### **2017 (v3.0) proposed changes to v2.1 of the Criteria for the Clinical use of Intravenous Immunoglobulin in Australia**

| **v2.1 CONDITION NAME: Coagulation factor inhibitors** |
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| **v3.0 CONDITION NAME: Acquired haemophilias and congenital haemophilia with inhibitors** |
| **PROPOSED APPROACH:** **To retain** **Acquired haemophilias and congential haemophilia with inhibitors as a condition in *Exceptional circumstances only* with the changes as outlined.** | **SUMMARY OF RATIONALE:** The recommended changes are supported by factors including that: * The role of Ig therapy in these rare conditions has been endorsed by the Australian Haemophilia Centre Directors’ Organisation.
* Ig therapy is often central to the management of patients with acquired von Willebrand disease associated with an IgG paraprotein given that systemic therapy including chemotherapy or other immunosuppressant therapy is often neither indicated nor effective in this patient group.
* For other patients with these potentially fatal conditions, Ig therapy remains an important treatment option that should be retained.
* Usage is low and stable and in line with expected prevalence and should not change as a result of these criteria.
* This condition is listed as a ‘blue’ condition (medium priority in times of shortage and recommended for use) in the UK NHS immunoglobulin Guidelines (UK Department of Health, 2011) and is also listed in the national Canadian IVIg Utilisation Management Guidelines (Ontario Regional Blood Coordinating Network, 2016) as recommended for funded use.
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| **v2.1 CONDITION CATEGORY:**  Condition for which Ig use is in Exceptional circumstances only (Chapter 7)**v3.0 CONDITION CATEGORY:**  Condition for which Ig use is in Exceptional circumstances only (Chapter 7) |
| **Role of Ig therapy:** Antibodies against blood coagulation factors may occur in patients with inherited haemophilia or those with previously normal coagulation, and are life threatening situations for all. Ig therapy plays a slightly different role in the various scenarios. Ig therapy has an internationally accepted role in the reduction of bleeding in patients with acquired von Willebrand syndrome and IgG paraproteins given that systemic therapy including chemotherapy or other immunosuppressive therapy is often neither indicated nor effective (Collins et al, 2013).In patients with Congenital haemophilia A with acquired factor VIII inhibitors, Congenital haemophilia B with acquired factor IX inhibitors or Acquired haemophilia A, evidence supports the use of Ig as part of a second line immune tolerance protocol. In Australia currently, this protocol is very rarely used but is likely to be required every three to five years, and so access should be retained. IVIg may serve a limited but supportive role in managing patients who are bleeding, or at high risk of bleeding, with limited response to first-line immunosuppression. These are life threatening events. (Collins et al, 2013 and Guglielmone et al, 2011). In all of these circumstances, advice regarding the management of patients with acquired inhibitors and the use of Ig can be accessed from a local Haemophilia Treatment Centre. |

