clostridium difficile infection | Guidance | NICE*

[32] Stevens DL et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections. 2014 update by the IDSA. Clin Infect Dis 2014;59:e10-52

[33] Parks T et al. Clin Infect Disease 2018;67:1434-6

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database)	Prior panel approval required
			supported by Stevens DL.[34]			
Suspected tetanus case	Person with clinical symptoms suggestive of localised or generalised tetanus ("in the absence of a more likely diagnosis, an acute illness with muscle spasms or hypertonia AND diagnosis of tetanus by a healthcare provider") Guidance on the management of suspected tetanus cases and the assessment and management of tetanus-prone wounds - GOV.UK	See eligibility criteria	• Wound debridement • Antimicrobials • Ig based on weight • Supportive care • Vaccination with tetanus toxoid following recovery	**Ig – intravenous (IVIg):** Dosage based on equivalent dose of anti-tetanus antibodies of 5000 IU for individuals < 50kg and 10000 IU for individuals > 50kg	Resolution of tetanus infection	No
Tetanus prone injury (prophylaxis)	Tetanus specific Ig (TIg) has limited stock and is recommended for susceptible individuals sustaining high risk tetanus prone injuries as defined in guidance.[35]	See eligibility criteria	• Thorough cleaning of wound essential • Ig for Prophylaxis • Booster of tetanus-containing vaccine for long term protection	**Tetanus specific Ig – intramuscular (IM-TIg)** • 250 IU for most uses • 500 IU if more than 24 hours have elapsed or there is a risk of heavy contamination or following burns The dose is the same for adults and children **Ig – subcutaneous (SCIg) / intramuscular (IMIg):** If TIg (for im use) cannot be sourced, Ig for subcutaneous or intra-muscular use may be given as an alternative. Based on testing for the presence of anti-tetanus antibodies of alternative Ig products, the volume required to achieve the recommended dose of 250 IU are included: Guidance on the management of suspected tetanus cases and the assessment and management of tetanus-prone wounds - GOV.UK. Although no time frame is specified in the guidance, IM-TIg/Ig following a tetanus prone wound is only likely to confer	Prevention of tetanus infection	No

[34] UpToDate. Invasive group A streptococcal infection and toxic shock syndrome: Treatment and prevention. Available from: *Invasive group A streptococcal infection and toxic shock syndrome: Treatment and prevention - UpToDate*

[35] Public Health England. Tetanus: advice for health professionals. Available from: *Tetanus information for health professionals (publishing.service.gov.uk)*

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database)	Prior panel approval required
				benefit when given within incubation period of tetanus (10-21 days)		
Varicella zoster	Individuals for whom oral antivirals are contraindicated due to malabsorption or some cases of renal toxicity. Ig is indicated for those individuals who fulfil all of the following: 1) Significant exposure to chickenpox (varicella) or shingles (zoster) during the infectious period 2) At increased risk of severe chickenpox i.e. immunosuppressed individuals, neonates and pregnant women 3) No antibodies to varicella-zoster virus (based on VZV antibody testing) 4) Unable to take oral antivirals due to malabsorption or renal toxicity Updated guidance on post exposure prophylaxis have been published in January 2025. Advice is available at: https://www.gov.uk/government/publications/post-exposure-prophylaxis-for-chickenpox-and-shingles Neonates of mothers who have developed chicken pox within 7 days of birth (either before or after delivery and who cannot obtain Varitect (Varicella-zoster immunoglobulin) in a timely manner.	Unless contra-indicated, oral antivirals would be considered first-line Neonates treated with Varitect	Oral antivirals are considered first-line	0.2 g/kg (i.e. 4 ml/kg for a 5 % solution) Brands have not been specified as no formal testing of products has been undertaken IVIg should be administered ideally within 7 days of exposure in eligible individuals. Where the exposure has been identified beyond 7 days, IVIg can be offered up to 14 days after exposure.	• Prevention of chicken pox infection • Prevention of severe chicken pox • Prevention of chicken pox infection • Prevention of severe chicken pox	Prior approval is via discussion with UKHSA health protection team Find your local protection team here: https://www.gov.uk/health-protection-team
Viral pneumonitis post-transplantation: HSCT and solid organ	Definitive diagnosis of viral pneumonitis – Varicella Zoster Virus (VZV), Respiratory Syncytial Virus (RSV), Human Parainfluenza Virus (HPIV)	**VZV** - See comments under position of Ig **RSV/HPIV** – patients with mild disease confined to the upper respiratory tract	**VZV** – Ig is reserved for patients with disseminated disease. For guidance on treatment of patients with significant exposure to chickenpox or herpes zoster please see use of Ig in specific infectious diseases.	1 – 2 g/kg in divided doses	• Radiological improvement • Length of hospital stay • Survival	Yes If prior approval is not possible then treatment should proceed, and retrospective approval should be sought.

