Specialist Working Group for Immunology

Proposed changes to the *Criteria for the clinical use of intravenous immunoglobulin in Australia, Second Edition*

ITEM	CRITERIA FOR THE CLINICAL USE OF INTRAVENOUS IMMUNOGLOBULIN IN AUSTRALIA, EDITION 2	PROPOSED REVISIONS TO THE CRITERIA	SWG RATIONALE FOR PROPOSED CHANGE (A) Administrative) (B) Progressive (C) Programmed
Condition Name	**Primary immunodeficiency diseases (PID) with antibody deficiency** **This excludes:** 1. **specific antibody deficiency (see page 110);** 2. **IgG subclass deficiency (not funded see page 112).**	**Primary immunodeficiency diseases (PID) with antibody deficiency**	Condition name retained**.**
Specialty	Immunology	Immunology	
Chapter	5	5	
Specific Conditions	In each case, a specific PID diagnosis must be established under the supervision of a specialist clinical immunologist and the diagnosis must be advised for IVIg to be approved.	• Severe combined immunodeficiency (SCID) • Combined immunodeficiency generally less profound than SCID (e.g. thymoma) • Combined immunodeficiency with associated or syndromal features (e.g.Wiskott Aldrich syndrome; ataxia telangiectasia) • Severe reduction in all Ig isotypes with decreased or absent B-cells (e.g.XLA def) • Severe reduction in at least two Ig	Specific condition will be a mandatory field in the ig system. IUIS criteria have been used to capture diagnostic groups as specific conditions. Given that the full detail may be overwhelming to prescribers, it is proposed that the major subheadings would be used. (A)

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		isotypes with low/normal B-cells (CVID) • Severe reduction in serum IgG and IgA with normal/elevated IgM (e.g. CD40L def) • Lymphoproliferative syndrome (e.g.XLP1, XLP2, CD27 def), • Possible CVID • Transient hypogammaglobulinaemia of infancy • Other	
Level of Evidence	Evidence of probable benefit (Category 2a).	Evidence of probable benefit (Category 2a).	
Description and Diagnostic Criteria	PID comprise a group of more than 120 separate conditions. Many of these are manifest by failure of protective antibody production. Key diagnoses include common variable immunodeficiency (CVID), severe combined immunodeficiencies, transient hypogammaglobulinaemia of infancy, Wiskott Aldrich syndrome and X-linked agammaglobulinaemia. In certain conditions, such as Wiskott Aldrich syndrome, antibody failure may not be manifest as hypogammaglobulinaemia but functional antibody responses will be impaired. Some PID does not involve antibody failure, such as chronic granulomatous disease and deficiencies of complement components. In these	More than 280 primary immunodeficiency diseases have been identified. Many of these cause antibody deficiency. In some cases, antibody deficiency is associated with B-cell deficiency (e.g. X-linked agammaglobulinaemia), while in others, B-cells are present. Antibody deficiency can be the only manifestation of PID, or there can be other defects as well (e.g. T-cell deficiency, autoimmunity). Not all PIDs cause antibody defects and, therefore, immunoglobulin replacement is not always indicated. Recognised primary immunodeficiencies for which immunoglobulin replacement is universally indicated are: X-linked agamma/hypogammaglobulinaemia, Severe combined immunodeficiency, Wiskott-Aldrich	This section has been reviewed and revised to reference the European Society of Immunodeficiency Diseases (ESID) which is the current international standard for diagnosis. The reference to ESID criteria was revised following public consultation feedback. It is acknowledged that the criteria are under development and need to be varied slightly in their application as qualifying criteria for Ig therapy (see below). A statement noting that a low IgG alone is not a sufficient indication for Ig replacement was added. (A)

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	cases, antibody replacement therapy is not justified.	syndrome, X-linked lymphoproliferative syndrome, Hyper IgM syndrome and Severe T-cell immunodeficiency. The revised European Society for Immunodeficiency Diseases (ESID) (2014) diagnostic criteria for common variable immune deficiency (CVID) require the diagnosis to be established after the fourth year of life (but symptoms may be present before) and at least one of the following: • increased susceptibility to infection • autoimmune manifestations • granulomatous disease • unexplained polyclonal lymphoproliferation • affected family member with antibody deficiency. AND A marked decrease of immunoglobulin G (IgG) and marked decrease of IgA with or without low IgM levels (measured at least twice; less than the normal reference range for their age). AND At least one of the following: • poor antibody response to vaccines	