| **ITEM** | **CRITERIA v.2.1**  | **PROPOSED REVISIONS TO THE CRITERIA** | **SPECIALIST WORKING GROUP RATIONALE FOR ADDITIONS/CLARIFICATIONS** |
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| **Condition Name** | **Coagulation factor inhibitors (alloantibodies and autoantibodies), including acquired haemophilia, acquired von Willebrand syndrome, inhibitors to factor VIII in haemophilia A, and inhibitors to factor IX in haemophilia B** | **Acquired haemophilias and congential haemophilia with inhibitors** | Name amended to shorten and better reflect the group of diagnoses. |
| **Specialty** | Haematology | Haematology  | Unchanged |
| **Category** | *Exceptional circumstances only* | *Exceptional circumstances only* | Unchanged |
| **Specific Conditions** | Coagulation factor inhibitors | Congenital haemophilia A with acquired factor VIII inhibitor Congenital haemophilia B with acquired factor IX inhibitor Acquired haemophilia AAcquired haemophilia B Acquired von Willebrand syndrome Acquired bleeding disorder, other coagulation factors (Prothrombin, factor V, factor VII, factor X, factor XI, and factor XIII) | Specific conditions listed to support data analysis. |
| **Level of Evidence** | Evidence of probable benefit – more research needed (Category 2a) |  Evidence of probable benefit – more research needed (Category 2a) | Unchanged and unlikely to change due to the rarity of the condition. |
| **Justification for Evidence Category** |   | IVIg has a role as part of a second-line immune tolerance protocol involving immunoadsorption and immunoglobulin replacement, in addition to immunosuppression and factor replacement, the Malmo protocol (Nilsson et al, 1988 and Berntorp et al, 2000 and Franchini & Lippi, 2008 and Zeitler et al, 1991). There is evidence for the beneficial effect of this protocol in patients with:• Congenital haemophilia A with acquired factor VIII inhibitors• Congenital haemophilia B with acquired factor IX inhibitors• Acquired haemophilia A. IVIg has an accepted role in the reduction of bleeding in patients with acquired von Willebrand syndrome and IgG paraproteins (Collins et al, 2013).IVIg has an uncertain role in the reduction of bleeding in patients with other acquired bleeding disorders associated with the development of specific coagulation factor inhibitors. There is conflicting data, and conflicting recommendations. There is no role for IVIg as first-line, or as monotherapy in the reduction of bleeding in these disorders. However, IVIg may serve a limited but supportive role in managing patients who are bleeding, or at high risk of bleeding, with limited response to first-line immunosuppression. (Collins et al, 2013 and Guglielmone et al, 2011). In all of these circumstances, advice regarding the management of patients with acquired inhibitors and the use of Ig can be be accessed from a local Haemophilia Treatment Centre. Patients with Acquired von Willebrand syndrome with IgM autoantibodies/paraprotein may be better amenable to plasmapheresis, but local guidelines should apply. Evidence suggests these patients do not respond to Ig therapy. (Federici et al, 1998; Federici, 2005 and Collins et al, 2013). | Justification of evidence section has been drafted in line with the literature. |
| **Indications** |   | **IVIg as part of Malmo tolerisation protocol – replacement following immunoadsorption****As adjunct therapy in the treatment of acquired coagulation factor inhibitors****Active bleeding in acquired von Willebrand disease associated with an IgG paraprotein** |  Three indications have been developed in consultation with the Australian Haemophilia Centre Directors’ Organisation to support the different qualifying criteria and dosing regimens required.  |
| **Description and Diagnostic Criteria** |  Management of these rare and severe bleeding disorders should be undertaken only by or in consultation with haemophilia treatment centres. When indicated, intravenous immunoglobulin (IVIg) only forms part of the management of these complex patients, with additional haemostatic support required. IVIg may be considered in the following circumstances: Inhibitors to factor VIII (FVIII) in haemophilia A and inhibitors to factor IX (FIX) in haemophilia B, especially in cases where there has been failure of immune tolerisation and poor response to recombinant factor VIIa or factor eight inhibitor bypassing activity (FEIBA) — only as part of the Bonn–Malmö protocol for immune tolerance induction.Autoimmune acquired von Willebrand syndrome — correction of FVIII and von Willebrand factor levels for the management of bleeding and before invasive procedures, except cases associated with IgM paraprotein where response is unlikely. Use is indicated in failure to respond to chemotherapy/immunosuppressants or where there is insufficient time for chemotherapy/immunosuppressants to be given. Initial therapy either 0.4 g/kg for 5 days or 1 g/kg for 2 days. Continued therapy 1 g/kg once every 3–4 weeks.Acquired haemophilia A for:a. support of correction of FVIII level for the management of bleeding, and before invasive procedures in individuals in whom steroid or immunosuppressive therapy is contraindicated or has failed to eradicate the inhibitor (2 g/kg over 2–5 days); orb. support of correction of FVIII level following failure of first-line therapies (steroids and immunosuppressants) and poor response to recombinant factor VIIa or FEIBA when used as part of the Bonn–Malmö protocol.Other acquired (autoimmune) coagulation inhibitors (e.g. acquired Factor V inhibitors) to correct factor level for the management of bleeding and before invasive procedures in cases where other therapeutic approaches have failed or are contraindicated (2 g/kg over 2 to 5 days). |  Inhibitors to coagulation factors are antibodies that can interfere with the function of specific clotting proteins including factor VIII, factor IX and less commonly, other coagulation factors. Inhibitors can be allo-antibodies as occurs in congenital haemophilia in response to infused product, or auto-antibodies as occurs in acquired haemophilia which may be seen in the setting of other autoimmune disease, malignancy, post-partum or in response to certain drugs. The incidence of acquired cases is very low and usually respond to steroids (first-line), and IVIg would only usually be considered in the setting of ongoing bleeding. Patients may present with abnormal bleeding which can be severe and life threatening, and in these circumstances treatment is best co-ordinated in association with Haemophilia Treatment Centres. The presence and level of inhibitor should be confirmed where possible by a factor specific Bethesda assay. Where laboratory confirmation is not able to be easily performed, as in acquired von Willebrand disease, significantly reduced response to infused factor concentrate or demonstration of new onset of reduced clotting factors levels can be used to make the diagnosis. | The description and diagnostic criteria section has been updated in consultation with the Australian Haemophilia Centre Directors’ Organisation to reflect the findings of more recently published evidence on disease presentation, progression and management. |
| **Diagnosis is required** |   | Yes | By which specialty | Haematologist  | The Specialist Working Group and the Australian Haemophilia Centre Directors’ Organisation recommend that the diagnosis should be limited to Haematologists due to the life threatening nature of these conditions and the need for laboratory verification. |
| **Diagnosis must be verified** | No | By which specialty |  |
| **Exclusion Criteria** |   | Acquired von Willebrand syndrome with IgM autoantibodies/paraprotein | Evidence does not support Ig therapy in this condition (Federici et al, 1998; Federici, 2005 and Collins et al, 2013). |
| **Qualifying Criteria** |  | **IVIg as part of Malmo tolerisation protocol – replacement following immunoadsorption*** Congenital haemophilia A or B with inhibitors, or acquired haemophilia A