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database)	Prior panel approval required
			RSV, HPIV – patients with lower respiratory infections. In patients with RSV infection, Ig would be used as an adjunct to ribavirin. **RSV, HPIV** - **patients with RSV and HPIV upper respiratory infections post-HSCT**. Consider Ig in the presence of some or all of the following risk factors.[36] • Older age • Graft-versus- host disease • Lymphopenia: <0.2 x 10^9/L • Neutropenia • Mismatched/unrelated donor • Immediate aftermath of HSCT (<1 month)			

[36] Hirsch et al. Clin Infect Dis. 2013 Jan 15; 56(2): 258–266

Use of Immunoglobulin in "Other" Indications

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database	Prior panel approval required
Allo-immune neonatal haemochromatosis or gestational allo-immune liver disease (GALD)	• Pregnant mothers with a previous adverse pregnancy outcome and clear post-mortem evidence of foetal haemochromatosis **OR** • Women who have had an offspring with neonatal liver failure confirmed to be allo-immune neonatal haemochromatosis • Affected neonates • Decision to treat with Ig made by a consultant obstetrician with input from a liver unit specialist	None	For those patients fulfilling eligibility criteria, there are no alternatives to Ig For further information please refer to the NHS England Clinical Commissioning Policy: Maternal intravenous immunoglobulin (IVIg) for the prevention of allo-immune fetal and neonatal haemochromatosis[37]	Maternal dose: Ig is administered by intravenous infusion at a dose of 1 g/kg (dose capped at 60 g per week) to at risk mothers at 14 weeks, 16 weeks and then weekly from 18 weeks gestation until delivery between 37 and 38 weeks. The weight used to calculate the dose will be the mother's weight at booking. Neonatal dose: 1 g/kg The need for repeated doses, which may be required in exceptional cases, should be based on clinical need and locally agreed policy.	• Foetal loss (including gestation) • Gestation at delivery • Neonatal outcomes	Yes .
ANCA-associated systemic vasculitides (AAV)	• Patients with refractory/relapsing AAV in whom conventional immunosuppressive therapy is contra-indicated e.g. presence of severe infection or in pregnancy as bridging therapy • The role of Ig in the treatment of ANCA-negative small vessel vasculitis is unclear, and each case will need to be assessed on individual grounds.	No specific exclusion criteria – see comments under selection criteria	Ig is reserved as adjunctive or very rarely as sole therapy for the minority of patients in whom conventional immunosuppressive therapy is contra-indicated	Total dose of 2 g/kg over 2 – 5 days every 4 weeks. The optimal duration of therapy is not known though most patients are likely to achieve remission after 3 months. Ig should be discontinued after 3 months in the absence of clinical improvement.	• Clinically meaningful improvement in Birmingham Vasculitis Score (BVAS)/PVAS - to capture paediatric assessment tool • Fall in inflammatory markers • Improvement in organ function	Yes
Autoimmune uveitis - short term use	• Severe aggressive sight-threatening disease unresponsive to conventional immunosuppressive treatment (topical and systemic steroids and oral or injectable immunosuppressants)	See comments under position of Ig	Ig is reserved for exceptional cases where conventional immunosuppressive agents are contra-indicated or ineffective or associated with intolerable adverse effects, especially in the context of autoimmune retinopathy. Adalimumab is regarded as the treatment of choice for other forms of severe, refractory uveitis and is	1 - 1.5 g/kg 2 – 3 infusions given 6 – 8 weeks apart to assess benefit	• Clinically meaningful improvement or stabilisation in visual acuity • Imaging endpoints • Electrodiagnostic studies	Yes

