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Proposed changes to the *Criteria for the clinical use of intravenous immunoglobulin in Australia, second edition*
(The Criteria)

Response to public consultation

Public consultation period 15 June – 27 July 2015

Introduction

Public consultation was conducted from Monday 15 June to Monday 27 July 2015, during which time the revision and rationale documents of the proposed changes to Chapters 5 and 6 of the Criteria (Edition 3) were available on the public consultation page of the NBA website for the information of key stakeholders and the general public. An electronic version of the revised Criteria was also made available through BloodSTAR User Acceptance Testing environment. The NBA invited a range of stakeholders, committees, working groups and interested people to provide submissions. Communication of the public consultation included:

- Letters to medical specialist societies, associations and colleges, and consumer groups
- Letters to active Prescribers
- Message on BloodChat
- Message on BloodPortal
- Email to NBA Immunoglobulin forum subscribers and Network of Committee members

The Specialist Working Groups (SWGs) met to review and consider all responses to the public consultation submissions and, where necessary, revised the proposed changes in accordance with the submissions.

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1. Summary of public consultation submissions

Twenty-three formal submissions were received, 11 by organisations and 12 by individuals.

2. Overview of main decisions taken in response to submission comments

A summary of general comments is presented below, followed by changes to specific conditions made in response to submissions.

General comments

Given that the Criteria now include the use of both subcutaneous and intravenous Ig formulations, the title will be amended to 'Criteria for the Use of Immunoglobulin Therapy in Australia'. Importantly, the Criteria is not a clinical practice guideline, it intends only to provide information about criteria for accessing immunoglobulin funded under the national blood arrangements.

It is acknowledged that the work undertaken to date by the Specialist Working Groups have considered the adaptation of existing conditions in Chapters 5 and 6 for suitability to an Immunoglobulin therapy ordering and clinical outcomes database (BloodSTAR). While some conditions in Chapter 7 have been under review to develop more formal criteria, patients with conditions listed in Chapter 7 will continue to be eligible for Ig in exceptional circumstances. Chapter 7 will be considered in the next phase of work and will be considerably updated and new indications will be considered in due course.

It is acceptable for a telephone or video-consultation with the appropriate specialist to be utilised in order to ensure that patients who are not located in a metropolitan area can receive access to timely treatment. A comment will be included to indicate that the use of telephone or video consultation would be at the discretion of the diagnosing/treating specialist.

Full details with references for all the scoring and assessment methods used within the Criteria will be provided in full detail and be accessible within the BloodSTAR system.

Governments in due course will consider a national process for appeal mechanisms for patients that may be ineligible within the Criteria.

Referral to the product insert is included in the current Criteria and is intended to refer users for additional information (other than dose) that is not included in the current publication. Such information includes but is not limited to the risks of adverse events.

Chapter 5: Conditions for which IVIg has an established therapeutic role

Chronic inflammatory demyelinating polyneuropathy

- The assessment system will be changed to INCAT- ONLS as it is more sensitive to lower limb changes than the INCAT.

Idiopathic (autoimmune) thrombocytopenia purpura (ITP) in adults

- The terminology for phases of disease has been revised and definitions included with revisions to the Description and Diagnostic criteria section.
- Criteria have been modified to more clearly emphasise clinically significant bleeding and the risk of bleeding in addition to platelet count.
- Criteria for clinical response to Ig treatment have been revised in line with the feedback provided:
 - The definition of clinical response to Ig therapy has been changed: “Response to Ig treatment demonstrated resolution of active bleeding or a reduction in evidence of bleeding correlating with a doubling of baseline platelet count and/or an increment in platelet count of greater than $10 \times 10^9/L$ within 7 days “
- Indications have been amended in relation to phase of disease terminology and the order of presentation has been changed:
 - Newly diagnosed ITP — Initial Ig therapy.
 - ITP in pregnancy -Initial Ig therapy
 - ITP with life-threatening haemorrhage or the potential for life-threatening haemorrhage.
 - Newly diagnosed or persistent ITP – subsequent therapy (diagnosis < 12 months)
 - Refractory persistent or chronic ITP — splenectomy failed or contraindicated and second-line agent unsuccessful.
 - Ongoing treatment for ITP responders during pregnancy and the postpartum period.
 - ITP and inadequate platelet count for planned surgery.
 - HIV-associated ITP.
- The indication relating to severe ITP has been removed.
- The qualifying criteria for HIV associated ITP have been amended in line with feedback.

Inflammatory myopathies – polymyositis (PM), dermatomyositis (DM) and necrotising autoimmune myositis (NAM)

- An option has been added to support Ig treatment where speech pathology assessment indicates that a video fluoroscopy would carry significant risk to patients with PM/DM with dysphagia.
- A separate indication has been added for children given that a combination of a characteristic rash, raised muscle enzymes, an objective measure of muscle weakness e.g. Childhood Myositis Assessment Scale (CMAS) and typical MRI scan abnormalities are considered sufficient for diagnosis, with muscle biopsy reserved for atypical cases. Qualifying and review criteria have been revised for children.
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Inflammatory myopathies – Inclusion body myositis (IBM)

- An option has been added to support Ig treatment where speech pathology assessment indicates that a video fluoroscopy would carry significant risk to patients with IBM and dysphagia
-

Primary immunodeficiency diseases with antibody deficiency

- The description and diagnostic criteria section has been modified to clarify that the ESID diagnostic criteria for PID have been used as a guide in the development of the qualifying criteria for Ig therapy in Australia. It is acknowledged that a low IgG alone is not a sufficient indication for immunoglobulin replacement and that many patients will be well despite the finding of a serum IgG below the normal range for age.
- The qualifying criteria related to specific antibody deficiency have been modified to recognise that when patients have an IgG<2g/L , there will be a failure to develop protective antibody post vaccination when they comply with all other criteria and a patient with profound deficiency should not be unduly exposed to additional risks from invasive bacterial infection.
- Guidance has been added regarding sampling for dual testing for serum IgA and IgG.

Secondary hypogammaglobulinaemia related to haematological malignancy and post HSCT

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- The following statement has been added to the description and diagnostic criteria section “Secondary hypogammaglobulinaemia may occasionally be complicated by a disseminated enterovirus infection, particularly in patients who have received B cell depletion therapy for a B cell lymphoproliferative disorder.”
- Exclusion criteria have been revised to more clearly refer the user to the correct condition. Within the BloodSTAR system, the user will be automatically directed to the correct screen.
- Duplicate measurements for serum IgG are recommended by the Immunology SWG given the invasive nature and cost of Ig treatment, such that a diagnosis of secondary hypogammaglobulinaemia requires confirmation. Additional scripts have been added to guide the prescriber as to IgG sampling. These are: "Serum IgG less than the lower limit of the reference range measured on two separate occasions (at least one hour apart and at least one sample taken when the patient does not have an active infection)."
- Statements regarding IgA and IgM levels have been revised to improve the clinical guidance being provided. "If serum IgM and IgA levels are trending upwards and close to normal, this may suggest recovery of the immune system and a trial might be commenced if the patient is well. Once the patient has normal IgA and IgM levels, the IgG is also likely to be normal and a trial off therapy may be undertaken." It is recognised that the decision to trial off Ig therapy is a clinical one.
- An evidence item to support the capture of paraproteins that may interfere with the interpretation of serum immunoglobulin results has been added.

Chapter 6: Conditions for which IVIg has an emerging therapeutic role

Autoimmune encephalitis mediated by antibodies targeting cell surface (previously known as limbic encephalitis – non paraneoplastic and Potassium antibody associated encephalopathy)

- A new condition is being proposed in response to feedback that will replace the above conditions in Chapter 7.
- Qualifying criteria have been developed to include a description of the clinical phenotype and the presence of neural antibodies to cell surface neural antigens, unless results are unavailable.
- Ig will be approved for an induction cycle (2g/kg over 5 days) with 2 maintenance doses (each up to 0.4g/kg) with review at 2 weeks to determine whether a significant clinical response has been demonstrated and that testing confirms the presence of relevant antibodies, prior to further authorisation.
- If patients respond and are authorized for ongoing therapy, further reviews will be undertaken 6 monthly to determine further clinical improvement or stability in symptoms.
- Trials off Ig therapy will be planned unless a valid reason is provided as to why a trial is contraindicated or not planned.

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Bullous pemphigoid

- Criteria have been revised to require positive autoantibody testing and/or biopsy confirmation rather than both.

Cicatricial pemphigoid

- Criteria have been revised to require positive autoantibody testing and/or biopsy confirmation rather than both.
- Clinical Immunologist has been added as a treating specialist for this condition.

Fetal and neonatal alloimmune thrombocytopenia (FNAIT)

- Condition name has been revised
- Qualifying criteria have been amended to include previous affected sibling (in addition to previous fetal death) in the setting of platelet specific maternal antibodies (to paternal antigens) known or suspected to have caused this condition.

Haemophagocytic syndrome

- The diagnostic criteria have been revised to include content from the reference (Jordan et al, 2011) and the qualifying criteria have been changed to reflect consistency with these revised diagnostic criteria.

Idiopathic (autoimmune) thrombocytopenia purpura (ITP) in children

- Phases of disease have been revised and definitions included with revisions to the Description and Diagnostic criteria section and relevant terms in indications for treatment.

Lambert–Eaton myasthenic syndrome (LEMS)

- Minor change to clarify that immunosuppression is not used in paraneoplastic LEMS

Pemphigus foliaceus

- Criteria have been revised to require positive autoantibody testing and/or biopsy confirmation rather than both.
- Clinical Immunologist has been added as a treating specialist for this condition.

Pemphigus vulgaris

- Criteria have been revised to require positive autoantibody testing and/or biopsy confirmation rather than both.
- Clinical Immunologist has been added as a treating specialist for this condition.

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- At review, the response to Ig treatment will be limited to a clinical assessment and not require anti-keratinocyte antibodies.

Post-transfusion purpura

- A text box to support the recording of clinical benefit from Ig therapy has been added and the outcome measure amended as suggested.

Secondary hypogammaglobulinaemia unrelated to haematological malignancy

- The following statement has been added to the description and diagnostic criteria section "Secondary hypogammaglobulinaemia may occasionally be complicated by a disseminated enterovirus infection, particularly in patients who have received B cell depletion therapy for a B cell lymphoproliferative disorder."
- Exclusion criteria have been revised to more clearly refer the user to the correct condition. Within the BloodSTAR system, the user will be automatically directed to the correct screen.
- Duplicate measurements for serum IgG are recommended by the Immunology SWG given the invasive nature and cost of Ig treatment, such that a diagnosis of secondary hypogammaglobulinaemia requires confirmation. Additional scripts have been added to guide the prescriber as to IgG sampling. These are: "Serum IgG less than the lower limit of the reference range measured on two separate occasions (at least one hour apart and at least one sample taken when the patient does not have an active infection)."
- Statements regarding IgA and IgM levels have been revised to improve the clinical guidance being provided. "If serum IgM and IgA levels are trending upwards and close to normal, this may suggest recovery of the immune system and a trial might be commenced if the patient is well. Once the patient has normal IgA and IgM levels, the IgG is also likely to be normal and a trial off therapy may be undertaken." It is recognised that the decision to trial off Ig therapy is a clinical one.

Specific antibody deficiency (including IgG subclasses)

- The description and diagnostic criteria section has been redrafted to include both specific IgG testing and IgG serotype testing. The changes have been made in consultation with each of the testing laboratories that perform serotype testing to ensure that the content is consistent with current laboratory practice in Australia.
- The qualifying criteria have been modified to include that when serum IgG<2g/L and the patient would be at significant risk from a delay to providing Ig replacement (eg following an invasive bacterial infection), IgG can be prescribed without waiting for vaccination testing.

3. Responses to public consultation by specialty

| Neurology | | | |
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| # | Section | Comments | Response |
| Acute disseminated encephalomyelitis (ADEM) | | | |
| 1 | Specific conditions | <p>My main feedback is that the list of autoimmune encephalitides is outdated and reflects historical accretion rather than current pathophysiological knowledge and expert treatment. It also does not reflect current neurological practice or expert opinion.</p> <p>This is understandable, as the field of autoimmune encephalitides has undergone dramatic changes in the last few years, with new conditions being described several times a year, and with a rapidly expanding evidence base(1). As such, the criteria require review by an expert in this area. For instance, 'opsoclonus myoclonus ataxia' is not a defined pathophysiological entity, but a collection of neurological symptoms, of autoimmune or paraneoplastic aetiology, associated with various onconeural antibodies (Hu, Ri etc), which is known to occur in association with particular cancers (neuroblastoma, breast cancer), and also in cases where the trigger is unknown(2).The criteria neglect NMDA encephalitis, which is far more common than OM or 'potassium channel antibody-associated encephalopathy' (known in most cases now to be due to antibody-mediated attack not on the potassium channel but LGI1) (3). For NMDA encephalitis, IVIG is recommended by expert opinion as first-line treatment (4). It is now relatively well-recognised and established by experts in the field that auto-immune encephalitides can be divided into two main categories, those in which the antigen target is extracellular, the immune response more humoral, and the response to immunotherapy (including IVIG) excellent, and conversely, those in which in target is intracellular, the immune response more cell-mediated, and the response to immunotherapy poor(1, 2).</p> <p>I would therefore recommend that 'Antibody-mediated autoimmune encephalitides' be designated as a stand-alone group in the 'Emerging Therapeutic Role' Category, and the various targets (NMDA, LGI1 etc) listed in the supporting information, and 'Cell-mediated auto-immune encephalitides' (anti-Hu, anti-Ri, etc) be placed in the Exceptional Circumstances only group.</p> <p>The use of IVIG in these conditions is far more widespread and common than, say, opsoclonus-myoclonus, PANDAS (again a very disputed entity), NMO, MS and ADEM.</p> | <p>Thank you for your feedback. The work to date by the Neurology Specialist Working Group has examined the adaptation of existing conditions in Chapters 5 and 6 and proposed changes were presented for public consultation and feedback. Chapter 7 is now being considered including the access criteria for Antibody mediated autoimmune encephalitis. This will be considerably updated and new indications will be considered in due course.</p> |

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| # | Section | Comments | Response |
| | | <ol style="list-style-type: none"> 1. Didelot A, Honnorat J. Paraneoplastic disorders of the central and peripheral nervous systems. Handbook of clinical neurology. 2014;121:1159-79. PubMed PMID: 24365410. Epub 2013/12/25. eng. 2. Paul NL, Kleinig TJ. Therapy of paraneoplastic disorders of the CNS. Expert review of neurotherapeutics. 2015 Feb;15(2):187-93. PubMed PMID: 25614953. 3. Lai M, Huijbers MG, Lancaster E, Graus F, Bataller L, Balice-Gordon R, et al. Investigation of LGI1 as the antigen in limbic encephalitis previously attributed to potassium channels: a case series. Lancet Neurol. 2010 Aug;9(8):776-85. PubMed PMID: 20580615. Epub 2010/06/29. eng. 4. Titulaer MJ, McCracken L, Gabilondo I, Armangue T, Glaser C, Iizuka T, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol. 2013 Feb;12(2):157-65. PubMed PMID: 23290630. Pubmed Central PMCID: 3563251. | |
| Chronic inflammatory demyelinating polyneuropathy (CIDP) | | | |
| 2 | Qualifying criteria | <p>I have suffered from CIDP since 2003 but took until 2010 to get a diagnosis. I was put on IVIG but developed Ulcerative Colitis at this time and was taken off IVIG just in case this was an adverse reaction. I suffered with a UC flare for a few years and the condition was fulminant with prednisone not having the desired impact and I was placed on Imuran and Pentasa. I had a lot of time off work and was severely restricted in my activities. I acquired a C.Diff infection in 2012 and was placed in Westmead Hospital. At this time, my CIDP flared and I was unable to walk even a short distance unaided and the use of my hands was limited. I was given flagyl for the C.Diff, iron infusion (and other medications as I was extremely weak) and 5 doses of IVIg. I left Westmead after 10 days using a walking stick and it was several weeks before I could walk unaided. I have been on IVIG since. Also, since that time my UC had become stable and by August 2013 my UC had gone completely with no signs or symptoms. I am still on Imuran and Pentasa but I attribute my UC remission to the IVIG. My CIDP has been described as stable but this is not without the use of other strategies such as regular weight training. I have severe muscle wastage in the calves and have no ankle reflexes and my foot reflexes are distorted. I can walk fairly well as I take care where I walk and on what surfaces, I take care to exercise what muscles I have in my legs to ensure I can</p> | Comments noted with thanks |