AND* Unresponsive to first line treatment by tolerisation including steroids and immunosuppressant agents

OR* Immunosuppressant therapy is contraindicated

AND* Ig prescribed as part of the Malmo protocol in consultation with a Haemophilia Treatment Centre

**IVIg as adjunct therapy in the treatment of acquired coagulation factor inhibitors*** Presence of acquired coagulation factor inhibitors with evidence of bleeding or a risk of bleeding is determined

AND* Unresponsive to first line treatment including steroids and immunosuppressant agents

OR* Immunosuppressant therapy is contraindicated

**Active bleeding in acquired von Willebrand disease associated with an IgG paraprotein*** Evidence of acquired von Willebrand disease with evidence of bleeding or risk of bleeding

AND* No other indication exists for systemic chemotherapy or immunosuppressant therapy

AND* Ig therapy is given in consultation with a Haemophilia Treatment Centre
 |  All qualifying criteria have been developed in consultation with the Australian Haemophilia Centre Directors’ OrganisationValid contraindication reasons for Immunosuppressant therapy may include: Pregnancy, Significant infection including sepsis, Potential for life threatening infection, Malignancy and Marrow suppression and/or cytopenia. Acquired inhibitors are rare occurrences and require treatment whether the patient is bleeding or not. A description of the bleeding or any determined risk of bleeding is sufficient to qualify, noting that the patient may or may not demonstrate bruising or even minor bleeding. Particular risks would include pregnancy, post-partum or pre-surgery.  |
| **Review Criteria** |   |  **IVIg as part of Malmo tolerisation protocol – replacement following immunoadsorption**Review by a Haematologist is required within six months of treatment to determine whether the patient has responded, and six monthly thereafter. Documentation of clinical effectiveness is necessary for continuation of IVIg therapy. **On review of the initial authorisation period**Clinical effectiveness of Ig therapy can be demonstrated by: * Reduction in bleeding symptoms or in the risk of bleeding

AND* Reduction in or absence of inhibitors

**On review of a continuing authorisation period** For stable patients on maintenance treatment, review by a haematologist is required at six monthly.Clinical effectiveness of Ig therapy can be demonstrated by: * Reduction in bleeding symptoms or the risk of bleeding

AND* Reduction in or absence of inhibitors

**IVIg as adjunct therapy in the treatment of acquired coagulation factor inhibitors**Review is not mandated for this indication however, the following criteria may be useful in assessing the effectiveness of Ig therapy. Clinical effectiveness of Ig therapy may be demonstrated by: * Reduction in bleeding symptoms or the risk of bleeding