[37] National Health Service. Clinical Commissioning Policy: Maternal intravenous immunoglobulin (IVIg) for the prevention of alloimmune fetal and neonatal haemochromatosis. Available from: *1864_Maternal-intravenous-immunoglobulin-to-prevent-allo-immune-fetal-haemochromatosis.pdf (england.nhs.uk)*

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database	Prior panel approval required
			routinely commissioned by NHS England. (NICE TA460[38]). Infliximab is not routinely commissioned by NHS England for this indication.[39]			
Catastrophic antiphospolipid syndrome (CAPS)	Diagnosis of definite or probable CAPS: • Thromboses in 3 or more organs developing in less than a week • Histological evidence of microthrombosis in at least one organ • Persistent anti-phospholipid antibody positivity (lupus anti-coagulant and or anti-cardiolipin/anti-B2GPI of IgG or IgM isotype	Chronic recurrent thrombosis due to other causes Thrombosis associated with stable anti-phospholipid syndrome in the context of other disorders	Steroids, anticoagulants and plasma exchange) represents optimal therapy Ig is likely to be beneficial in selected cases associated with severe thrombocytopenia where plasma exchange is either unavailable or contra-indicated or in the event of deterioration following plasma exchange	2 g/kg over 4 - 5 days	• Clinically meaningful improvement • Reduction in anti-phospholipid antibody levels	Yes
Immunobullous diseases - long term use	• Severely affected **AND** • Conventional corticosteroid treatment with adjuvant immunosuppressive agents has failed or is inappropriate	See comments under position of Ig	Ig is reserved as adjunctive therapy for patients with severe disease refractory to conventional immunosuppressive therapy. Rituximab is increasingly supplanting Ig as the preferred treatment for resistant disease and is routinely commissioned by NHS England[40] .In such patients it is listed as a 3rd line treatment alongside Ig. However, rituximab should be favoured over Ig, given the stronger evidence base supporting its use.	1 - 2 g/kg over 2 – 5 days. There may be a need for maintenance Ig in exceptional patients unresponsive or intolerant of rituximab. In such cases every attempt should be made to define the minimal effective dose of Ig by undertaking periodic dose reduction and or lengthening the interval between treatment	• Reduction in recurrence of disease/relapse • Dose reduction/discontinuation of other immunosuppressive therapy • Improved quality of life • Resolution of blisters/healing affected skin • Resolution of pruritus	Yes
Kawasaki disease – short term use	Clinical diagnosis of Kawasaki disease by a paediatrician, paediatric infectious disease	None	Ig in combination with anti-inflammatory doses of aspirin is the treatment of choice	2 g/kg single dose, in conjunction with high-dose aspirin; a second dose may be	• Resolution of fever • Improvement in acute phase markers	No

[38]National Institute for Health and Care Excellence: *Adalimumab and dexamethasone for treating non-infectious uveitis.* Available from*:* *Overview | Adalimumab and dexamethasone for treating non-infectious uveitis | Guidance | NICE*

[39] National Health Service. Clinical Commissioning Policy: Infliximab (Remicade) as Anti-TNF Alpha Treatment Option for Paediatric Patients with Severe Refractory Uveitis. Available from: *d12pb-paediatric-pats-uveitis-inflixi-fin.pdf (england.nhs.uk)*

[40] National Health Service. Clinical Commissioning Policy: Rituximab for Immunobullous Disease. Available from: *https://www.england.nhs.uk/wp-content/uploads/2021/06/cc-policy-rituximab-for-immonobullous-disease-ocular-v2.pdf*