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		(and/or absent isohemagglutinins); i.e. absence of protective levels despite vaccination where defined • low switched memory B-cells (<70% of age-related normal value). AND Secondary causes of hypogammaglobulinaemia have been excluded. 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. Genetic diagnoses are continually being updated as described in the classification system for the International Union of Immunology Societies (IUIS).	
Justification for Evidence Category	The Biotext (2004) review reported level 2a evidence for the use of IVIg in the treatment of common variable immunodeficiency and primary hypogammaglobulinaemia.	The Biotext (2004) review reported level 2a evidence for the use of intravenous immunoglobulin (IVIg) in the treatment of common variable immunodeficiency and primary hypogammaglobulinaemia.	Unchanged

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Diagnosis is required	In each case, a specific PID diagnosis must be established under the supervision of a specialist clinical immunologist and the diagnosis must be advised for IVIg to be approved.	Yes	Which Speciality	Clinical Immunologist	Unchanged – see above under specific conditions for capturing of exact diagnosis.
Diagnosis must be verified		No	Which Specialty		
Exclusion Criteria Bullet list of exclusion criteria	The following conditions should not be approved under this indication: 1. Miscellaneous hypogammaglobulinaemia (see *Secondary hypogammaglobulinaemia*, page 106) 2. Specific antibody deficiency (see page 110) 3. IgG subclass deficiency (not funded; see page 112).	The following conditions should not be approved under this indication: • secondary hypogammaglobulinaemia unrelated to haematological malignancy • specific antibody deficiency • IgG subclass deficiency. • secondary hypogammaglobulinaemia related to haematological malignancy			

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Indications	Management of infection related to antibody deficiency.	**Recognised primary immunodeficiencies for which immunoglobulin replacement is universally indicated (see listing under Diagnostic criteria)** **Common variable immune deficiency - based on ESID 2014 criteria** **Possible CVID – (below normal serum IgG but normal serum IgA level)** **Transient hypogammaglobulinaemia of infancy (children aged less than 4 years)**	Two indications are recommended to allow different qualifying criteria to be used for eligibility. The first indication is required as often patietns are very ill in ICU and a definitive diagnosis may not be determined at the time of prescription. The second indication is essentially CVID that will support the majority of patients. Following public consultation, 'probable CVID' was changed to 'possible CVID' - these patients would mostly evolve into Specific Ab deficiency althought a small percentage would have CVID. Discussion agreed that very few children with transient hypogammaglobulinaemia actually require ig therapy, but some do and should not be placed onto lifelong Ig therapy at that time. (A)
Qualifying Criteria	In each case, a specific PID diagnosis must be established under the supervision of a specialist clinical immunologist and the diagnosis must be advised for IVIg to be approved.	**Recognised primary immunodeficiencies for which immunoglobulin replacement is universally indicated.** • The patient has a confirmed or suspected clinical diagnosis of primary immunodeficiency that must be advised. AND Evidence of hypogammaglobulinaemia. (Blood samples for IgG testing should be taken on two occasions, at least one hour apart and at least one sample taken when the patient does not have an infection.) Where a diagnosis has initially been	For the first indication where patients have a recognised primary immunodeficiency, the diagnosis type includes: i. X-linked agamma/hypogammaglobulinaemia ii. Severe combined immunodeficiency iii. Wiskott-Aldrich syndrome iv. X-linked lymphoproliferative syndrome v. Hyper IgM syndrome vi. Severe T-cell immunodeficiency If the diagnosis is not confirmed at the first dose, the confirmed diagnosis must be updated prior to further Ig treatment. It is recognised that genetic confirmation is not always possible, but a clinical diagnosis can be made. (A)

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		suspected, confirmation will be required for access to continuing Ig therapy. **Common variable immune deficiency - based on ESID 2014 criteria** • The patient is older than four years of age at diagnosis (although symptoms may present earlier). AND • There is evidence of a marked decrease of IgG and a marked decrease of IgA (measured at least twice and less than the normal reference range for age) with or without low IgM levels and causes of secondary hypogammaglobulinaemia have been excluded. (Blood samples for IgG and IgA testing should be taken on two occasions, at least one hour apart and at least one sample taken when the patient does not have an infection.) AND • The patient has a documented failure to develop protective antibody response to conjugated or unconjugated pneumococcal vaccine (unless the patient's serum IgG<2 g/L and a delay to providing Ig replacement would present	The diagnostic criteria for CVID from the European Society for Immunodeficiency Diseases have been used as the eligibility criteria for access to long term Ig therapy in CVID. It was acknowledged that some current patients may require to be 'grandfathered' but that moving forwards – the international diagnostic criteria should be applied. Guidance added regarding sampling for serum IgG and IgA where relevant. (A) For patients not meeting the full criteria, a further indication has been developed to support initial treatment with review. It is recognised that when the IgG<2g/L in such patients, there will be a failure to develop protective antibody post vaccination when they