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| | | <p>get around, I eat well but am battling low iron which has been a concern left over from my severe UC but is improving. It is a combination of IVIG, Imuran, Pentasa, regular exercise and healthy diet that keeps me going and enables me to work and have a reasonable quality of life. I firmly believe just as Imuran has been prescribed for my UC it is also beneficial for my CIDP and similarly IVIG helps keep my UC in remission and my CIDP stable. I am concerned being taken off IVIG may lead to a flare of my UC, my CIDP or even both, with significant health and quality of life consequences. Acquiring a C.Diff infection that caused both my UC and CIDP to flare literally nearly killed me and I firmly believe my other strategies maintaining regular exercise and healthy living gave me the strength to survive this triple impact. In this regard, just looking at CIDP and IVIG use and not looking at the whole of the body and life of the patient may result in unintended consequences. It is not just IVIG that keeps me going but a suite of strategies. Being paralysed with CIDP is really bad and a UC flare is a living hell. It has been a long journey to get to where I am now and it is a constant balancing act to be able to work and have a life at the same time suffering two chronic autoimmune conditions for which there are no cures and treatments that may or may not work. Thankfully the suite of strategies are working now and I do not like to dwell on the quality of life I would not have, if any of these treatments or medications were withdrawn and one or more of the conditions went into a flare. I fully understand the cost of my combined treatments are approx \$6,000 per month and I am immensely grateful for this. I could not pay for this myself but as the Chair of the Guillain Barre Syndrome Association of NSW Inc. I have placed myself in a position where I am able to give back to the medical system and help others who have experienced the stress and trauma of GBS/CIDP. Further, I am also a member of Crohns/Colitis Australia. I do not want to have CIDP or UC and I do not want the public to have to pay huge sums for my treatment. I cannot change that but taking me off IVIG with the risk of a flare and perhaps a disability pension and early retirement if I can no longer work is of no benefit to me or the public purse. In addition, whilst my assertions are only anecdotal I believe IVIG should be trialled for Crohns/Colitis patients who have shown no improvement with other therapies, as I firmly believed it worked for me and still works.</p> | |
| 3 | Qualifying and Review Criteria | <p>Treatment of CIDP- walking compromised or significant disability AND Relapse of CIDP- within 6 months of commencement of trial off IVIg</p> | Thank you for your input. The SWG considered the various rating scores to which you |

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| | | <p>Re clinical outcome scales- comments relevant for criteria and types of treatment: Clinical rating scales in CIDP are rapidly changing. The most recently devised rating scale suggested as a suitable measure to assess response to therapy or presence of relapse is the Adjusted INCAT score - first published in original form as INCAT/ODSS scale in 2002 by the Inflammatory Neuropathy Consortium division of the Peripheral Nerve Society. <i>Merkies et al, Clinimetric evaluation of a new overall disability scale in immune mediated polyneuropathies JNNP 2002.</i></p> <p>In 2006, this was shown to be better than other more general disability scales in evaluating clinical course of CIDP, (<i>Merkies et al JNNP 2006- Getting closer to patients...</i>)</p> <p>More recently, due to concerns about limitations and/or inadequate "responsiveness" of this scoring system in both clinical trials and the clinical setting, newer validated rating scales have been devised and validated by the "inflammatory" subgroups of the international Peripheral Nerve Society. These are:</p> <p>1. ONLS- Overall Neuropathy Limitations Scale (<i>Graham and Hughes A modified peripheral neuropathy scale: the Overall Neuropathy Limitations Scale</i>) JNNP 2006. This was shown to be an improvement on the original INCAT/ODSS due to the "ceiling effect" of the lack of any better motor function than walking 10 metres and it was adjusted to reflect a better motor function of being able to run or climb a flight of stairs.</p> <p>Then in 2008, Hughes et al republished the INCAT/ODSS scale as the "Adjusted INCAT Scale" based on the ONLS. Currently there are, rather confusingly, references to-BOTH terms appearing still in very recent literature and neuropathy presentations. The "ICE" study re the role of IVIg in CIDP treatment and maintenance (2008). Although adjusted INCAT and MRC scores were recently evaluation has shown that some of the secondary measures- eg vigorimeter grip strength (not widely available in Australia currently) was more sensitive that a 1-point change in adjusted INCAT score {<i>Vigorimeter grip strength in CIDP: a responsive tool that rapidly measures the effect of IVIg- Vanhoutte et al, Eur J Neurol May 2013</i>}.</p> <p>2. Finally, since 2010-2011 there have been moves to introduce a totally new disability scale</p> | <p>refer and is familiar with the references mentioned, including the use of R-ODS and grip strength. It was felt that the scale selected had to be familiar to all neurologists, easy to perform in the clinical setting, and not require specific equipment. For CIDP, the rating system will be changed to INCAT-ONLS as it is more sensitive to lower limb changes than the INCAT.</p> |

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| | | <p>for CIDP that was derived from WHO criteria and tested with Rasch analysis- the R-ODS score or Rasch built Overall Disability Score, with the adjustment for inflammatory neuropathies called I-R-ODS. Graham and Hughes (2006) pointed out that the INCAT/ODSS score was originally modified from the Guys neurological Disability Scale, used for assessment of MS. Very recent studies have shown that the I-RODS is now showing greater responsiveness than either the INCAT scales or summed MRC scales for changes in clinical status of CIDP and GBS. (<i>Vanhoutte et al J PNS June 26 2015), Impairment measures versus inflammatory -RODS in GBS and CIDP: A responsiveness comparison.</i>)</p> <p>Conclusion:</p> <p>At least one of clinical scale options in all the sections relating to CIDP should be I-RODS (please check with PN Society re cut-offs for "relapse" currently being utilized)</p> <p>Failure to respond on MRC/INCAT despite global clinical impression of a response, or patient impression of relapse but not detectable on either MRC or INCAT should suggest use (and "currently in favour with PNS") of I-RODS before option of IVIg is abandoned. For further example of trend away from INCAT, see <i>Phase 4 CIDP Alemtuzumab trial- evaluating 1-RODS/ CIDP RODS and ONLS as rating scales (2012-2016)</i> General Re all rating scales to be used - please publish preferred version IN FULL on Bloodstar/Blood Bank website with original references for clinician to refer to- for CIDP and all other diseases.</p> <p>NB Several difference versions could cause confusion, and delays in treatment could occur if the clinical has difficulty identifying or accessing a particular journal, to locate a full copy of the rating scale in order to generate a score.</p> <p>SPECIAL CASES</p> <p>Please also consider an "appeal system" for special cases with either a specialist clinician or panel to review cases where one or more clinicians believe a patient would benefit from receiving/not ceasing IVIg despite not meeting new published criteria (for CIDP or any other disease).</p> | |
| 4 | Qualifying Criteria | <p>(including IgG and IgA paraproteinaemic neuropathies)</p> <p>Adult or child (10 years or older) demonstrating significant disability or compromised</p> | Full details with references for all the scoring methods used |

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| | | walking as objectively measured by Inflammatory Neuropathy Cause and Treatment (INCAT) score of greater than 1 point OR Child less than 10 years demonstrating significant disability or compromised walking. (A baseline Modified Rankin ADL and Six Minute Walk Test should be performed in order to assess the patient's response at initial review). These scales may not be routinely used in the clinical area. Is it possible to be able to access these in the database? | within the Criteria will be provided and be accessible within BloodSTAR. |
| 5 | Dose | 1. Not all funded IVIGs have a Therapeutic Goods Administration (TGA) approved indication for CIDP or MMN. 2. The recommendation to Refer to the current product information sheet for further information under 'Dose' may be misleading as not all IVIGs are indicated for the condition and will not contain further information in the Product Information. 3. Where a funded IVIG has a TGA approved indication in CIDP & MMN there is no guidance for dosage in the Product Information for 'Relapse of CIDP or MMN patients within six months of commencement of trial off immunoglobulin therapy' | 1. Noted. 2. and 3. Referral to the product insert is included to refer users for additional information (other than dose) that is not included in the publication of the Criteria for use or BloodSTAR (eg risks of adverse events). |
| Guillain–Barré syndrome (GBS) | | | |
| 6 | Qualifying criteria | Please allow for I-RODS score changes to also be generated during assessment as an additional outcome measure (see above for details) at #5 | In the first instance, the assessment method as currently proposed for GBS will be retained. |
| 7 | Qualifying criteria | Initial therapy for GBS with significant disability and progression Requested treatment for a GBS pt and addressed the criteria as follows believing that this would be sufficient to gain access. I Selected: Criterion 1 Patient with GBS demonstrates significant disability as objectively measured by the GBS | The qualifying criteria are unchanged in intention from the current version (2) but have been reworded to provide greater clarity of the |

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| | | <p>disability Score of greater than one point(adapted from Hughes et al 1978)</p> <p>However the Criteria also require selection of Criterion 3.</p> <p>Criterion 3</p> <p>The progressive nature of the weakness indicates a trajectory to significant disability.</p> <p>Point of view is that if patient already has significant disability then their trajectory to significant disability is irrelevant. If criterion 2 is selected then you might also want the patient to have criterion 3. This would make the logic:</p> <p>[Criteria Group 1]</p> <p>Criterion 1</p> <p>OR</p> <p>[Criteria Group 2]</p> <p>- Criterion 2</p> <p>AND</p> <p>- Criterion 3</p> | <p>meaning of 'disease progression'. There are two requirements to the current criteria: severity and a trend towards worsening disability. If a patient has plateaued and there is no continuing progression, then Ig is not indicated, irrespective of the level of disability.</p> |
| Inflammatory myopathies: Inclusion body myositis (IBM) | | | |
| 8 | Qualifying criteria | <p>Dysphagia limiting dietary intake with involvement of pharyngeal muscles as demonstrated by videofluoroscopy</p> <p>Is video fluoroscopy readily available to use routinely to assess this? Is choking on food with a diagnosis of IBM not sufficient?</p> | <p>An option has been added to support Ig treatment where speech pathology assessment indicates that a video fluoroscopy would carry significant risk to patients with IBM and dysphagia and PM/DM with dysphagia.</p> |
| 9 | Dose | <p>1. Not all funded IVIGs have a TGA approved indications for MG, LEMS, Stiff person syndrome, Inflammatory myopathies (IBM) or Inflammatory myopathies (PM,DM,NAM).</p> <p>2. The recommendation to Refer to the current product information sheet for further information under 'Dose' may be misleading as not all IVIGs are indicated for the conditions</p> | <p>1. Noted.</p> <p>2. Referral to the product insert is included to refer users for additional information (other than dose) that is not</p> |

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| | | and thus will not contain further information in the Product Information. | included in the publication of the Criteria for use or BloodSTAR (eg risks of adverse events). |
| 10 | Qualifying Criteria | <p>Significant dysphagia limiting dietary intake with involvement of pharyngeal muscles as demonstrated by videofluoroscopy.</p> <p>In some circumstances, it is too dangerous due to aspiration risk to perform this study but a Speech Pathologist may be able to identify that the patient has a likely neuromuscular dysphagia in the context of a biopsy proven case of muscle disease. An alternative of "bulbar muscle weakness as confirmed by Speech Pathologist clinical assessment if video fluoroscopy contraindicated" should be an alternative option.</p> <p>Appeal mechanism please</p> | <p>1. An option has been added to support Ig treatment where speech pathology assessment indicates that a video fluoroscopy would carry significant risk to patients with IBM and dysphagia and PM/DM with dysphagia.</p> <p>2. A national process for appeal mechanisms for ineligible patients will be considered by governments in due course.</p> |
| Inflammatory myopathies: Polymyositis (PM), Dermatomyositis (DM), Necrotising autoimmune myopathy (NAM) | | | |
| 11 | Qualifying Criteria | <p>Patients with biopsy proven PM, DM or NAM who have muscle weakness or dysphagia unresponsive to corticosteroids and other immunosuppressant medications.</p> <p>1) There is no mention of Juvenile Dermatomyositis (JDM), Juvenile Polymyositis (JPM) in the listed conditions in this category. This leaves children with JDM without access to IVIg under the qualifying conditions</p> <p>2) Muscle biopsies are rarely performed in JDM (see attached article from our centre; other centres have noted the same). The clinical presentation of the disease in combination with an MRI confirming diffuse myositis has supplanted biopsy in all but those cases where the presentation is unusual. A child with JDM may respond poorly to steroids/immunosuppressives without the diagnosis being in question. The requirement for a muscle biopsy to access IVIG in this situation is overly burdensome and unnecessary.</p> | <p>Thank you for your submission. A separate indication has been added for children to support the different approach to diagnosis, assessment and management. In particular, the proposed diagnostic approach and assessment methodology has been included in the amended qualifying and review criteria.</p> |

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| | | 3) The use of The Medical Research Council Sum (12) score as the means by which weakness is measured- is not validated in JDM/ JPM and thus should not be used to assess applications and response to therapy. The Childhood Myositis Assessment Scale (CMAS) is validated for this purpose. | |
| 12 | Qualifying Criteria | <p>Significant dysphagia limiting dietary intake with involvement of pharyngeal muscles as demonstrated by video fluoroscopy.</p> <p>In some circumstances, it is too dangerous due to aspiration risk to perform this study but a Speech Pathologist may be able to identify that the patient has a likely neuromuscular dysphagia in the context of a biopsy proven case of muscle disease. An alternative of "bulbar muscle weakness as confirmed by Speech Pathologist clinical assessment if video fluoroscopy contraindicated" should be an alternative option.</p> <p>Appeal mechanism please</p> | <p>1. An option has been added to support Ig treatment where speech pathology assessment indicates that a video fluoroscopy would carry significant risk to patients with IBM and dysphagia and PM/DM with dysphagia.</p> <p>2. A national process for appeal mechanisms for ineligible patients will be considered by governments in due course.</p> |
| 13 | Qualifying Criteria | <p>Significant muscle weakness as measured by Medical Research Council (MRC) Sum (12) Score to a value of less than 56 points</p> <p>Can the database offer these scales to click on for the ordering physician? These scales may not be routinely used in the clinical areas.</p> | Full details with references for all the scoring methods used within the Criteria will be provided and be accessible within BloodSTAR. |
| 14 | Dose | <p>1. Not all funded IVIGs have a TGA approved indications for MG, LEMS, Stiff person syndrome, Inflammatory myopathies (IBM) or Inflammatory myopathies (PM,DM,NAM).</p> <p>2. The recommendation to Refer to the current product information sheet for further information under 'Dose' may be misleading as not all IVIGs are indicated for the conditions and thus will not contain further information in the Product Information.</p> | <p>1. Noted.</p> <p>2. Referral to the product insert is included to refer users for additional information (other than dose) that is not included in the publication of</p> |