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database	Prior panel approval required
	consultant or paediatric immunologist			given if no response, or if relapse within 48 hrs		
Paediatric inflammatory multisystem syndrome temporarily associated to COVID-19 (PIMS-TS) - short term use	Clinical diagnosis of PIMS-TS by a paediatrician, paediatric consultant in infection or paediatric immunologist Clinical diagnosis of PIMS-TS in an adult (also known as MIS-C or AIMS-TS) by a consultant in infection or immunologist or appropriate specialist MDT Because of the similarities between PIMS-TS and Kawasaki disease, the use of Ig was approved in 2020 for any child fulfilling diagnostic criteria for PIMS https://www.rcpch.ac.uk/. More recent data suggests that steroids should be considered as first-line therapy, especially for children 6 years old and over without symptoms of Kawasaki disease – see comments under position of immunoglobulin.		Consider steroids as first-line therapy while reserving IVIg for those cases where there is difficulty in distinguishing Kawasaki disease from MIS-C. In practice, this is particularly challenging in children under 6 years in whom IVIg may need to be considered as first-line therapy. IVIg was originally recommended as a first-line treatment for MIS-C based on its clinical similarities to Kawasaki disease. New data from an international observational cohort of 2009 patients with MIS-C from 39 countries randomised to receive IVIg alone (n=680), IVIg plus steroids (n= 698) and steroids alone (n=487) suggests that initial treatment with steroids was a safe and effective alternative to IVIg or combined therapy.[41] There were no significant differences between treatment arms for primary outcomes – need for ventilation, inotropic support or death. In addition, the occurrence and resolution of coronary artery aneurysms did not differ significantly between treatment groups.		

[41] Channon-Wells et al Lancet Rheumatology 2023;5:e184-99

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database	Prior panel approval required
Prevention of autoimmune congenital heart block (CHB) (anti-Ro)	**Prophylactic** Ig therapy has previously been given during pregnancy when: • There is a history of autoimmune congenital heart block in at least one previous pregnancy, **AND** • Maternal anti-Ro and/or anti-La antibodies are present. However, more recent evidence has cast doubt on the beneficial effects of Ig with hydroxychloroquine being regarded as 1st line therapy – see comments under position of immunoglobulin	See comments under position of Ig	Hydroxychloroquine is regarded as the treatment of choice. Ig may be considered in exceptional cases refractory to hydroxychloroquine or if the patient is unable to tolerate hydroxychloroquine, but there is uncertainty regarding its efficacy. At a dose of 0.4 g/kg every 3 weeks administered from weeks 12 through to week 24 of gestation, immunoglobulin was ineffective in preventing the development of CHB in neonates in two prospective open-label trials; based on a case series a higher dose (1 g/kg) alongside high dose oral prednisolone may possibly be effective.	Two infusions of 1 g/kg/day, the first at 14 weeks and the second at 18 weeks of gestation The weight used to calculate the dose will be the mother's weight at booking.	Improvement in the degree of heart block at birth	Yes
Transplantation (solid organ) – short term use	**Antibody Incompatible Transplant (AIT)** Patients in whom renal, heart, liver or lung transplant is prevented because of antibodies **Antibody Mediated Rejection (AMR)** Patients experiencing steroid resistant rejection or where other therapies are contraindicated after renal, heart, liver and/or lung transplant	See comments under position of Ig	While Ig is included in many protocols, there is a paucity of high-quality evidence to support its use. A systematic review of AMR in kidney transplant recipients categorised the evidence supporting the use of IVIg as being 'very low.'[42] Where Ig is used in combination with plasma exchange, any beneficial effects of Ig are likely to be negated by subsequent plasma exchange. For this reason, the use of Ig immediately prior to plasma exchange is not supported. The addition of rituximab to Ig appears to	**AIT:** Up to 2 g/kg to be repeated as per Donor Specific Antibodies (DSA); in renal desensitisation at 0.1 g/kg for 8 – 12 doses **AMR:** Treatment protocols vary in the UK ranging from low dose 100mg/kg after plasma exchange or high dose 2g/kg	**AIT and AMR:** Renal: • Type of renal transplant • HLA class DSA (where available) • Rejection episodes • Patient survival • Graft survival • Renal function = eGFR (MDRD) • Cardiothoracic: • DSA • Length of ITU and hospital stay • Graft function (heart = rejection fraction; lung = spirometry; liver = liver function, clotting indices)	No