AND* Reduction in or absence of inhibitors

**Active bleeding in acquired von Willebrand disease associated with an IgG paraprotein**Review by a Haematologist is required within six months of treatment to determine whether the patient has responded, and six monthly thereafter. Documentation of clinical effectiveness is necessary for continuation of IVIg therapy. **On review of the initial authorisation period*** Reduction in bleeding symptoms or risk of bleeding

**On review of a Continuing authorisation period*** Reduction in bleeding symptoms or risk of bleeding
 | Review criteria and treatment periods have been developed in consultation with the Australian Haemophilia Centre Directors’ Organisation, supported by the literature.  |
| **Dose** |  Dosing above 1 g/kg per day is contraindicated for some IVIg products.Refer to the current product information sheet for further information.The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient. | **IVIg as part of Malmo tolerisation protocol – replacement following immunoadsorption****Induction Dose - 1 g/kg as a divided dose over 3 days****Maintenance Dose – 1 g/kg in divided dose over 3 days, weekly as part of the Malmo protocol**The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.Refer to the current product information sheet for further information on dose, administration and contraindications.**IVIg as adjunct therapy in the treatment of acquired coagulation factor inhibitors****Induction Dose – Up to 2 g/kg as a single or divided dose. Up to two additional doses may be requested for responding patients, given in combination with immunosuppressant therapy from three to six weekly.**The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.Refer to the current product information sheet for further information on dose, administration and contraindications.**Active bleeding in acquired von Willebrand disease associated with an IgG paraprotein****Induction Dose – 2 g/kg as a divided dose over 2-5 days****Maintenance Dose – 1 g/kg three to four weekly**The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.Refer to the current product information sheet for further information on dose, administration and contraindications. | Dosing levels and treatments periods have been developed in consultation with the Australian Haemophilia Centre Directors’ Organisation, supported by the literature. |

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| **References****(most recent update: May 2016)** |
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| **POTENTIAL OPERATIONAL IMPACT** |
| While the revised criteria provide greater guidance for access to Ig therapy, there is not expected to be any operational impact as a result of these changes as they are in line with current clinical practice. There will be some additional data entry required compared to the previous Ig request process, but it is considered marginal. |
| **POTENTIAL IMPACT ON PATIENTS, DEMAND AND EXPENDITURE** |
| **Description of impact on patients:** | It is recognised that the proposed changes are bringing the criteria into line with established clinical practice and do not represent any real change to the clinical management of patients. The changes have been developed in consultation with the Australian Haemophilia Centre Director’s Organisation. The formal access criteria now proposed provide better guidance as to when Ig therapy will provide the greatest benefit in the treatment of patients with these rare conditions. The changes require that a haematologist makes the diagnosis and manages the ongoing treatment which is likely to reflect current practice due to the types of testing needed to diagnose and manage patients with these conditions. Existing patients on ongoing treatment will already be regularly reviewed by their haematologist so the requirement for six monthly checks to confirm that Ig therapy is effective in reducing the inhibitor level and/or the risk of bleeding will not place an added burden on patients. New patients authorised to receive Ig therapy will require an initial check after the first six months of Ig treatment to confirm that Ig therapy is reducing the inhibitor level and /or has reduced the risk of bleeding. This and any ongoing reviews can be performed as part of the specialist’s usual monitoring process. If patients have not improved after the six months treatment, Ig therapy will be ceased and substituted with a different treatment approach. If improvement has been demonstrated, further checks every six months are required to confirm that Ig maintenance therapy remains effective.  |
|  | **2011-12** | **2012-13** | **2013-14** | **2014-15** | **2015-16** | The Specialist Working Group estimated magnitude of effect:No impact against projected demand |
| **Patient number** | **9** | **9** | **10** | **10** | **13** |
| **Total Grams issued** | **2,069** | **3,159** | **3,786** | **2,790** | **4,528** |
| **% Total Grams issued** | **0.06%** | **0.09%** | **0.09%** | **0.06%** | **0.09%** |
| **Specialist Working Group knowledge development opportunities and recommendations** |
| None identified at this stage. |

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| **END OF PUBLIC CONSULTATION DOCUMENT****Next review: Twelve to eighteen months from BloodSTAR v3.0 implementation** |