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| | | | the Criteria for use or BloodSTAR (eg risks of adverse events). |
| 15 | Indication | <p>As the rheumatologist in charge at the Gold Coast University Hospital I have been responsible for the care of a number of patients with immunodeficiency states over the last 30 years, as we do not have an immunologist. This is the most obvious area for IVIG. We now have a new full-time staff specialist in rheumatology and hopefully we will have an immunologist in the not too distant future.</p> <p>As a rheumatologist, on rare occasions we have needed to use IVIG when other treatment has failed. The most common of these is dermatomyositis which has not responded adequately to immunosuppression and corticosteroids in high doses. Similarly it may be employed in polymyositis. There are no adequately blinded study is on this treatment to my knowledge but there is a large anecdotal literature and this has been accepted by the Red Cross Blood Bank when we have applied for the use of this agent. These are rare disorders and consequently I would not think that the demand for IVIG would be high.</p> <p>2 other areas exist where we have occasionally used IVIG, namely vasculitis and Bechet's disease. In both instances this has been when conventional therapy including immunosuppression and cytotoxics have failed. In vasculitis we have been using rituximab more frequently as this has TGA approval for 2 of the commoner conditions.</p> <p>I would agree that there is a necessity to demonstrate the effectiveness of IVIG therapy in any patient who has been placed on treatment. Once a satisfactory remission has been obtained, then usually the IVIG is the first to be reduced or removed.</p> <p>I welcome the opportunity to assist in further in regards to developing the criteria should this be needed.</p> | Noted. |
| Lambert–Eaton myasthenic syndrome (LEMS) | | | |
| 16 | Qualifying Criteria | <p>Severe LEMS with impairment as demonstrated by Medical Research Council (MRC) Sum (12) Score</p> <p>These scales may not be routinely used in the clinical area. Is it possible to be able to access</p> | Full details with references for all the scoring methods used within the Criteria will be provided and be accessible |

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| | | these in the database? | within BloodSTAR. |
| 17 | Indication | Accordingly immunosuppression has not generally been applied in paraneoplastic LEMS. Does this mean that paraneoplastic LEMS is not eligible for IVIg? | The reference to immunosuppression in paraneoplastic LEMS has been modified to confirm that "immunosuppression is not generally applied in paraneoplastic LEMS" does not mean that IVIg cannot be used for immunomodulation. |
| 18 | Dose | <p>1. Not all funded IVIGs have a TGA approved indications for MG, LEMS, Stiff person syndrome, Inflammatory myopathies (IBM) or Inflammatory myopathies (PM,DM,NAM).</p> <p>2. The recommendation to Refer to the current product information sheet for further information under 'Dose' may be misleading as not all IVIGs are indicated for the conditions and thus will not contain further information in the Product Information.</p> | <p>1. Noted.</p> <p>2. Referral to the product insert is included to refer users for additional information (other than dose) that is not included in the publication of the Criteria for use or BloodSTAR (eg risks of adverse events).</p> |
| Multifocal motor neuropathy (MMN) | | | |
| 19 | Qualifying criteria | <p>Please print source and full text of adjusted INCAT score</p> <p>If RODS becomes used regularly by PN Society in MMN studies in next couple of years, then a RODS measurement will need to be added as an option for patients who might be part of larger studies.</p> <p>Appeal mechanism please.</p> | <p>1. Full details with references for all the scoring methods used within the Criteria will be provided and be accessible within BloodSTAR.</p> <p>2. BloodSTAR will be sufficiently flexible to support change and updating of scoring systems as required by</p> |

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| | | | changes in the standard of care. 3. A national process for appeal mechanisms for ineligible patients will be considered by governments in due course. |
| 20 | Dose | <p>1. Not all funded IVIGs have a Therapeutic Goods Administration (TGA) approved indication for CIDP or MMN.</p> <p>2. The recommendation to Refer to the current product information sheet for further information under 'Dose' may be misleading as not all IVIGs are indicated for the condition and will not contain further information in the Product Information.</p> <p>3. Where a funded IVIG has a TGA approved indication in CIDP & MMN there is no guidance for dosage in the Product Information for 'Relapse of CIDP or MMN patients within six months of commencement of trial off immunoglobulin therapy'</p> | <p>1. Noted.</p> <p>2. and 3. Referral to the product insert is included to refer users for additional information (other than dose) that is not included in the publication of the Criteria for use or BloodSTAR (eg risks of adverse events).</p> |
| Myasthenia gravis (MG) | | | |
| 21 | Qualifying criteria | <p>Myasthenia Gravis Composite Score</p> <p>These scales may not be routinely used in the clinical area. Can they be accessed on the database?</p> | Full details with references for all the scoring methods used within the Criteria will be provided and be accessible within BloodSTAR. |
| 22 | Qualifying criteria | <p>Myasthenic crisis as an alternative treatment to plasma exchange.</p> <p>AND</p> <p>As maintenance therapy for moderate to severe MG when other treatments have been ineffective or caused intolerable side effects.</p> <p>Please print both reference and full text of MG Composite Score</p> | <p>1. Full details with references for all the scoring methods used within the Criteria will be provided and be accessible within BloodSTAR.</p> <p>2. A national process for</p> |

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| | | Appeal mechanism needed- as above. | appeal mechanisms for ineligible patients will be considered by governments in due course. |
| 23 | Dose | <p>1. Not all funded IVIGs have a TGA approved indications for MG, LEMS, Stiff person syndrome, Inflammatory myopathies (IBM) or Inflammatory myopathies (PM,DM,NAM).</p> <p>2. The recommendation to Refer to the current product information sheet for further information under 'Dose' may be misleading as not all IVIGs are indicated for the conditions and thus will not contain further information in the Product Information.</p> | <p>1. Noted.</p> <p>2. Referral to the product insert is included to refer users for additional information (other than dose) that is not included in the publication of the Criteria for use or BloodSTAR (eg risks of adverse events).</p> |
| Opsoclonus-myoelonus ataxia (OMA) | | | |
| 24 | Specific conditions | <p>My main feedback is that the list of autoimmune encephalitides is outdated and reflects historical accretion rather than current pathophysiological knowledge and expert treatment. It also does not reflect current neurological practice or expert opinion.</p> <p>This is understandable, as the field of autoimmune encephalitides has undergone dramatic changes in the last few years, with new conditions being described several times a year, and with a rapidly expanding evidence base(1). As such, the criteria require review by an expert in this area. For instance, 'opsoclonus myoclonus ataxia' is not a defined pathophysiological entity, but a collection of neurological symptoms, of autoimmune or paraneoplastic aetiology, associated with various onconeural antibodies (Hu, Ri etc), which is known to occur in association with particular cancers (neuroblastoma, breast cancer), and also in cases where the trigger is unknown(2).The criteria neglect NMDA encephalitis, which is far more common than OM or 'potassium channel antibody-associated encephalopathy' (known in most cases now to be due to antibody-mediated attack not on the potassium channel but LGI1) (3). For NMDA encephalitis, IVIG is recommended by expert opinion as first-line treatment (4). It is now relatively well-recognised and established by experts in the field that auto-immune encephalitides can be divided into two main categories, those in</p> | <p>Thank you for your feedback. The work to date by the Neurology Specialist Working Group has examined the adaptation of existing conditions in Chapters 5 and 6 and proposed changes were presented for public consultation and feedback. Chapter 7 is now being considered including the access criteria for Antibody mediated autoimmune encephalitis. This will be considerably updated and new indications will be considered</p> |

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| | | <p>which the antigen target is extracellular, the immune response more humoral, and the response to immunotherapy (including IVIG) excellent, and conversely, those in which in target is intracellular, the immune response more cell-mediated, and the response to immunotherapy poor(1, 2).</p> <p>I would therefore recommend that 'Antibody-mediated autoimmune encephalitides' be designated as a stand-alone group in the 'Emerging Therapeutic Role' Category, and the various targets (NMDA, LGI1 etc) listed in the supporting information, and 'Cell-mediated auto-immune encephalitides' (anti-Hu, anti-Ri, etc) be placed in the Exceptional Circumstances only group.</p> <p>The use of IVIG in these conditions is far more widespread and common than, say, opsoclonus-myoclonus, PANDAS (again a very disputed entity), NMO, MS and ADEM.</p> <ol style="list-style-type: none"> 1. Didelot A, Honnorat J. Paraneoplastic disorders of the central and peripheral nervous systems. Handbook of clinical neurology. 2014;121:1159-79. PubMed PMID: 24365410. Epub 2013/12/25. eng. 2. Paul NL, Kleinig TJ. Therapy of paraneoplastic disorders of the CNS. Expert review of neurotherapeutics. 2015 Feb;15(2):187-93. PubMed PMID: 25614953. 3. Lai M, Huijbers MG, Lancaster E, Graus F, Bataller L, Balice-Gordon R, et al. Investigation of LGI1 as the antigen in limbic encephalitis previously attributed to potassium channels: a case series. Lancet Neurol. 2010 Aug;9(8):776-85. PubMed PMID: 20580615. Epub 2010/06/29. eng. 4. Titulaer MJ, McCracken L, Gabilondo I, Armangue T, Glaser C, Iizuka T, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol. 2013 Feb;12(2):157-65. PubMed PMID: 23290630. Pubmed Central PMCID: 3563251. | in due course. |
| Stiff person syndrome | | | |
| 25 | Qualifying criteria | <p>Please print full text and list source of ratings scale used -Modified Rankin and Distribution of Stiffness Index.</p> <p>Appeal mechanism please.</p> | 1. Full details with references for all the scoring methods used within the Criteria will be provided and be accessible |

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| | | | <p>within BloodSTAR.</p> <p>2. A national process for appeal mechanisms for ineligible patients will be considered by governments in due course.</p> |
| 26 | Dose | <p>1. Not all funded IVIGs have a TGA approved indications for MG, LEMS, Stiff person syndrome, Inflammatory myopathies (IBM) or Inflammatory myopathies (PM,DM,NAM).</p> <p>2. The recommendation to Refer to the current product information sheet for further information under 'Dose' may be misleading as not all IVIGs are indicated for the conditions and thus will not contain further information in the Product Information.</p> | <p>1. Noted.</p> <p>2. Referral to the product insert is included to refer users for additional information (other than dose) that is not included in the publication of the Criteria for use or BloodSTAR (eg risks of adverse events).</p> |
| 27 | Indications | <p>There are a growing number of neurological disorders associated with high titres of autoantibodies to neuronal antigens for which IVIG may be of benefit (eg syndrome of pharmaco-resistant epilepsy, diabetes and pernicious anaemia associated with anti-GAD). The current list in the criteria for use is selective and probably out of date. It might be preferable to broaden this to a generic category such as:</p> <p>Non-paraneoplastic central nervous system autoimmune disease in which there is:</p> <ol style="list-style-type: none"> 1. No evidence of structural brain lesion 2. Evidence of a high titre of antibodies to neuronal antigen 3. Poor response to conventional therapy. | <p>Thank you for your feedback. The work to date by the Neurology Specialist Working Group has examined the adaptation of existing conditions in Chapters 5 and 6 and proposed changes were presented for public consultation and feedback. Chapter 7 is now being considered including the access criteria for Antibody mediated autoimmune encephalitis. This will be considerably updated and new indications will be considered</p> |

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| | | | in due course. |
| All conditions | | | |
| 28 | Qualifying Criteria | I would suggest that links be incorporated to the scores required for the diagnostic and prescribing criteria as the majority of people do not use the scores suggested routinely. The review for most conditions seems to be after 4/12, whereas I have routinely waited 6/12, so this will have to be a change to my practice, unless there is a loosening of the suggested time frames for review. | Full details with references for all the scoring methods used within the Criteria will be provided and be accessible within BloodSTAR. |
| 29 | Qualifying Criteria | <p>Re all rating scales to be used - please publish preferred version IN FULL on Bloodstar/Blood Bank website with original references for clinician to refer to- for CIDP and all other diseases.</p> <p>NB: Several different versions could cause confusion, and delays in treatment could occur if the clinical has difficulty identifying or accessing a particular journal, to locate a full copy of the rating scale in order to generate a score.</p> <p>SPECIAL CASES Please also consider an "appeal system" for special cases with either a specialist clinician or panel to review cases where one or more clinicians believe a patient would benefit from receiving/not ceasing IVIg despite not meeting new published criteria (for CIDP or any other disease).</p> | <p>1. Full details with references for all the scoring methods used within the Criteria will be provided and be accessible within BloodSTAR.</p> <p>2. A national process for appeal mechanisms for ineligible patients will be considered by governments in due course.</p> |
| 30 | Review criteria | <p>6 monthly specialist as for haematology and immunology reviews, not annually. Physician/GP shared care review for remote/rural patients.</p> <p>Criteria for response need to be strict and quantifiable and assessed centrally (Red Cross).</p> | 1. Review periods have been considered for each neurological condition and recommendations made to support the requirements for specific phases of clinical treatment and disease including reducing the trial period from 6 to 4 months in order to cease treatment |

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| | | | earlier where response has not been demonstrated. 2. Noted. |
| Epilepsy (Chapter 7) | | | |
| 31 | Chapter in Criteria | <p>There are a growing number of neurological disorders associated with high titres of autoantibodies to neuronal antigens for which IVIg may be of benefit (eg syndrome of pharmaco-resistant epilepsy, diabetes and pernicious anaemia associated with anti-GAD). The current list in the criteria for use is selective and probably out of date. It might be preferable to broaden this to a generic category such as:</p> <p>Non-paraneoplastic central nervous system autoimmune disease in which there is:</p> <ol style="list-style-type: none"> 1. No evidence of structural brain lesion 2. Evidence of a high titre of antibodies to neuronal antigen 3. Poor response to conventional therapy. | <p>Thank you for your feedback. The work to date by the Neurology Specialist Working Group has examined the adaptation of existing conditions in Chapters 5 and 6 and proposed changes were presented for public consultation and feedback. Chapter 7 is now being considered including the access criteria for Antibody mediated autoimmune encephalitis. This will be considerably updated and new indications will be considered in due course.</p> |
| Limbic encephalitis-nonparaneoplastic (Chapter 7) | | | |
| 32 | Chapter in Criteria | <p>There are a growing number of neurological disorders associated with high titres of autoantibodies to neuronal antigens for which IVIg may be of benefit (eg syndrome of pharmaco-resistant epilepsy, diabetes and pernicious anaemia associated with anti-GAD). The current list in the criteria for use is selective and probably out of date. It might be preferable to broaden this to a generic category such as:</p> <p>Non-paraneoplastic central nervous system autoimmune disease in which there is:</p> <ol style="list-style-type: none"> 1. No evidence of structural brain lesion 2. Evidence of a high titre of antibodies to neuronal antigen | <p>Thank you for your feedback. The work to date by the Neurology Specialist Working Group has examined the adaptation of existing conditions in Chapters 5 and 6 and proposed changes were presented for public</p> |