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		significant risk) 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). AND • The patient has demonstrated an increased susceptibility to infection or the patient has autoimmune manifestations, granulomatous disease, unexplained polyclonal proliferation or an affected family member with antibody deficiency. **Possible CVID –(Low serum IgG and normal serum IgA level)** It is acknowledged that a low IgG alone is not a sufficient indication for immunoglobulin replacement therapy. Many patients will be well despite the finding of a serum IgG below the normal range for age. • The patient is older than four years of age at diagnosis (although symptoms may present earlier). AND • There is evidence of a marked decrease of	comply with all other criteria and a patient with profound deficiency should not be unduly exposed to additional risks from invasive bacterial infection. Additional script added to recognise that many patients with a low IgG do not require ig therapy.

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		IgG (measured at least twice and less than the normal reference range for age) with normal IgA with or without low IgM levels and causes of secondary hypogammaglobulinaemia have been excluded. (Blood samples for IgG testing should be taken on two occasions, at least one hour apart and at least one sample taken when the patient does not have an infection.) AND The patient has a documented failure to develop protective antibody response to conjugated or unconjugated pneumococcal vaccine or protein vaccine challenge (unless serum IgG<2 g/L and the patient would be at significant risk from a delay to providing Ig replacement such as following an invasive bacterial infection) 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). AND • The patient has demonstrated an increased susceptibility to infection or the patient has autoimmune manifestations,	Guidance added regarding blood sampling for IgG. Guidance added regarding when IgG<2 g/L and patient at signifcant risk from delay to treat. These patients will be trialled off Ig therapy in due course and a confirmed diagnosis will be able to be made at a later time.

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		granulomatous disease, unexplained polyclonal proliferation or an affected family member with antibody deficiency. **Transient hypogammaglobulinaemia of infancy (children aged less than 4 years)** The majority of young children with transient hypogammaglobulinaemia do not require immunoglobulin therapy. However, if the patient has had recurrent suppurative infections that threaten organ function, review by a clinical immunologist is recommended for consideration of Ig therapy. Some patients may require treatment during the winter months only and others will benefit from more prolonged treatment. • The patient is younger than four years of age at diagnosis AND • There is evidence of a marked decrease of IgG (measured at least twice and less than the normal reference range for age) and causes of secondary hypogammaglobulinemia have been excluded AND • The patient has demonstrated an	For children less than 4 years old, a further indication is available. Patients would either cease therapy or become eligible under a different indication at 4 years old. Script added for guidance regarding when Ig therapy is indicated.

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		increased susceptibility to infection.	
Review Criteria	Review criteria for primary immunodeficiency diseases with antibody deficiency are not mandated. Nevertheless, the following may be of value to the clinician: • frequency of clinical episodes of infection • trough levels; and • renal function.	**Recognised primary immunodeficiencies for which immunoglobulin replacement is universally indicated.** Review by a Clinical Immunologist is required at six months and annually thereafter. Documentation of clinical effectiveness is necessary for continuation of IVIg therapy. The review criteria for primary immunodeficiency diseases are to ensure adequate replacement of antibody deficiency and to demonstrate clinical benefit from treatment. **On review of an authorisation period** • An assessment of the clinical benefit during the review period will be made, and trough or serum immunoglobulin levels (IgG, IgA and IgM) and a history of infection must be reviewed AND • If a genetic diagnosis (as per IUIS classification) has been made, this must be advised. OR • Where a diagnosis has initially been suspected, confirmation by a clinical immunologist is required for access	Review criteria for CVID have been defined to demonstrate clinical benefit and the monitoring of Ig trough/serum levels to support dose management. (A) In the second indication, the opportunity to revise or advise the diagnosis has also been provided given that some patients will not have a confirmed diagnosis at the time of the first dose. Where a diagnosis has initially been suspected, confirmation is required for access to continuing Ig therapy. Where a genetic diagnosis is not possible, a clinical diagnosis is sufficient. (A)