[42] Roberts DM et al. The treatment of acute antibody-mediated rejection in kidney transplant recipients – a systematic review. Transplantation. 2012;94:775-783

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database	Prior panel approval required
			be of benefit in lowering HLA antibody titres			
Scleromyxedema	Patients will be eligible for Ig treatment if they fulfil **ALL** of the following criteria: • Diagnosed with scleromyxedema following a biopsy by a joint rheumatology and dermatology clinic within a rheumatology or dermatology specialised centre with expertise in autoimmune connective tissue disease. • The diagnosis was made in line with the widely acknowledged scleromyxedema diagnostic classification (Rongioletti and Rebora, 2001) where the patient should have ANY three of the following four criteria: o Generalised, papular and sclerodermoid eruption o Presence of monoclonal gammopathy o Absence of thyroid disease o Histological triad of mucin deposition, fibroblast proliferation and fibrosis as confirmed by biopsy	Patients with contraindications to therapy with human normal immunoglobulin are not eligible for treatment.	First, second or any line treatment. Clonal plasma cell is a key feature of scleromyxoederma. Consider plasma cell-directed therapies (anti-CD38, proteosome inhibitors, lenalidomie and its analogues) as an alternative to Ig.	Starting dose is 1-2g/kg by ideal body weight initially delivered at a frequency of every 4 weeks. Initially treatment should be delivered over 2-5 days. The dose can be modified according to treatment response Please refer to NHS England policy Human normal immunoglobulin for scleromyxedema (adults) Dose adjustment: Dose adjustment should be considered at 3, 6 and 12 months after starting treatment. The dose can be reduced by increasing the interval between treatments up to 6 weekly rather than 4 weekly. Alternatively, the dose given during each infusion can be reduced from 2g/kg. The minimum effective clinical dose to maintain remission should be established for each individual patient.	At 3, 6 and 12 months after starting treatment and beyond: • Absence or presence of systemic involvement, including progression to dermatoneuro syndrome as a marker of neurological involvement • Hospital admissions per year relating to scleromyxedema • Modified Rodnan skin score • Level of paraprotein	Yes

General notes: Dosing optimisation in neurology for maintenance

An ongoing issue for diseases that require long-term Ig treatment is that once significant and functional responsiveness to intravenous Ig (IVIg) is demonstrated for a patient using standard immunomodulatory dosing, the 'maintenance' dosing required to maintain the therapeutic response is not well characterised. In this update, the dosing recommendations for some neurological indications include 'time to relapse' as the interval between doses. This approach is supported by evidence from The Oxford Programme for Immunomodulatory Immunoglobulin Therapy, which was set up to review multifocal motor neuropathy (MMN) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) treatment with immunoglobulin. In view of the uncertainty of both remission and disease progression in CIDP and MMN, The Oxford Programme reviewed the dose and infusion frequency of patients on a regular basis and showed that increasing the infusion interval proved successful in some patients and resulted in treatment discontinuation[43]. Very rarely, a small minority of patients with CIDP and MMN may require higher doses of Ig (> 2g/kg/every 6 weeks) as maintenance treatment. Such patients should be closely monitored either in or in close liaison with specialist centres with specific expertise in the management of autoimmune neuropathies. Regular reasonable disease-relevant attempts should be made to establish continued requirements or the minimum effective dose by supported cessation trials, down titration of dose or extending the interval between infusions.