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| | | 3. Poor response to conventional therapy. | consultation and feedback. Chapter 7 is now being considered including the access criteria for Antibody mediated autoimmune encephalitis. This will be considerably updated and new indications will be considered in due course. |
| 33 | Indication/ Chapter in Criteria | <p>Anti-NMDAR encephalitis</p> <p>Anti-N-methyl-D-aspartate-receptor encephalitis is an antibody mediated neurological disease initially described in 2005. Patients present with psychiatric symptoms (agitation, paranoia, hallucinations and aggression) which progresses to dyskinesias, seizures, autonomic instability, decreased consciousness, catatonia and central hypoventilation leading to a need for ventilator support in ICU.</p> <p>There is compelling evidence suggesting the role for IgG1 and IgG2 antibodies in binding to the GluN1 subunit of the NMDA-receptor. A proportion of cases are associated with underlying teratomas and tumour removal may be curative.</p> <p>Treatment thus consists of immunotherapy and tumour resection. First line immunotherapy typically includes intravenous methylprednisolone and IVIg or plasmapheresis. Due to the behavioural and/or autonomic manifestations of the disease, plasmapheresis, with large bore catheters may be clinically inappropriate. Second line treatment includes rituximab and cyclophosphamide. The consensus opinion is that one would progress to second line treatment if no clinical improvement is observed after 10 days of first line therapy.</p> <p>Owing to the recent recognition of this condition and its rarity, there are no RCTs examining the efficacy of IVIg in anti-NMDA receptor encephalitis. Most publications are of case reports or case series. Cohort studies as described below have been undertaken. In these studies, systemic steroids and IVIg are prescribed in tandem. None have prospectively compared the efficacy of IVIg vs plasmapheresis.</p> <p>Titulaer et al described a cohort study of 577 adult and paediatric patients (of whom 501 had follow-up of at least 4 months) with anti-NMDAR encephalitis. 197 (38%) had an</p> | <p>Thank you for your feedback. The work to date by the Neurology Specialist Working Group has examined the adaptation of existing conditions in Chapters 5 and 6 and proposed changes were presented for public consultation and feedback. Chapter 7 is now being considered including the access criteria for Antibody mediated autoimmune encephalitis. This will be considerably updated and new indications will be considered in due course.</p> |

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| | | <p>underlying neoplasm which was resected in 189. First line immunotherapy was defined as the use of steroids, IVIg or plasma exchange alone or in combination. Amongst the 501 patients, 461 (92%) were treated with first line immunotherapy (of these, 202 patients received steroids and IVIg) and 134 (27%) progressed to second line immunotherapy. Of the patients who received first line treatment, 251 patients achieved treatment response (defined by a reduction in the modified Rankin score to < 4 within 4 weeks). Over the first 24 months, 241 of 251 reached a modified Rankin score of 0-2 (median 3 months). At 24 months 111 of 115 patients had a good outcome.</p> <p>Armangue et al reported similar findings in 20 patients aged less than 19 years with anti-NMDAR encephalitis. 19 patients received first line immunotherapy at the first episode of encephalitis. All patients received at least a short course of high dose steroids and 14 received IVIg (median 2 cycles, range 1-12 cycles). At median follow up of 17.5 months, 17 (85%) had substantial improvement, 2 had moderate or severe disability and 1 died. The median time from start of immunotherapy to first sign of improvement was 11.5 days. International best practice is to use IVIg as first line treatment, as described below.</p> <p>Proposed change: Currently, patients with this condition would access IVIg under the descriptor: limbic encephalitis – non-paraneoplastic. This is listed as an exceptional circumstance - Chapter 7 in the Criteria. We propose that this indication be captured as a Chapter 6 indication – emerging therapeutic role.</p> | |

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Haematology

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| Autoimmune haemolytic anaemia (AIHA) | | | |
| 34 | Qualifying criteria | <p>To reduce haemolysis in patients with AIHA not responding to corticosteroid therapy and Intermittent therapy for AIHA in patients unsuitable for splenectomy or immunosuppression</p> <p>Statement: Haemolysis persists after at least 14 days of conventional corticosteroid therapy</p> <p>Comment: In severe or symptomatic anaemia, waiting for 14 days for response to corticosteroids is likely to lead to blood transfusion, which is not the best option. Blood transfusion is potentially risky as it is difficult to obtain cross match compatible blood and transfusion may worsen haemolysis</p> | Traditionally, steroids are the first line therapy for AIHA. IVIg may be indicated where patients do not respond after 14 days steroid treatment. |
| Feto-maternal/neonatal alloimmune thrombocytopenia (FMAIT/NAIT) | | | |
| 35 | Dose | <p>1. When calculating neonatal doses of IVIG a 3.6kg baby would require a 3.6g of IVIG which if given would result in wastage of product. I am querying whether they should not receive 3gm which would be equivalent to 1 vial Intragam P</p> <p>2. Higher doses 1gm/kg twice weekly may be required in the highest risk pregnancies, not sure if this should be mentioned. E.g. History of a previous antenatal ICH may necessitate higher doses of IVIG.</p> | <p>1. Thank you for the feedback. The functionality of rounding of vials in relation to dosing has been developed and corrected.</p> <p>2. Review has indicated that there is insufficient evidence for higher dosing in women with a history of previous fetus with ICH, at this time.</p> |
| 36 | Qualifying criteria | If a previous pregnancy has been affected by NAIT then thrombocytopenia in the second affected child is always as or more severe than in the previous infant. Intracranial haemorrhage is responsible for most of the morbidity and mortality and occurs in up to 20% cases, most commonly antenatally (Bussel et al, N Engl J Med. 1997;337(1):22). Thus it is not necessary to demonstrate fetal thrombocytopenia in the antenatal setting to initiate treatment with IVIG if there is a previously affected sibling with thrombocytopenia and | Qualifying criteria have been amended to include previous affected sibling (in addition to previous fetal death) in the setting of platelet specific maternal antibodies (to |

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| | | parental antigen testing is compatible with NAIT. If the father is known and is heterozygous for the involved HPA antigen then PCR testing via amniocentesis can be performed for fetal platelet genotype and treatment is not required for an antigen-negative fetus (Pacheco LD et al, Obstet Gynecol 2011; 118:1157). Fetal blood sampling is associated with a risk of fetal loss and is not widely available. | paternal antigens) known or suspected to have caused this condition. |
| 37 | Chapter in Criteria | This is currently listed under “Emerging therapeutic role”. However, IVIg is now standard of care for antenatal management of FMAIT. Invasive (fetal blood sampling) monitoring is no longer performed to guide therapy. Outcomes from FMAIT where IV IgG has been given are almost universally good, although optimal dose, schedule etc. are not defined. Alternative therapies such as frequent fetal blood sampling and intrauterine platelet transfusions are associated with major risks and have been largely abandoned in recent years. Suggest antenatal management of FMAIT is listed under “Established therapeutic role”. See the review paper by Salomon and Rosenberg, the systematic review by Rayment et al (2011) and the papers by Pacheco (2011) and by the group of James Bussel. | Thank you for the feedback. It is recognised that the use of Ig is regarded as standard practice in FNAIT and in the next phase of work, a systematic review will be undertaken to formalise and support the decision to reassess the evidence base. This will be scheduled for the next phase of work for the Specialist Working Group. |
| Haemophagocytosis | | | |
| 38 | Qualifying criteria | It is not appropriate to insist on a bone marrow biopsy evidence in the diagnosis of HLH. The diagnostic criteria of HLH are clearly defined (Jordan et al, Blood 2011; 118:4041) and haemophagocytosis in the bone marrow is only one of many criteria. The internationally accepted criteria for the diagnosis of HLH should be followed. | The diagnostic criteria have been revised to include referencing the literature provided and the qualifying criteria have been changed to reflect consistency with the revised diagnostic criteria. |
| Idiopathic (autoimmune) thrombocytopenic purpura (ITP) | | | |
| 39 | Indication/Qualifying criteria/Review criteria/Description and diagnostic | Adult and children ITP In response to the current draft the HSA NZ council makes a number of general comments regarding the use of IVIG in ITP. Additionally specific comments in detail are summarised in the accompanying response template. | Thank you for the considered and detailed feedback. For specific changes made in response to this advice - please |

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| | criteria | <p>1. The terms acute, chronic, severe, and refractory are not well defined in the document or used consistently through-out the document. Accepted definitions by International Working Group are accepted internationally and should be used. ITP is now considered as either “Newly diagnosed” (<3 months), “Persistent” (3-12 months), or “Chronic” (>12 months). Refractory disease is reserved for patients failing splenectomy. Severe ITP is reserved for patients with clinically significant bleeding mandating therapy or new bleeding mandating a change in therapy. Modifications to the indications and the Description and Diagnostic criteria are suggested below in the accompanying response template.</p> <p>2. There seems to be an inappropriate emphasis on platelet count as the determinant of need for IVIG. Haematologists generally reserve IVIG for patients with life-threatening bleeding or clinically significant bleeding (e.g. mucosal purpura) that indicates a risk of serious bleeding. These criteria need to be incorporated into the qualifying criteria. Several suggestions to the qualifying criteria are made in the accompanying response template for the various indications for use.</p> <p>3. New to the guidelines is the mandatory requirement of prior response to IVIG for further access to IVIG therapy. This response criterion is reviewed and required to be satisfied for ongoing use of IVIG in 3 indications :-(1) “Refractory acute ITP – splenectomy failed or contraindicated and second-line unsuccessful” ; (2) “Ongoing treatment for ITP responders during pregnancy the post-partum period” ; and (3) “Chronic ITP”. The criteria for response in each case is defined as “At least a two-fold increase in platelet count and platelet count > 30 x 10⁹/L was demonstrated within 72 hours of previous immunoglobulin treatment and a reduction in evidence of bleeding if relevant”. This definition has been taken from the International Working Group (Table 2, Rodeghiero et al BLOOD 2009;113:2386), a publication in which the authors propose response criteria to harmonise future clinical research studies and which the authors acknowledge require validation. This definition of response adopted in the IVIG document is problematic. It firstly ignores the existing data that describe the temporal relationship of platelet response to IVIG. While some patients do indeed respond within 72 hours, over 50% of IVIG- responders demonstrate an increment in</p> | <p>refer to the main section of the report. In short:</p> <p>1. Phases of disease have been revised and definitions included with revisions to the Description and Diagnostic criteria section.</p> <p>2. Criteria have been modified to more clearly emphasize clinically significant bleeding and bleeding risk in addition to platelet count.</p> <p>3. Criteria for clinical response to Ig treatment have been revised in line with feedback and advice regarding support for collection of relevant information is noted.</p> <p>4. Representation from the College has been invited and the College will continue to be consulted with future changes.</p> <p>5. Indication has been revised in relation to phase of disease.</p> <p>6. The description and</p> |

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| | | <p>platelet count after 72 hours but within 7 days. (Godeau B et al British Journal Haematology 1999;107(4):716; Chong BH et al Asia-Pacific J Oncol Hematol 2010;2(2):7-12) The time requirement should be extended to 7 days. Secondly the requirement for at least a doubling of platelet count and achievement of a platelet count $>30 \times 10^9/L$ ignores clinically important control of bleeding by a smaller rise in platelet count. This is especially relevant in patients with severe thrombocytopenia and bleeding not responding to current treatment (for example baseline of <5, platelet rise to $15 \times 10^9/L$ with IVIG, with clinical resolution of bleeding). We suggest the following definition of prior response be substituted into the IVIG document where appropriate (see accompanying response template):-</p> <p>Prior response to IVIG is defined as any of the following:-</p> <ul style="list-style-type: none"> (a) Resolution of active bleeding (b) A reduction in evidence of bleeding correlating with a doubling of platelet count or rise in platelet count $> 10^9/L$ within 7 days (c) In patients without active bleeding a doubling of baseline platelet count and a rise in platelet count $> 30 \times 10^9/L$ was demonstrated within 7 days of previous IVIG. <p>4. We support the mandatory collection of clinical information around IVIG use in patients with ITP.</p> <p>The information collected must be however clinically relevant to inform government, physicians and consumers and to demonstrate responsible use of an expensive blood product. We would contend that informative data should include phase of disease for primary ITP, notation of other relevant clinical context of ITP (e.g. pregnancy), baseline platelet count prior to IVIG, presence of bleeding, type of bleeding, weight and dose of IVIG received. Information regarding the response to IVIG should be collected and should reflect comments in item 3 around resolution of bleeding and best platelet response achieved within 7 days of administration. HSA NZ Council is aware of interested individuals with expertise in ITP clinical research who could assist in the evaluation and analysis of this important clinical data. An online data collection system could be developed for such purpose at least in ITP where clinical endpoints are readily assessable.</p> <p>5. Refractory acute ITP - This is an inappropriate term. As described this indication is not refractory but simply responding poorly to initial cortico-steroid therapy. Maybe a more</p> | <p>diagnostic criteria section has been revised and the indication relating to severe ITP has been removed.</p> <p>7. The indication has been revised and qualifying criteria amended.</p> |

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| | | <p>appropriate term could be "ITP-initial therapy" and this may apply to all phases of disease (newly diagnosed, persistent or chronic).</p> <p>6. This discussion requires updating on several points. Pathogenesis is not solely shortened platelet survival but also includes (1) reduced platelet production due to immune-induced reduced megakaryopoiesis and (3) immune mediated direct platelet lysis. ITP is no longer divided into acute and chronic forms. According to International Working Group ITP maybe "Newly diagnosed" (within 3 months), "Persistent" (3-9 months) or "Chronic" (> 12 months). Some definition of "Refractory" and "Severe" should be provided. Refractory could be failed splenectomy or splenectomy contra-indicated and second line therapy unsuccessful. Severe according to the International Working Group is ITP with clinically significant bleeding mandating therapy or new bleeding mandating a change in therapy. There is overlap here with the current qualifying criteria of ITP with life threatening haemorrhage or potential for life-threatening haemorrhage which is really severe ITP. We favour keeping this criteria.</p> <p>7. Refractory acute ITP - Initial Therapy - This should be retitled to "ITP - Initial therapy" and the qualifying criteria should be as follows:</p> <p>1. Clinically significant bleeding with platelet count < 30 x 10⁹/L OR 2. Risk of clinically significant bleeding with platelet count < 30 x 10⁹/L AND No platelet response to conventional dose cortico-steroids given for 14 days (unless valid reason provided (e.g intolerance or corticosteroid contra-indicated) In addition to the above comments in relation to ITP, there are a number of changes we request in the criteria relating to other Haematological conditions.</p> | |
| 40 | Qualifying Criteria | <p>Adult and children ITP Newly diagnosed or persistent ITP - subsequent therapy (diagnosis ≤ 12 months) 1. Clinically significant bleeding with platelet count < 30 x 10⁹/L OR 2. Risk of clinically significant bleeding with platelet count < 30 x 10⁹/L AND</p> | Agreed, the changes reflect these criteria. |

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| | | Conventional dose cortico-steroids or immunosuppressant therapy have failed to correct the platelet count and therapy with at least one second line agent has been unsuccessful in raising platelet count above $30 \times 10^9/L$. Approval should be given for 6 months. | |
| 41 | Qualifying Criteria | Adult ITP Chronic ITP - subsequent therapy (diagnosis ITP > 12 months) 1. Clinically significant bleeding with platelet count < $30 \times 10^9/L$ OR 2. Risk of clinically significant bleeding with platelet count < $30 \times 10^9/L$ AND Conventional dose cortico-steroids or immunosuppressant therapy have failed to correct the platelet count and therapy with at least one second line agent has been unsuccessful in raising platelet count above $30 \times 10^9/L$. Approval should be given for 6 months. | Once a diagnosis of Chronic ITP has been made, the criteria require that a splenectomy will have been performed (unless contraindicated) and failure to respond with a second line agent. |
| 42 | Qualifying Criteria | Adult ITP Refractory acute ITP - splenectomy failed or contraindicated and second-line agent unsuccessful This should be retitled to "Refractory ITP - splenectomy failed or contraindicated and second-line agent unsuccessful". The qualifying criteria should be as follows: 1. Clinically significant bleeding with platelet count < $30 \times 10^9/L$ OR 2. Risk of clinically significant bleeding with platelet count < $30 \times 10^9/L$AND..... ..Splenectomy has failed OR Splenectomy is contraindicatedAND..... Therapy with second line agent has been unsuccessful in raising platelet count above $30 \times 10^9/L$ or in preventing clinically significant bleeding. Approval should be given for 12 months | Agreed - the criteria are consistent with this requirement. See detail in main report. |
| 43 | Qualifying criteria | Adult ITP | Noted. |