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		to continuing Ig therapy. **Common variable immune deficiency** Initial review by a Clinical Immunologist is required at six months and at least annually thereafter. Documentation of clinical effectiveness is necessary for continuation of IVIg therapy. The review criteria for primary immunodeficiency diseases are to ensure adequate Ig replacement of antibody deficiency and to demonstrate clinical benefit from treatment. **On review of an authorisation period** • An assessment of the clinical benefit during the review period will be made, and trough or serum immunoglobulin levels (IgG, IgA and IgM) and a history of infection must be reviewed AND • If a genetic diagnosis (as per IUIS classification) has been made, this can be advised. **Possible CVID –ESID diagnostic criteria met except normal serum IgA level**	

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		Initial review by a Clinical Immunologist is required at six months and ongoing reviews at least annually to assess clinical benefit. Documentation of clinical effectiveness is necessary for continuation of Ig therapy. Cessation of Ig therapy should be considered after each 12 months of treatment. If serum IgM and IgA levels are trending upwards and near 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. Ig therapy should be extended as required to enable cessation of therapy in September/October, with repeat clinical and/or immunological evaluation before re-commencement of therapy. **On review of an authorisation period** • An assessment of the clinical benefit during the review period will be made and recent trough or serum immunoglobulin levels (IgG,IgA and IgM) and a history of infection must be reviewed. AND • When IgA and IgM are trending towards normal and the patient is	Additional guidance provided regarding IgA and IgM levels.

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		well, a trial off therapy, may be considered to allow immunological re-evaluation or a reason is provided why a trial is not planned. **Transient hypogammaglobulinaemia of infancy** Initial review is required by a Clinical Immunologist at six months and ongoing reviews at least annually to assess clinical benefit. Documentation of clinical effectiveness is necessary for continuation of Ig therapy. Cessation of Ig therapy should be considered at least after 24 months of treatment. 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 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. Ig therapy should be extended as required to enable cessation of therapy in September/October, with repeat clinical and/or immunological evaluation before re-commencement of therapy. **On review of an authorisation period**	Guidance statement regarding IgA and IgM levels added

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		• An assessment of the clinical benefit during the review period will be made and recent trough or serum immunoglobulin levels (IgG,IgA and IgM) and a history of infection must be reviewed. AND • When IgA and IgM are trending towards normal and the child is well, a trial off therapy, may be considered or a reason is provided why a trial is not planned. When the child is over 4 years old, a decision must be made regarding a trial off treatment or qualification may be appropriate under a different indication such as possible or confirmed CVID.	
Dose	**Maintenance dose:** 0.4 g/kg every four weeks, modifying dose and schedule to achieve IgG trough level of at least the lower limit of the age-specific serum IgG reference range. **Loading dose:** One additional dose of 0.4 g/kg in the first month of therapy is permitted if the serum IgG level is markedly reduced. Chronic suppurative lung disease: Dosing to achieve IgG trough level of up to 9 g/L is	**Recognised primary immunodeficiencies for which immunoglobulin replacement is universally indicated (see listing under Diagnostic criteria)** **Loading Dose** - One to two additional doses of 0.4 g/kg in the first month of therapy is permitted if the serum IgG level is <4g /L. **Maintenance** - 0.4 g/kg every four weeks or more frequently to achieve IgG trough level of at least the lower limit of the age-specific serum IgG reference range. A total dose of up	The SWG recommends that one to two loading doses should be allowed in those diagnoses of PID for which immune replacement is universally indicated during the first month of treatment where the IgG level is <4g/L as patients are often very ill. It was observed that in other conditions, such as neurology, much higher loading doses are permitted. (B) **Please note: The above recommendation will require specific government approval as it is an increase in dosing for this group of patients.** In general, consistency in dosing has been

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	permitted if chronic suppurative lung disease is not adequately controlled at an IgG trough level at the lower limit of the age- specific serum IgG reference range. Subcutaneous administration of immunoglobulins is a suitable alternative to IVIg in this disease. **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.**	to 1 g/kg may be given over any four-week period, which might be by divided doses more frequently than monthly. 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.** **All other indications within PID condition** **Loading Dose** - One additional doses of 0.4 g/kg in the first month of therapy is permitted if the serum IgG level is <4g /L. **Maintenance** - 0.4 g/kg every four weeks or more frequently to achieve IgG trough level of at least the lower limit of the age-specific serum IgG reference range. A total dose of up to 1 g/kg may be given over any four-week period, which might be by divided doses more frequently than monthly. The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.	provided with other immune replacement conditions including the limitation of an upper dose of 1g/Kg. This should encourage more frequent dosing but at a lower monthly dose rather than giving higher doses monthly which leads to very high and then very low blood Ig levels. Better clinical outcomes will result from achieving more constant blood replacement levels throughout the month. (A)

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		Refer to the current product information sheet for further information.	

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