An alternative approach based on establishing the 'time to relapse' following the first or second dose followed by dose reduction has also been proposed and is equally feasible20. This ensures patients who need no more than 1 or 2 doses are not exposed to unnecessary doses and those with ongoing needs are optimised to a minimal dose.

Based on evidence from randomised trials, it is likely that up to 40% of patients with CIDP may be able to discontinue treatment[44] after 6 - 12 months, although a significant proportion may relapse and require retreatment. For this reason, periodic trials of cessation of treatment are recommended, especially in patients who appear to be stable even if optimally treated. The demonstration of continued IVIg requirement by forced suspension on more than 2 or 3 occasions over a 5-year period probably indicates ongoing long-term dependence and further withdrawals are highly unlikely to be effective. Referral to a specialist neurology centre is recommended as early as possible.

In inflammatory myositis, maintenance treatment with IVIg for a prolonged period (usually less than 12 months) may be required in a small minority of patients. In these cases, every effort should be made to establish the minimum clinically effective dose by either reduction of dose or lengthening the intervals between infusions. Cessation trials should be attempted at least annually to establish on-going need for treatment[45].

[43] Lucas M et al. J Clin Immunol. 2010 May;30 Suppl 1:S84-9.
[44] Adrichem M et al. J Peripher Nerv Syst. 2016 Sep;21(3):121-7.
[45] Foreman et al. Internal Med J 2017;47:112-115

For those disease indications in children and young adults where IVIg and plasma exchange (PLEX) are equally efficacious, IVIg may be preferentially considered if poor peripheral venous access or challenges in service delivery preclude the use of PLEX.

Specific exclusion criteria against the use of immunoglobulin have not been listed, but it is important to carry out benefit-risk analyses in certain patient groups: patients at high risk of thromboembolism (hypertension, diabetes, smoking, hypercoagulable states) should be counselled regarding the prothrombotic risks of immunoglobulin.

IgA deficiency is no longer considered a contra-indication to the use of immunoglobulin and should not be withheld because of theoretical concerns of adverse reactions. The role of anti-IgA antibodies in causing reactions is controversial and measurement of anti-IgA antibodies prior to undertaking treatment is not warranted.

Appendix B – Not Routinely Commissioned Indications

The Ig Expert Working Group (EWG) concluded that there was either insufficient evidence to support the routine commissioning of Ig to treat the following indications or that there was evidence to support a not routinely commissioned position:

- Acquired red cell aplasia NOT due to parvovirus B19
- Adrenoleukodystrophy
- Alzheimer's disease
- Amyotrophic lateral sclerosis
- Aplastic anaemia NOT due to parvovirus infection
- Asthma
- Atopic dermatitis/eczema
- Autoimmune neutropenia
- Autologous BMT
- Cerebral infarction with antiphospholipid antibodies
- Chronic facial pain
- Chronic fatigue syndrome
- Chronic idiopathic urticaria
- Chronic immune thrombocytopenia (ITP)
- Chronic regional pain syndrome
- CNS vasculitis
- Critical illness neuropathy
- Diabetic neuropathy
- Graves' ophthalmopathy
- Haemolytic uraemic syndrome
- Immunodeficiency secondary to paediatric HIV infection
- Inclusion body myositis
- Intractable childhood epilepsy
- IVF failure
- Multiple sclerosis
- Neonatal sepsis (prevention or treatment)
- Opsoclonus-myoclonus syndrome - adult carcinoma related
- Paediatric myocarditis
- PANS/PANDAS
- Paraneoplastic syndromes not known to be T or B cell mediated
- POEMS (polyneuropathy organomegaly, endocrinopathy/oedema, monoclonal protein, skin changes)
- Pyoderma gangrenosum
- Recurrent spontaneous pregnancy loss
- Rheumatoid arthritis
- Sepsis in the intensive care unit not related to specific toxins or C. difficile
- SLE with secondary immunocytopenias
- Systemic juvenile idiopathic arthritis
- Toxic epidermal necrolysis, including Steven Johnson Syndrome