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| | | ITP with life threatening haemorrhage or the potential for life-threatening haemorrhage No change suggested. | |
| 44 | Qualifying criteria | Adult ITP Initial therapy for ITP in pregnancy No change suggested | Noted. |
| 45 | Qualifying criteria | Adult ITP Ongoing treatment for ITP responders during pregnancy and post-partum period. Response criteria requires amendment as follows:- Prior response to IVIG is defined as any of the following:- 1. Resolution of active bleeding 2. A reduction in evidence of bleeding correlating with a doubling of platelet count or rise in platelet count $> 10^9/L$ within 7 days 3. In patients without active bleeding a doubling of baseline platelet count and a rise in platelet count $> 30 \times 10^9/L$ was demonstrated within 7 days of previous IVIG | Response criteria have been amended in line with feedback. |
| 46 | Qualifying criteria | Adult ITP ITP and inadequate platelet count for planned surgery The criteria of "minor dental work (platelet count $>30 \times 10^9/L$)" is probably not required. Tooth extraction could be performed without IVIG with a platelet count of $<30 \times 10^9/L$ and with adjunctive therapy with tranexamic acid 1g 3-4 times daily for example. The minor and major criteria for dental work therefore need further definition. | The complexity of dental work is not predictable even when a single tooth requires removal. The decision as to how to manage the risks of proceeding in a particular situation in ITP is a clinical one and the criteria have been retained. |
| 47 | Qualifying criteria | Adult ITP Severe ITP This is the same as category "ITP with life threatening haemorrhage or potential for life-threatening haemorrhage". Delete Severe ITP category. | This indication has been removed. |
| 48 | Qualifying criteria | Adult ITP Chronic ITP This is replaced by new categories either "ITP - initial therapy" for first time use of IVIG in patients with Chronic ITP (diagnosis > 12 months) and "Chronic ITP-subsequent therapy" for | Chronic ITP has been merged with refractory persistent ITP - see ITP section in main report. |

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| | | ongoing dosing with IVIG. | |
| 49 | Qualifying criteria | Adult ITP HIV-associated ITP There needs to be a similar emphasis on bleeding. Would suggest this category be amended as follows:- Failure of anti-retroviral therapy AND One of the following:- 1. Intracranial haemorrhage and platelet count $< 80-100 \times 10^9/L$ 2. Other life-threatening haemorrhage and platelet count $< 50 \times 10^9/L$ 3. Risk of clinically significant bleeding with platelet count $< 30 \times 10^9/L$ | The criteria have been revised in line with the feedback. |
| 50 | Review criteria | Adult ITP All indications Outcome date to be measured should include the following: Resolution of bleeding Prevention of bleeding Maximum platelet count achieved within 7 days of IVIG | Outcome data have been revised in line with the feedback. |
| 51 | Review criteria | Newly diagnosed or persistent ITP - subsequent therapy (diagnosis ≤ 12 months) Review must be undertaken six monthly by haematologist. Response to qualify for ongoing therapy includes as any of the following:- 1. Resolution of active bleeding 2. A reduction in evidence of bleeding correlating with a doubling of baseline platelet count or an increment in platelet count $> 10^9/L$ within 7 days 3. In patients without active bleeding a doubling of baseline platelet count and a rise in platelet count $> 30 \times 10^9/L$ was demonstrated within 7 days of previous IVIG Ongoing use of IVIG should be primarily to prevent bleeding while other treatment options are explored including splenectomy. Approval for 6 months | Agreed - the outcome and response data have been revised in line with feedback. |
| 52 | Review criteria | Chronic ITP - subsequent therapy (diagnosis > 12 months) Review must be undertaken six monthly by haematologist. Response to qualify for ongoing therapy includes as any of the following:- | Agreed - the outcome and response data have been revised in line with feedback. |

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| | | <ol style="list-style-type: none"> 1. Resolution of active bleeding 2. A reduction in evidence of bleeding correlating with a doubling of baseline platelet count or an increment in platelet count $> 10^9/L$ within 7 days 3. In patients without active bleeding a doubling of baseline platelet count and a rise in platelet count $> 30 \times 10^9/L$ was demonstrated within 7 days of previous IVIG <p>Ongoing use of IVIG should be primarily to prevent bleeding while other treatment options are explored including splenectomy.</p> <p>Approval for 6 months</p> | |
| 53 | Review criteria | <p>Refractory ITP - splenectomy failed or contraindicated and second-line agent unsuccessful</p> <p>Review must be undertaken 12 monthly by haematologist.</p> <p>Response to qualify for ongoing therapy includes as any of the following:-</p> <ol style="list-style-type: none"> 1. Resolution of active bleeding 2. A reduction in evidence of bleeding correlating with a doubling of baseline platelet count or an increment in platelet count $> 10^9/L$ within 7 days 3. In patients without active bleeding a doubling of baseline platelet count and a rise in platelet count $> 30 \times 10^9/L$ was demonstrated within 7 days of previous IVIG. <p>Approval for 12 months</p> | Agreed -the outcome and response data have been revised in line with feedback |
| 54 | Qualifying criteria | <p>ITP in pregnancy</p> <p>Pregnant women are eligible when the current platelet count represents potential risk:</p> <ul style="list-style-type: none"> • $<30 \times 10^9/L$ with risk of haemorrhage • $<50 \times 30 \times 10^9/L$ with life-threatening haemorrhage or • $<80-100 \times 10^9/L$ and impending delivery. <p>Should the highlighted text say 50-80?</p> <p>It does not really make sense for the platelet count to be less than a range. Should there just be one figure in each dot point, i.e. $<80 \times 10^9/L$ with life-threatening haemorrhage, $<100 \times 10^9/L$ and impending delivery?</p> | Thank you for the feedback - an error has been noted and the ranges have been removed and values amended in line with the feedback. |
| 55 | Dose | Suggested dose of 2 days of $0.4g/L$ is not my standard practice. System gave me a total of $0.8g/kg$ when guideline is $1-2g/kg$ | The system initially displays a default value which can be amended by the user, if |

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| | | | required. A default value is used to encourage prescribers to consider the lowest possible effective dose. |
| 56 | Condition name | The term Immune thrombocytopenia, rather than idiopathic (autoimmune thrombocytopenic purpura is now more favoured. When I search for ITP under dose it does not come up. I needed to write idiopathic | Agreed - the condition name has been changed to Immune Thrombocytopenic Purpura for conditions relating to both children and adults. |
| 57 | Qualifying criteria | Refractory acute ITP - initial therapy Statement: There has been no improvement in response to conventional doses of corticosteroid therapy for at least 14 days (unless valid reason is provided) Comment: 14 days is too long to wait for a response to steroids, especially if the platelet count is <10. Suggest 5 days instead | In the absence of bleeding, 14 days is thought to be a safe period for response to steroid treatment. If the patient is bleeding, this would be a valid reason to prescribe Ig in less than 14 days which is supported by the criteria and the BloodSTAR system. |
| 58 | Qualifying criteria | ITP with life-threatening haemorrhage or the potential for life- threatening haemorrhage Statement: When conventional doses of corticosteroids (for at least 14 days) have failed to improve count (unless a valid reason is provided) Comment: 14 days is too long to wait for a response to steroids, especially if the platelet count is <10. Suggest 5 days instead | In the absence of bleeding, 14 days is thought to be a safe period for response to steroid treatment. If the patient is bleeding, this would be a valid reason to prescribe Ig in less than 14 days which is supported by the criteria and the BloodSTAR system. |
| 59 | Qualifying criteria | Refractory acute ITP -splenectomy failed or contra indicated and second-line agent unsuccessful Statement: At least a two-fold increase in platelet count (and platelet count >30x10 ⁹ /L) was | The Criteria for clinical response has been revised including extending the timeframe before |

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| | | <p>demonstrated within 72 hours of previous immunoglobulin (Ig) treatment</p> <p>Comment: Sometimes the peak effect of IVIg is not seen until 7-10 days after the dose, and platelet count may only increase slightly in the first 72 hours. The current description would exclude patients who actually respond to IVIg</p> <p>Please clarify two-fold increase, and ideally with examples so as to avoid confusion. E.g. if platelet count is 6, would two fold increase mean platelet count needs to be >18?</p> | <p>improvement in platelet count is required to be demonstrated. The revised criterion is: Response to Ig treatment demonstrated a resolution of active bleeding or a reduction in evidence of bleeding correlating with a doubling of baseline platelet count and/or an increment in platelet count -of greater than 10x10⁹/L within 7 days.</p> |
| 60 | Qualifying criteria | <p>Ongoing treatment for ITP responders during pregnancy and the postpartum period</p> <p>Statement: The maximum platelet count achieved within 72 hours of last Ig treatment was greater than 30x10⁹/L</p> <p>Comment: Sometimes the peak effect of IVIg is not seen until 7-10 days after the dose, and platelet count may only increase slightly in the first 72 hours. The current description would exclude patients who actually respond to IVIg</p> | <p>The Criteria for clinical response has been revised including extending the timeframe before improvement in platelet count is required to be demonstrated. The revised criterion is: Response to Ig treatment demonstrated a resolution of active bleeding or a reduction in evidence of bleeding correlating with a doubling of baseline platelet count and/or an increment in platelet count of greater than 10x10⁹/L within 7 days.</p> |
| Neonatal haemochromatosis (NH) | | | |
| 61 | Dose | Will also give doses of IVIG which are in between vial size which may or may not be | 1. Thank you for the feedback. |

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| | | appropriate? | <p>The functionality of rounding of vials in relation to dosing has been developed and corrected.</p> <p>2. Review has indicated that there is insufficient evidence for higher dosing in women with a history of previous fetus with ICH, at this time.</p> |
| 62 | Dose | <p>1. No IVIg has a TGA approved indication for NH.</p> <p>2. The recommendation to Refer to the current product information sheet for further information under 'Dose' is misleading as no IVIg is indicated for the condition and available Product Information will not contain further information for this condition.</p> | <p>1. Noted.</p> <p>2. Referral to the product insert is included for additional information (other than dose) that is not included in the publication of the Criteria for use or BloodSTAR (eg risks of adverse events).</p> |
| Post-transfusion purpura (PTP) | | | |
| 63 | Qualifying criteria and review criteria | <p>The use of criteria to judge response, i.e. platelet count of >30 or doubling of pre-treatment count within 72 hours is made without any evidence in this rare disorder. These criteria are the same as that proposed for ITP, for which we have indicated above are too stringent, leading to the potential exclusion of patients who have experienced clinical benefit from receiving further treatment . A level of platelet count or its doubling cannot be a substitute for clinical judgment as to whether a clinical benefit has been achieved eg in the prevention of bleeding. It is also not appropriate to simply transfer the criteria for ITP to PTP which are completely different disorders.</p> | <p>In PTP, the creation of outcome measures is for the recording of data only. The qualifying criteria for Ig are the same for every dose that may be required (clinical diagnosis or suspicion of PTP with platelet count <30x10⁹/L and a risk of life threatening bleeding. Therefore, responder status is irrelevant in the qualifying criteria for PTP.</p> |

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| | | | However, a text box to support the recording of clinical benefit has been added and outcome data amended as suggested. |
| Secondary hypogammaglobulinaemia — related to haematological malignancy and post HSCT | | | |
| 64 | Exclusion criteria Review criteria | <p>1. Hypogammaglobulinaemia can result from both lymphoproliferative diseases and from B cell depletion therapies which are used to treat the diseases. In hypogammaglobulinaemia resulting from either or both causes, there are appropriate reasons to treat with intravenous gammaglobulin. Placing one cause (B cell depletion therapy) as an exclusion criteria in the other (secondary hypogammaglobulinaemia due to malignancy) is not appropriate and potentially prevents patients who are hypogammaglobulinaemic due to either or both reasons to be excluded from treatment.</p> <p>2. In the same category, the evaluation of the severity of IgG depletion as an indication specifies that 2 separate measurements must be made. This is not appropriate in critically ill patients in whom the timely and often urgent provision of IVIG is required.</p> | <p>1. Exclusion criteria have been revised to more clearly refer the user to the correct condition. Within the BloodSTAR system, the user will be automatically directed to the correct screen.</p> <p>2. Duplicate IgG measurements are recommended by the Immunology SWG given the invasive nature and cost of Ig treatment, such that a diagnosis of secondary hypogammaglobulinaemia requires confirmation. There are test performance and laboratory issues - if the level is borderline in acute infection, it may change quickly back to the normal range. The samples should be taken at least 1 hour apart and one must be taken when the patient is not suffering from an active infection. Ig infusions should</p> |

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| | | | not be administered to patients with acute infections due to the risk of a phlogistic reaction. Additional scripts have been added to guide the prescriber as to IgG sampling. These are: "Serum IgG less than the lower limit of the reference range measured on two separate occasions (at least one hour apart and at least one sample taken when the patient does not have an active infection)." |
| 65 | Qualifying criteria | <p>Prevention of recurrent bacterial infections due to hypogammaglobulinaemia associated with haematological malignancies and Prevention of recurrent bacterial infections due to hypogammaglobulinaemia post HSCT</p> <p>Statement: Serum IgG less than the lower limit of the age-related reference range measured on two separate occasions</p> <p>Comment: One low serum IgG level should be sufficient if it is performed within the last month as the test has good reproducibility</p> | Duplicate IgG measurements are recommended by the Immunology SWG given the invasive nature and cost of Ig treatment, such that a diagnosis of secondary hypogammaglobulinaemia requires confirmation. There are test performance and laboratory issues - if the level is borderline in acute infection, it may change quickly back to the normal range. The samples should be taken at least 1 hour apart and one must be taken when the patient is not suffering from an active |

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| | | | infection. Ig infusions should not be administered to patients with acute infections due to the risk of a phlogistic reaction. Additional scripts have been added to guide the prescriber as to IgG sampling. These are: "Serum IgG less than the lower limit of the reference range measured on two separate occasions (at least one hour apart and at least one sample taken when the patient does not have an active infection)." |
| Secondary hypogammaglobulinaemia unrelated to Haematological malignancy or haemopoietic stem cell transplant (HSCT) | | | |
| 66 | Qualifying criteria | <p>Severe bacterial infections associated with hypogammaglobulinaemia caused by a recognised disease process or B cell depletion therapy and/or immunosuppressant therapy.</p> <p>"Baseline IgA and IgM levels should be provided to allow assessment of immune recovery on review" and "normalising IgA and IgM may suggest recovery of the immune system".</p> <p>Normalising suggests not yet in normal range – at what levels of still low albeit improved IgA and IgM would the NBA recommend a trial off IVIG? Are there data or references to support this suggestion?</p> | <p>Statements regarding IgA and IgM levels have been revised to improve the clinical guidance being provided. "If serum IgM and IgA levels are trending upwards and close to normal, this may suggest recovery of the immune system and a trial might be commenced if the patient is well. Once the patient has normal IgA and IgM levels, the IgG is also likely to be normal</p> |

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| | | | and a trial off therapy may be undertaken." It is recognised that the decision to trial off Ig therapy is a clinical one. |
| Rhesus isoimmunisation (Chapter 7) | | | |
| 67 | | The use of IV IgG in early management of Rhesus (D) isoimmunisation is not listed at all. Rarely, women are encountered who have high titres of high affinity anti-D antibodies who require intervention at a gestation before intrauterine transfusion is possible. In those women IV IgG has been used successfully until cordocentesis and in utero transfusion is feasible. | The public consultation was regarding proposed changes to Chapters 5 and 6 only. While some conditions in Chapter 7 are currently under review to develop more formal criteria, patients with conditions listed in Chapter 7 will continue to be eligible for Ig in exceptional circumstances. In accordance with the recommendations and expert opinion points of the Patient Blood management guideline -Module 6 -neonatal and paediatric, changes will be made to current entry in Chapter 7 to include - "In maternity patients with a fetus affected by HDFN who is at high risk of early fetal hydrops or death, a course of weekly IVIg should be considered." Further development will be undertaken on Chapter 7 in the next phase of work by the Specialist Working Groups. |

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| Bullous pemphigoid (BP) | | | |
| 68 | Qualifying criteria | <p>1. "Moderate to severe BP disease confirmed by blood testing and biopsy".</p> <p>2. "Persistent disease and severe side effects prohibit the continuation of corticosteroids and immunosuppressant agents"</p> <p>1. a) This should read confirmed by blood testing and/or biopsy rather than both. Antibodies in serum are only detected in less than 80% of cases.</p> <p>b) Must be made clear the side effects or contraindications list is NOT designed as an exhaustive list as there are many other side effects and contraindications (steroid psychosis for example) which may prevent use of non-IVIG treatments.</p> <p>2. Must be made clear the side effects or contraindications list is NOT designed as an exhaustive list as there are many other side effects and contraindications (steroid psychosis for example) which may prevent use of non-IVIG treatments.</p> | <p>1. (a) Agreed. Criteria have been revised to require positive autoantibody testing and/or biopsy confirmation rather than both.</p> <p>1 (b) and 2. The system supports a drop down menu of side effects including the option to document "other" reason.</p> |
| Cicatricial pemphigoid (CP) or mucous membrane pemphigoid (MMP) | | | |
| 69 | Qualifying criteria | <p>1. "Moderate to severe CP/MMP disease proven by biopsy and serology with involvement of multiple sites".</p> <p>2. "Severe side effects prohibit the continuation of corticosteroids and immunosuppressive agents unless corticosteroids or immunosuppressant agents are contraindicated".</p> <p>1. This should read confirmed by biopsy and/or serology rather than both. Antibodies in serum are only detected in around 20% of cases.</p> | <p>1. Agreed. Criteria have been revised to require positive autoantibody testing and/or biopsy confirmation rather than both.</p> <p>2. The system supports a drop down menu of side effects including the option to document "other" reason.</p> |

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| | | 2. Must be made clear the side effects or contraindications list is NOT designed as an exhaustive list as there are many other side effects and contraindications (steroid psychosis for example) which may prevent use of non-IVIG treatments. | |
| Pemphigus foliaceus (PF) | | | |
| 70 | Qualifying criteria | <p>Qualification for IVIg for pemphigus requires confirmation of the diagnosis by skin biopsy and positive blood test. However, published data indicate that only 80% of patients with biopsy confirmed pemphigus exhibit positive serology results. (Depending upon the method and the auto-antibody being examined, lower positive rates have also been reported). Thus, as a best case scenario, 1 in 5 patients with pemphigus would fail to meet the proposed qualification for IVIg. The NBA may wish to note the following inconsistencies:</p> <p>1. The diagnosis of pemphigus must be established by either a dermatologist or immunologist.</p> <p>2. The diagnosis of cicatricial pemphigus or mucous membrane pemphigus must be made by either dermatologist or ophthalmologist however ongoing review must be performed by either a dermatologist or immunologist.</p> <p>We propose that the diagnosis of cicatricial pemphigus or mucous membrane pemphigus may also be made by immunologists.</p> | <p>1. Agreed. Criteria have been revised to require positive autoantibody testing and/or biopsy confirmation rather than both.</p> <p>2. Agreed. Clinical Immunologist has been added.</p> |
| Pemphigus vulgaris (PV) | | | |
| 71 | Qualifying criteria | <p>1. "Moderate to severe proven PV disease, including widespread oral lesions, laryngeal involvement and/or erosions in skinfolds (vegetans) and pemphigus serology – antikeratinocyte antibody titre".</p> <p>2. Severe side effects prohibit the continuation of corticosteroids and immunosuppressant agents.</p> <p>1. This paragraph doesn't make sense - it should be in line with descriptions for Bullous and Cicatricial Pemphigoid e.g. "Clinical PV proven by biopsy and/or serology".</p> <p>2. Must be made clear the side effects or contraindications list is NOT designed as an exhaustive list as there are many other side effects and contraindications (steroid psychosis</p> | <p>1. Agreed. Criteria have been revised to require positive autoantibody testing and/or biopsy confirmation rather than both. 2. The system supports a drop down menu of side effects including the option to document "other" reason.</p> |

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| | | for example) which may prevent use of non-IVIG treatments. | |
| 72 | Review criteria | <p>Review is required every six months by a dermatologist. Response must be demonstrated at the initial review at six months and improvement must be demonstrated for continuation of supply.</p> <p>Clinical Immunologist should be added to Dermatologists in line with Bullous Pemphigoid and Cicatricial Pemphigoid.</p> | Agreed. Clinical Immunologist has been added. |
| 73 | Review criteria | <p>A reduction in anti-keratinocyte antibody titre is demonstrated compared to the qualifying value.</p> <p>There are significant concerns with since:</p> <ol style="list-style-type: none"> 1) commonly used assays are only semi-quantitative 2) assays are not standardised across the country raising issues of standardisation and equity according to test 3) only 80-90% of patients have antibodies levels detectable at diagnosis 4) although levels do correlate with disease activity it is entirely possible to have improvement in disease activity clinically without a change in the antibody levels (similar to many autoimmune diseases) | Consistency is now provided across the pemphigoid conditions for confirmation by autoantibody testing and/or biopsy. At review, the response to Ig treatment will be limited to a clinical assessment. |
| Primary immune deficiency (PID) (antibody deficiency) | | | |
| 74 | Indication | <p>The patient has demonstrated an increased susceptibility to infection.</p> <p>OR</p> <p>The patient has autoimmune manifestations, granulomatous disease, unexplained polyclonal proliferation or an affected family member with antibody deficiency.</p> <p>The requirement for invasive infection is too stringent. The aim of replacement therapy once other criteria have been met is to avoid this complication. This criterion should be an OR rather than an AND.</p> | Agreed. The qualifying criterion is 'OR' which is consistent with ESID criteria. A minor error has been corrected to qualify the proliferation to be 'lymphoproliferation'. |
| 75 | Indication | <p>Disseminated enteroviral infection</p> <p>RE: Application for the addition of disseminated enteroviral infection to the indications for</p> | Agreed. The SWG will consider the inclusion of Disseminated |

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| | | <p>use of Intravenous Immunoglobulins {IVIg}</p> <p>Thank you for your attention and consideration of the following document. We write to propose that this indication be considered as an addition to the criteria for the clinical use of intravenous immunoglobulin.</p> <p>Enteroviral infections, which encompass infections due to viruses from the Enterovirus genus, including coxsackieviruses, polioviruses and echoviruses, have long been a well known complication of primary immunodeficiency (PID) due to impaired antibody mediated immunity, particularly seen in patients with hypo- or agammaglobulinaemia {1-9}. These individuals are prone to more severe, potentially life-threatening or chronic disease, including meningoencephalitis, polymyositis, myocarditis and hepatitis {3}.</p> <p>B-cells, though their role is not fully understood, are believed to be central to the immunity against these viruses. Supporting this, as already stated, is the increased susceptibility of individuals with antibody deficiency, including patients with X-Linked agammaglobulinaemia, Hyper-IgM Syndrome and Common Variable Immunodeficiency {3, 10}, as well as major histocompatibility complex class II deficiency {11}. Similarly, those with such deficiencies are slow to clear and continue to shed virus, either post oral poliovirus vaccine or infection {8,12-15}. It has also been shown that immune serum transfer may control disease {10,16,17} and that the severity of neonatally acquired infections is also dependent on the presence of maternally acquired serotype-specific antibodies{18}.</p> <p>Outside the PID setting, disseminated, severe, enteroviral infections have also been shown to complicate B-cell depleting and haematological malignancy therapies, with multiple case reports in the literature (19,20), though the latter is usually associated with low immunoglobulin levels. Cases have been reported in the setting of both rituximab and its newer relative, obinutuzumab (21) (22) {20} (23) (24) (25-29). These drugs lead to profound B-cell lymphopenia and possible hypogammaglobulinaemia, however not all patients whose treatment was complicated by enteroviral infections had low levels of immunoglobulins {20}. These drugs are gaining</p> | <p>Enterovirus Infection in its next phase of work to be included in Chapter 7 for exceptional use. In addition, the following statement has been added to the description and diagnostic criteria section for both Secondary hypogammaglobulinaemia related and unrelated to haematological malignancy: "Secondary hypogammaglobulinaemia may occasionally be complicated by a disseminated enterovirus infection, particularly in patients who have received B cell depletion therapy for a B cell lymphoproliferative disorder."</p> |

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| | | <p>momentum in their use, in particular for B-cell malignancies, but also autoimmune conditions. There is also a reported case of viral myocarditis in the setting of rituximab use in a child with steroid-dependent idiopathic nephrotic syndrome (30). Thus, we are likely to seen an increase in incidence of enteroviral infections in this population.</p> <p>The role of IVIg therapy in enteroviral infections is not fully delineated. In the setting of immunodeficiency, prophylactic IVIg has improved the prognosis significantly. It has also been shown to be effective in many reported cases(21). However, in some patients, there is either a short-lasting or no benefit(3). In neonatal enteroviral infections, Yen et al. showed that IVIg, particularly early administration, was associated with a favourable prognosis (18). This is also seen in a retrospective comparison during a large outbreak of Enterovirus 71 in Taiwan (31). In that country, IVIg in in the national treatment guidelines using a stage-based management system (31). There are also multiple case reports supporting the use of high dose IVIg in patients (4). One group has also shown modulation of both pro- and anti-inflammatory cytokines with clinical improvement in patients with enteroviral infection and that early treatment provides greater benefit {32}</p> <p>While there are no good randomised, placebo-controlled clinical trials available, based on case/cohort data and on the lack of other effective treatment, we would advocate that in such severe complications of enterovirus infections, such as meningo-encephalitis, myocarditis and polymyositis, IVIg offers the best hope of treatment. We advocate for its approval, for its early use and in particular in cases of immunosuppression, where B-cell immunity is likely to be diminished, including with B-cell depletion therapy, with or without hypogammaglobulinaemia.</p> | |
| 76 | Qualifying criteria | The patient has a documented failure to develop protective antibody response to conjugated or unconjugated pneumococcal vaccine or protein vaccine challenge or the patient has absent haemagglutinins (if not blood group AB) or the patient has low switched memory B cells (<70% of age-related normal value) | Agreed - the criteria have been modified to include that when serum IgG<2g/L and the patient would be at significant |

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| | | This should not be needed in clear cut cases with very low IgG - adding this onto the criteria will likely delay newly diagnosed patient with more urgent clinical need getting access to therapy due to extra time required to demonstrate impaired vaccine responses or abnormal flow characteristics. | risk from a delay to providing Ig replacement (eg following an invasive bacterial infection), IgG can be prescribed without waiting for vaccination testing. |
| 77 | Qualifying criteria | <p>Where a diagnosis has initially been suspected, confirmation is required for access to continuing Ig therapy</p> <p>Definition of confirmation needs to be given as genetic testing for some diagnoses is not available within Australia.</p> <p>As we understand it, the ESID 2014 criteria are classification criteria for the purposes of the ESID registry rather than formal, clinically validated criteria (as per the ESID website http://esid.org/Working-Parties/Registry/Diagnosis-criteria).</p> <p>We would suggest caution in basing access on strict adherence to these criteria, as this may have unintended consequences such as creating spurious demand for tests (such as switched memory B cells) for which the evidence base is not well established in this context, delaying the supply of product for newly diagnosed patients in whom treatment is a matter of clinical urgency, and in broadening the non-infective indications creating a pathway for supply with questionable indications (e.g. borderline low IgG and switched memory B cells with ill-defined autoimmune or granulomatous manifestations).</p> <p>It is not clear to what extent there is discretion on the part of the treating immunologist. Similarly, the definition of “confirmation” of a recognised primary immunodeficiency is not made clear, which is important given that continued supply is contingent on this.</p> | Agreed. Criteria have been amended to clarify that the requirement is for confirmation of a clinical diagnosis by a clinical immunologist rather than confirmation by genetic testing. |
| Secondary hypogammaglobulinaemia unrelated to Haematological malignancy or haemopoietic stem cell transplant (HSCT) | | | |
| 78 | Qualifying criteria | <p>Severe bacterial infections associated with hypogammaglobulinaemia caused by a recognised disease process or B cell depletion therapy and/or immunosuppressant therapy.</p> <p>“Baseline IgA and IgM levels should be provided to allow assessment of immune recovery on review” and “normalising IgA and IgM may suggest recovery of the immune system”.</p> | <p>Statements have been revised to provide greater guidance.</p> <p>"If serum IgM and IgA levels are trending upwards and</p> |

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| | | Normalising suggests not yet in normal range – at what levels of still low albeit improved IgA and IgM would the NBA recommend a trial off IVIG? Are there data or references to support this suggestion? | close to normal, this may suggest recovery of the immune system and a trial might be considered if the patient is well. Once the patient has normal IgA and IgM levels, the IgG is also likely to be normal and a trial off therapy should be undertaken." |
| 79 | Indication | <p>Disseminated enteroviral infection</p> <p>RE: Application for the addition of disseminated enteroviral infection to the indications for use of Intravenous Immunoglobulins (IVIg)</p> <p>Thank you for your attention and consideration of the following document. We write to propose that this indication be considered as an addition to the criteria for the clinical use of intravenous immunoglobulin.</p> <p>Enteroviral infections, which encompass infections due to viruses from the Enterovirus genus, including coxsackieviruses, polioviruses and echoviruses, have long been a well known complication of primary immunodeficiency (PID) due to impaired antibody mediated immunity, particularly seen in patients with hypo- or agammaglobulinaemia {1-9). These individuals are prone to more severe, potentially life-threatening or chronic disease, including meningoencephalitis, polymyositis, myocarditis and hepatitis {3).</p> <p>B-cells, though their role is not fully understood, are believed to be central to the immunity against these viruses. Supporting this, as already stated, is the increased susceptibility of individuals with antibody deficiency, including patients with X-Linked agammaglobulinaemia, Hyper-IgM Syndrome and Common Variable Immunodeficiency {3,10), as well as major histocompatibility complex class II deficiency{11). Similarly, those with such deficiencies are slow to clear and continue to shed virus, either post oral</p> | <p>Agreed. The SWG will consider the inclusion of Disseminated Enterovirus Infection in its next phase of work to be included in Chapter 7 for exceptional use. In addition, the following statement has been added to the description and diagnostic criteria section for both Secondary hypogammaglobulinaemia related and unrelated to haematological malignancy: "Secondary hypogammaglobulinaemia may occasionally be complicated by a disseminated enterovirus infection, particularly in patients who have received B cell depletion therapy for a B cell</p> |

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| | | <p>poliovirus vaccine or infection {8,12-15). It has also been shown that immune serum transfer may control disease {10,16,17) and that the severity of neonatally acquired infections is also dependent on the presence of maternally acquired serotype-specific antibodies{18).</p> <p>Outside the PID setting, disseminated, severe, enteroviral infections have also been shown to complicate B-cell depleting and haematological malignancy therapies, with multiple case reports in the literature (19,20), though the latter is usually associated with low immunoglobulin levels. Cases have been reported in the setting of both rituximab and its newer relative, obinutuzumab (21) (22) {20) (23) (24) (25-29). These drugs lead to profound B-cell lymphopenia and possible hypogammaglobulinaemia, however not all patients whose treatment was complicated by enteroviral infections had low levels of immunoglobulins {20). These drugs are gaining momentum in their use, in particular for B-cell malignancies, but also autoimmune conditions. There is also a reported case of viral myocarditis in the setting of rituximab use in a child with steroid-dependent idiopathic nephrotic syndrome (30). Thus, we are likely to see an increase in incidence of enteroviral infections in this population.</p> <p>The role of IVIg therapy in enteroviral infections is not fully delineated. In the setting of immunodeficiency, prophylactic IVIg has improved the prognosis significantly. It has also been shown to be effective in many reported cases(21). However, in some patients, there is either a short-lasting or no benefit(3). In neonatal enteroviral infections, Yen et al. showed that IVIg, particularly early administration, was associated with a favourable prognosis (18). This is also seen in a retrospective comparison during a large outbreak of Enterovirus 71 in Taiwan (31). In that country, IVIg is in the national treatment guidelines using a stage-based management system (31). There are also multiple case reports supporting the use of high dose IVIg in patients (4). One group has also shown modulation of both pro- and anti-inflammatory cytokines with clinical improvement in patients with enteroviral infection and that early treatment provides greater benefit {32)</p> <p>While there are no good randomised, placebo-controlled clinical trials available, based on case/cohort data and on the lack of other effective treatment, we would advocate that in</p> | lymphoproliferative disorder." |

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| | | such severe complications of enterovirus infections, such as meningo-encephalitis, myocarditis and polymyositis, IVIg offers the best hope of treatment. We advocate for its approval, for its early use and in particular in cases of immunosuppression, where B-cell immunity is likely to be diminished, including with B-cell depletion therapy, with or without hypogammaglobulinaemia. | |
| Secondary hypogammaglobulinaemia — related to haematological malignancy and post HSCT | | | |
| 80 | Exclusion criteria Review criteria | <p>Hypogammaglobulinaemia can result from both lymphoproliferative diseases and from B cell depletion therapies which are used to treat the diseases. In hypogammaglobulinaemia resulting from either or both causes, there are appropriate reasons to treat with intravenous gammaglobulin. Placing one cause (B cell depletion therapy) as an exclusion criteria in the other (secondary hypogammaglobulinaemia due to malignancy) is not appropriate and potentially prevents patients who are hypogammaglobulinaemic due to either or both reasons to be excluded from treatment.</p> <p>In the same category, the evaluation of the severity of IgG depletion as an indication specifies that 2 separate measurements must be made. This is not appropriate in critically ill patients in whom the timely and often urgent provision of IVIG is required.</p> | Statement has been modified by direct referencing of the relevant condition. The system will automatically direct the user to the correct relevant condition. |
| 81 | Qualifying criteria | <p>Prevention of recurrent bacterial infections due to hypogammaglobulinaemia associated with haematological malignancies and Prevention of recurrent bacterial infections due to hypogammaglobulinaemia post HSCT</p> <p>Statement: Serum IgG less than the lower limit of the age-related reference range measured on two separate occasions</p> <p>Comment: One low serum IgG level should be sufficient if it is performed within the last month as the test has good reproducibility.</p> | Given the cost and invasive nature of treatment, confirmation of the diagnosis is required. Guidance has been included that the samples for IgG testing should be taken at least one hour apart and at least one sample taken when the patient does not have an infection to confirm hypogammaglobulinaemia. |

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| 82 | Indication | <p>Disseminated enteroviral infection</p> <p>RE: Application for the addition of disseminated enteroviral infection to the indications for use of Intravenous Immunoglobulins {IVIg}</p> <p>Thank you for your attention and consideration of the following document. We write to propose that this indication be considered as an addition to the criteria for the clinical use of intravenous immunoglobulin.</p> <p>Enteroviral infections, which encompass infections due to viruses from the Enterovirus genus, including coxsackieviruses, polioviruses and echoviruses, have long been a well known complication of primary immunodeficiency {PID} due to impaired antibody mediated immunity, particularly seen in patients with hypo- or agammaglobulinaemia {1-9}. These individuals are prone to more severe, potentially life-threatening or chronic disease, including meningoencephalitis, polymyositis, myocarditis and hepatitis {3}.</p> <p>B-cells, though their role is not fully understood, are believed to be central to the immunity against these viruses. Supporting this, as already stated, is the increased susceptibility of individuals with antibody deficiency, including patients with X-Linked agammaglobulinaemia, Hyper-IgM Syndrome and Common Variable Immunodeficiency {3,10}, as well as major histocompatibility complex class II deficiency{11}. Similarly, those with such deficiencies are slow to clear and continue to shed virus, either post oral poliovirus vaccine or infection {8,12-15}. It has also been shown that immune serum transfer may control disease {10,16,17} and that the severity of neonatally acquired infections is also dependent on the presence of maternally acquired serotype-specific antibodies{18}.</p> <p>Outside the PID setting, disseminated, severe, enteroviral infections have also been shown to complicate B-cell depleting and haematological malignancy therapies, with multiple case reports in the literature (19,20), though the latter is usually associated with low immunoglobulin levels. Cases have been reported in the setting of both rituximab and its newer relative, obinutuzumab (21) (22) {20} (23) (24) (25-29). These drugs lead to profound B-cell lymphopenia and possible</p> | <p>Agreed. The SWG will consider the inclusion of Disseminated Enterovirus Infection in its next phase of work to be included in Chapter 7 for exceptional use. In addition, the following statement has been added to the description and diagnostic criteria section for both Secondary hypogammaglobulinaemia related and unrelated to haematological malignancy: "Secondary hypogammaglobulinaemia may occasionally be complicated by a disseminated enterovirus infection, particularly in patients who have received B cell depletion therapy for a B cell lymphoproliferative disorder."</p> |

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| | | <p>hypogammaglobulinaemia, however not all patients whose treatment was complicated by enteroviral infections had low levels of immunoglobulins {20}. These drugs are gaining momentum in their use, in particular for B-cell malignancies, but also autoimmune conditions. There is also a reported case of viral myocarditis in the setting of rituximab use in a child with steroid-dependent idiopathic nephrotic syndrome (30). Thus, we are likely to see an increase in incidence of enteroviral infections in this population.</p> <p>The role of IVIg therapy in enteroviral infections is not fully delineated. In the setting of immunodeficiency, prophylactic IVIg has improved the prognosis significantly. It has also been shown to be effective in many reported cases(21). However, in some patients, there is either a short-lasting or no benefit(3). In neonatal enteroviral infections, Yen et al. showed that IVIg, particularly early administration, was associated with a favourable prognosis (18). This is also seen in a retrospective comparison during a large outbreak of Enterovirus 71 in Taiwan (31). In that country, IVIg is in the national treatment guidelines using a stage-based management system (31). There are also multiple case reports supporting the use of high dose IVIg in patients (4). One group has also shown modulation of both pro- and anti-inflammatory cytokines with clinical improvement in patients with enteroviral infection and that early treatment provides greater benefit {32}</p> <p>While there are no good randomised, placebo-controlled clinical trials available, based on case/cohort data and on the lack of other effective treatment, we would advocate that in such severe complications of enterovirus infections, such as meningo-encephalitis, myocarditis and polymyositis, IVIg offers the best hope of treatment. We advocate for its approval, for its early use and in particular in cases of immunosuppression, where B-cell immunity is likely to be diminished, including with B-cell depletion therapy, with or without hypogammaglobulinaemia.</p> | |
| Specific antibody deficiency (SAD) | | | |
| 83 | Description and | IgG, preferably IgG2, antibodies to multiple serotypes of PcP should be assayed, with | The description and diagnostic |

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| | diagnostic criteria | <p>decisions on serotype selection based on their immunogenicity in relation to age</p> <p>The qualifying criteria recommend only Specific IgG response (otherwise unspecified) – this statement appears to suggest the NBA is advocating for serotype specific antibody responses to be measured.</p> <p>IgG serotype assays are only performed in 2 laboratories in Australia, of which one is currently not offering the test as it is validating a new assay. No assay in Australia or the USA offers IgG2 serotype specific PcP antibody levels. The workload for performing serotype specific antibody responses to PcP could not be absorbed by these 2 laboratories – a sudden shift in workload will result in significantly increased turnaround times for this testing and risk patients in need suffering unnecessary delays for access to treatment.</p> <p>The description statements should therefore be more explicit to include specific IgG testing rather than discussing serotype specific only.</p> | <p>criteria section has been redrafted to include both specific IgG testing and IgG serotype testing. The changes have been made in consultation with each of the testing laboratories that perform serotype testing to ensure that the content is consistent with current laboratory practice in Australia.</p> |
| 84 | Indication | <p>Life threatening infection or a series of serious infections following trial off therapy in patients with proven specific antibody deficiency</p> <p>These indications are significantly stricter than the initial indications (which state only history of abnormal and/or persistent infection) and therefore make it much harder for a patient who has had clinical improvement on IVIG to re-access treatment in the reassessment window.</p> <p>The American Academy of Asthma Allergy and Immunology (AAAAI) guidelines suggest “infusions should not be interrupted to learn about a patient’s tolerance for frequency of infusions as this will place the patients in harm’s way unnecessarily and also would be consistent with medical malpractice”</p> <p>[www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Practice%20Resources/IVI G-guiding-principles.pdf].</p> <p>This would be especially true for a patient who has had very clear clinical benefit with treatment, especially in those who have already developed co-morbidities from their disease such as bronchiectasis.</p> <p>Since life threatening is defined as any illness or condition developed in whereby the</p> | <p>The purpose of obtaining an infection history is to ensure that Ig is appropriately provided to patients incurring infections that are more serious than the general population.</p> |

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| | | individual is likely to die prematurely, then allowing a life threatening infection does put the patient at a significant risk, including the risk the patient doesn't survive the infection. The discrepancy between qualifying for commencing therapy and for re-commencing after trial off therapy should be resolved. | |
| 85 | Qualifying criteria | <p>The Criteria requires that patients exhibit a history of abnormally frequent and/or persistent bacterial infections. To qualify for resumption of IVIg following a trial of cessation of IVIg, patients need either suffer a life threatening infection or sustain two serious bacterial infections.</p> <p>We suggest that demonstration of a serious bacterial infection should suffice. (Furthermore, to require a patient have a life threatening infection also requires the patient survives, and rather contradicts the very basis of treatment to prevent infection).</p> | The purpose of obtaining an infection history is to ensure that Ig is appropriately provided to patients incurring infections that are more serious than the general population. |
| 86 | Qualifying criteria and Review criteria | <p>Immunoglobulin therapy should be provided when there is evidence of abnormally recurrent or persistent bacterial infections, or bronchiectasis and/or suppurative lung disease.... with a documented requirement for antibiotic therapy...</p> <p>1. The requirement for invasive infection is too stringent. The aim of replacement therapy once other criteria have been met is to avoid this complication.</p> <p>2. The role of IVIg in these patients is not to keep the number of infections low but to try and PREVENT infections – long periods on IVIg without infection is a sign of successful treatment and not an indication to withdraw. The documentation of effectiveness is therefore unclear – if patients get infections (as many do despite IVIg at a lower frequency than pre-IVIg) this is also not evidence of lack of efficacy.</p> <p>Regular trials off IVIg in patients with a clear PID diagnosis is inappropriate -previous American Academy of Asthma Allergy and Immunology (AAAAI) guidelines suggest “infusions should not be interrupted to learn about a patients tolerance for frequency of infusions as this will place the patients in harm’s way unnecessarily and also would be consistent with medical malpractice”</p> <p>[www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Practice%20Resources/IVI]</p> | The purpose of obtaining an infection history is to ensure that Ig is appropriately provided to patients incurring infections that are more serious than the general population. In SAD, trialling off Ig treatment is recommended over the summer months when patients are well as they may not require ongoing Ig treatment. If a contraindication exists, the patient should not be trialled off. Trials are not recommended in patients with a confirmed diagnosis of PID |

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| | | G-guiding-principles.pdf] | |
| Behcet's disease (chapter 8) | | | |
| 87 | Indication | <p>As the rheumatologist in charge at the Gold Coast University Hospital I have been responsible for the care of a number of patients with immunodeficiency states over the last 30 years, as we do not have an immunologist. This is the most obvious area for IVIG. We now have a new full-time staff specialist in rheumatology and hopefully we will have an immunologist in the not too distant future.</p> <p>As a rheumatologist, on rare occasions we have needed to use IVIG when other treatment has failed. The most common of these is dermatomyositis which has not responded adequately to immunosuppression and corticosteroids in high doses. Similarly it may be employed in polymyositis. There are no adequately blinded study is on this treatment to my knowledge but there is a large anecdotal literature and this has been accepted by the Red Cross Blood Bank when we have applied for the use of this agent. These are rare disorders and consequently I would not think that the demand for IVIG would be high.</p> <p>2 other areas exist where we have occasionally used IVIG, namely vasculitis and Bechet's disease. In both instances this has been when conventional therapy including immunosuppression and cytotoxics have failed. In vasculitis we have been using rituximab more frequently as this has TGA approval for 2 of the commoner conditions.</p> <p>I would agree that there is a necessity to demonstrate the effectiveness of IVIG therapy in any patient who has been placed on treatment. Once a satisfactory remission has been obtained, then usually the IVIG is the first to be reduced or removed.</p> <p>I welcome the opportunity to assist in further in regards to developing the criteria should this be needed.</p> | Noted. |
| Lupus nephritis (chapter 8) | | | |
| 88 | Chapter in Criteria | <p>Treatment of lupus nephritis in patients refractory/intolerant to other first line immunosuppressants with class III or class IV nephritis.</p> <p>AND</p> | Thank you for the advice. The changes for consultation have considered the adaptation of |

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| | | <p>Treatment of lupus nephritis when first line immunosuppressants are contraindicated.</p> <p>Systemic lupus erythematosus (SLE, lupus) is a multisystem autoimmune disease with diverse manifestations. Lupus nephritis is a common and severe manifestation of SLE and an important cause of acute and end-stage renal disease. A variety of effective treatment options are available for lupus nephritis.</p> <p>Whilst treatment may be guided by the patient's stage of renal disease and histology, a typical treatment algorithm would commence with mycophenolate mofetil or cyclophosphamide and steroids with dose escalation if remission is not induced. Azathioprine and mycophenolate are used for maintenance therapy.</p> <p>Rituximab may be used where patients have not responded adequately to induction therapy however this constitutes off-license use. A variety of newer (biological) agents targeting B cells, blocking T-cell co-stimulation, cytokines, kinases and transmembranous glycoproteins are also in development/clinical trials. These options are however, not yet routinely available.</p> <p>The various presentations of lupus have been successfully treated by IVIg in case reports. The most extensive experience is with lupus nephritis. While no RCT of IVIg in lupus nephritis was identified, a variety of case reports were found and are summarised below. (see attached table doc)</p> <p>Proposed indication: Treatment of lupus nephritis in patients refractory/intolerant to other first line immunosuppressants with class III or class IV nephritis. Treatment of lupus nephritis when first line immunosuppressants are contraindicated.</p> <p>As the rheumatologist in charge at the Gold Coast University Hospital I have been responsible for the care of a number of patients with immunodeficiency states over the last 30 years, as we do not have an immunologist. This is the most obvious area for IVIG. We now have a new full-time staff specialist in rheumatology and hopefully we will have an immunologist in the not too distant future.</p> <p>As a rheumatologist, on rare occasions we have needed to use IVIG when other treatment has failed. The most common of these is dermatomyositis which has not responded adequately to immunosuppression and corticosteroids in high doses. Similarly it may be</p> | <p>existing criteria in Chapters 5 and 6 to an electronic system. This recommendation will be considered by the Specialist Working Group as part of the next phase of changes to the Criteria.</p> |

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| | | <p>employed in polymyositis. There are no adequately blinded study is on this treatment to my knowledge but there is a large anecdotal literature and this has been accepted by the Red Cross Blood Bank when we have applied for the use of this agent. These are rare disorders and consequently I would not think that the demand for IVIG would be high.</p> <p>2 other areas exist where we have occasionally used IVIG, namely vasculitis and Bechet's disease. In both instances this has been when conventional therapy including immunosuppression and cytotoxics have failed. In vasculitis we have been using rituximab more frequently as this has TGA approval for 2 of the commoner conditions.</p> <p>I would agree that there is a necessity to demonstrate the effectiveness of IVIG therapy in any patient who has been placed on treatment. Once a satisfactory remission has been obtained, then usually the IVIG is the first to be reduced or removed.</p> <p>I welcome the opportunity to assist in further in regards to developing the criteria should this be needed.</p> | |

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| Kidney transplantation | | | |
| 89 | Indication | <p>Polyoma virus (BK virus) infection in the renal transplant</p> <p>The criteria for use in renal transplantation appear suitable for treatment and prevention of antibody-mediated rejection. There used to be a provision for IVIg use for treatment of polyoma virus (BK virus) infection in the renal transplant as well. That seems to be missing now. It would be good if that could be retained in some way but there is unlikely to be convincing evidence of efficacy in the literature.</p> | <p>The "treatment or prevention of graft rejection with contraindication to immunosuppressive therapies" covers the instance of BK infection. In BloodSTAR a drop down box will allow the recording of the contraindication reason which for BK infection would be "significant infection or sepsis".</p> |
| Lupus nephritis | | | |
| 90 | Chapter in Criteria and indication | <p>Treatment of lupus nephritis in patients refractory/intolerant to other first line immunosuppressants with class III or class IV nephritis.</p> <p>AND</p> <p>Treatment of lupus nephritis when first line immunosuppressants are contraindicated.</p> <p>Systemic lupus erythematosus (SLE, lupus) is a multisystem autoimmune disease with diverse manifestations. Lupus nephritis is a common and severe manifestation of SLE and an important cause of acute and end-stage renal disease. A variety of effective treatment options are available for lupus nephritis.</p> <p>Whilst treatment may be guided by the patient's stage of renal disease and histology, a typical treatment algorithm would commence with mycophenolate mofetil or cyclophosphamide and steroids with dose escalation if remission is not induced. Azathioprine and mycophenolate are used for maintenance therapy.</p> <p>Rituximab may be used where patients have not responded adequately to induction therapy however this constitutes off-license use. A variety of newer (biological) agents targeting B cells, blocking T-cell co-stimulation, cytokines, kinases and transmembranous glycoproteins</p> | <p>Thank you for the information. The current program of work is to adapt the current criteria (and existing conditions) to an electronic authorisation system. A broader review of the Criteria including new conditions will occur in due course and your submission has been retained for consideration during that process.</p> |

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| | | <p>are also in development/clinical trials. These options are however, not yet routinely available.</p> <p>The various presentations of lupus have been successfully treated by IVIg in case reports. The most extensive experience is with lupus nephritis. While no RCT of IVIg in lupus nephritis was identified, a variety of case reports were found and are summarised below. (see attached table doc).</p> <p>Proposed indication:</p> <p>Treatment of lupus nephritis in patients refractory/intolerant to other first line immunosuppressants with class III or class IV nephritis. Treatment of lupus nephritis when first line immunosuppressants are contraindicated.</p> | |

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| 91 | Criteria name | As the criteria now cover the use of Subcutaneous Immunoglobulin (SCIg) as well as Intravenous Immunoglobulin (IVIG), perhaps the title could be amended to 'Criteria for the Use of Immunoglobulin Therapy in Australia', in order to clarify that the Criteria extends to the use of SCIg. | Noted and agreed. |
| 92 | Consultation methods | The Australasian College for Emergency Medicine (ACEM) welcomes the opportunity to provide feedback on the Consultation on the proposed changes to the Criteria for the Clinical use of Intravenous Immunoglobulin in Australia (the Criteria) 2012, proposed by the National Blood Authority (NBA). ACEM is a not-for-profit organisation responsible for the training and ongoing education of emergency physicians, and for the advancement of professional standards in emergency medicine, in Australia and New Zealand. ACEM, as the peak professional organisation for emergency medicine in Australasia, has a vital interest in ensuring the highest standards of emergency medical care are maintained for all patients across Australasia. Following review, ACEM suggests that the Criteria explicitly state that it is acceptable for a telephone or video-consult with the appropriate specialist to be utilised, in order to ensure that patients who are not located in a metropolitan area can receive access to timely treatment. Thank you for the opportunity to provide feedback to the NBA on this issue | Thank you for the advice. A comment will be included to indicate that the use of telephone or video consultation would be at the discretion of the diagnosing/treating specialist. |
| 93 | Alternative treatments | <p>Terumo BCT appreciates the opportunity to comment during the public consultation on proposed changes to the criteria established in 2012 for the clinical use of Intravenous Immunoglobulin [Intravenous (IV) immunoglobulin (Ig)] in Australia.</p> <p>We understand that it is not the role of the criteria to provide clinical guidelines, nor supersede clinical judgment in the selection of the most appropriate treatments for patients. However, there is an opportunity to address alternative treatments in proposed algorithms that may help reduce reliance on IVIg, to enable better access for those conditions where there is no viable treatment alternative, whilst potentially realizing health efficiencies. In particular, we would like to highlight the potential role of Therapeutic Plasma Exchange (TPE) as an appropriate and viable alternative to several indications that IVIg is currently indicated.</p> <p>IVIg is funded directly by the National Blood Arrangements yet several potential alternatives are not, thus creating a challenging environment for healthcare providers and hospitals to choose the appropriate alternative treatment; creating health inefficiency. Recent data on</p> | The Criteria is not a clinical practice guideline, it intends only to provide information about criteria for accessing immunoglobulin funded under the national blood arrangements. |

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| | | <p>IVIg reveals a significant portion (1/3rd) of the national blood budget being spent on IVIg (per data for 2013-2014) at a cost of over \$427 million [1]. There has been an average annual increase in IVIg demand and costs of 11.4% and 14%, respectively, since 2003. Concerns have been raised that this rate of growth is unsustainable. We suggest that it may be possible to address health inefficiencies and curb the rate of growth in IVIg usage and variability without detrimental outcome to the patients.</p> <p>We believe that TPE could serve as an appropriate and viable alternative to several conditions for which IVIg is currently indicated.</p> <ul style="list-style-type: none"> • Appropriate: Historically, TPE was the treatment of choice for certain diseases and IVIg only proved non-inferiority or equivalence [2-17]. • Viable: Some TPE modalities, including the Spectra Optia Apheresis system, can perform TPE procedures via peripheral venous access with similar treatment times to IVIg infusions [18, 19]. <p>o A misperception exists that every TPE procedure must be done via insertion of a central/femoral line, altering the risk/benefit for the patient.</p> <p>With longer term efforts in creating disease specific guidelines, treatment algorithms, and recommendations, health efficiencies can be realized without detrimental impact on to the patients. We respectfully request that this to be taken into account during the consultation period.</p> <p>About Terumo BCT</p> <p>Terumo BCT, established in 1964 as COBE Laboratories, is a global leader in blood component, therapeutic apheresis, and cellular technologies. Terumo BCT is headquartered in Lakewood, Colorado, with sales in over 120 countries. Terumo BCT manufactures the Spectra Optia® Apheresis System, the successor to the COBE® Spectra Apheresis System. Both the Spectra Optia and COBE Spectra systems can be used to perform TPE and both have a long history of service in Australia. Please contact either of us with any questions you may have using our contact information listed below.</p> <p>Sincerely,</p> | |
| 94 | IVIg demand | Baxalta Incorporated welcomes the opportunity provided by the National Blood Authority (NBA) to take part in the public consultation on the proposed changes to the Criteria for clinical use of intravenous immunoglobulin (IVIg) in Australia ("the Criteria"). | Noted |

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| | | <p>Baxalta Incorporated is a global biopharmaceutical leader developing, manufacturing and commercializing therapies for orphan diseases and underserved conditions in haematology, oncology and immunology. Launched in 2015 following separation from Baxter International Inc, Baxalta's heritage in biopharmaceuticals spans decades. In Australia, we have supplied recombinant factor VIII, Factor Eight Inhibitor, Bypassing Agent (FEIBA) and Protein C concentrate since 2003, IVIg since 2012 and recombinant factor IX since 2014 to meet the needs of Australian patients.</p> <p>We agree with the NBA's view that the growth of IVIg demand by 11.4% is not sustainable. We therefore support the NBA's revision of the Criteria. Baxalta is committed to enhancing patient access to innovative and high quality therapy, on the basis of robust evidence. Please find attached Baxalta's response to the public consultation in the feedback template.</p> <p>Our main point of feedback concerns the recommendation in the revised Criteria to "review the current product information sheet for further information". In many conditions there is no additional information in the IVIg product information as there is no Therapeutic Goods Administration (TGA) approved indication. To illustrate this point, I would like to refer to the examples of conditions in the feedback template, the scope of which is limited to the conditions for which IVIg has an established therapeutic role. Of these conditions,</p> <ul style="list-style-type: none"> • there are four conditions where all IVIGs have a TGA approved indication (not included in the feedback template). • there are three conditions where no IVIg has a TGA approved indication, and • several conditions where only a few available IVIGs have a TGA approved indication. <p>Irrespective of the TGA approved indication, all tendered IVIGs are funded and supplied. The disconnect between the indications approved by the regulator and the routine funding and clinical use may contribute to high year on year growth of immunoglobulins in Australia. In view of the above, we believe that the NBA has the opportunity to achieve the objective of managing IVIg demand growth and create better value for patients and physicians, by reviewing the basis for IVIg funding. Baxalta would like to suggest the following measures</p> | |

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| | | <p>for consideration:</p> <ul style="list-style-type: none"> • IVIg demand growth can potentially be managed by prioritizing the allocation of funding for treatment towards those products that have received approval by the TGA for the indication of the sought treatment. Prioritisation of funding on-label use of products will provide an incentive for manufacturers to invest in research and build a strong evidence base for treatment with IVIg therapy. • In order to enable such investment decisions, Baxalta recommends that procurement of IVIg recognizes the demonstration of evidence, quality and innovation, and that procurement contracts foresee in a sufficient time period to allow for a return of investment in generating the evidence base. <p>I would be delighted to discuss these recommendations during a meeting at a time of your convenience.</p> <p>Yours sincerely,</p> | |
| 95 | Criteria ongoing review, dose | <p>1. On behalf of members of the Australasian Society of Clinical Immunology and Allergy (ASCIA) we wish to feedback both general and specific comments regarding changes to the criteria for the clinical use of intravenous immunoglobulin. Please refer to the attached feedback form for specific comments.</p> <p>ASCIA strongly supports improvements in the governance and management of government funded immunoglobulin products. This is a precious resource that needs to be appropriately utilised according to best practice. As such the clinical criteria are important in promoting clinically appropriate usage within Australia.</p> <p>The aims of the guidelines are to ensure that immunoglobulin is used by patients who clinically need it and benefit from its use. Implementation of guidelines that are too restrictive can remove the clinical discretion of the clinician managing the patient and can result in limiting access for patients who would benefit from its use. Withdrawing or limiting</p> | <p>1. Thank you for the advice. The purpose of NIGAC and the Specialist Working Groups is to provide for an ongoing committee structure with the appropriate expertise to support the ongoing review and development of the criteria.</p> <p>2. It is envisaged that proposed changes will be presented to governments for approval at least annually.</p> |

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| | | <p>access to effective therapy can create tensions between clinicians and patients. Driving access for these patients to the Jurisdiction Blood Committees may result in a two tier route to access to immunoglobulin, both funded by the government, with completely different mechanisms of access.</p> <p>Furthermore, recommendations for evaluation of efficacy of therapy need to be evidence based. We look forward to working with the NBA to revise existing and develop new criteria for the clinical use of immunoglobulin.</p> <p>2. The criteria should be subject to ongoing review. If evidence emerges at any time it should be acceptable for NBA to receive a submission to support a change in criteria. For example, TGA does not have deadlines for applications regarding pharmaceuticals.</p> <p>All patients must be weighed, suggest maximum doses recommended for each indication eg capped for 100kg person</p> | <p>The Specialist Working groups and NIGAC have considered this issue and currently there is insufficient evidence to support a national recommendation for maximum dosing by capping the maximum weight in all conditions at this time.</p> |
| 96 | Cost | <p>This is an expensive product with increasing use and as a haematologist in charge of our local transfusion service (tertiary referral co-located adult, women's and children's services and private) I am frequently asked by admin, finance and quality bureaucrats to 'do something' about the horrendous bill for this product. Occasionally I am asked to expend my limited resources to audit our use against guidelines; from my limited experience we seem to be within the prev guidelines but I have noted that the bulk of use is chronic, not acute and neuro/immuno and a lot of that is very long term with infrequent review. I could not always ascertain from the files that the patients were deriving benefit.</p> <p>I'm convinced that weighing patients, strict response criteria and regular clinical review will be helpful, as will the centralised ordering system when it is in place (although our expiry is low). I would also consider asking the patient to sign an additional consent form for use acknowledging that the IVIg will continue to be subsidised only as long as it confers a measurable benefit against the criteria for that illness (this is used by the PBS for expensive cancer drugs such as bortezomib). This can be helpful for the clinician when faced with a difficult choice for patient who enjoys IVIg and has an incurable disorder</p> <p>Finally, CSL make a lot of IVIg from plasma donated from Australian donors (as well as their</p> | <p>Noted.</p> |

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| | | overseas operations) and I hope the NBA can use purchasing power to reduce the price of the product | |
| 97 | BloodSTAR dosing | Unable to record how often an infusion occurs eg in subcutaneous infusion the dose is worked out on a monthly dose, but then is given in weekly/2nd weekly intervals. It may be a benefit that if SC or IV boxes are ticked that they go to specialised dosing forms. | The functionality of the system to support SCIg dosing is yet to be developed. |
| 98 | BloodSTAR | Thank you for the heads up, on the printed letter. Have looked at the site, looks remarkably good for somebody like me (an extremely casual user). Hopefully it can all be done online. Well done | Noted. |