



**Australian Government**

**Department of Health**

## **Application 1591:**

**Review of immunoglobulin use for**

**Secondary Hypogammaglobulinaemia  
unrelated to haematological malignancies, or  
post-haemopoietic stem cell transplantation  
(HSCT)**

# **PICO Confirmation**

**(to guide a new referral to MSAC)**

Summary of PICO criteria to define the question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

Component	Description
Patients	Patients with secondary hypogammaglobulinaemia unrelated to haematological malignancy or haemopoietic stem cell transplant (HSCT) who are currently eligible for immunoglobulin (Ig) treatment according to the Criteria for the Clinical use of Ig in Australia (Criteria version 3)
Intervention	Replacement IgG therapy with or without antibiotics, including: <ul style="list-style-type: none"> <li>• IgG by intravenous administration (IVIg) or</li> <li>• IgG subcutaneous administration (SCIg)</li> </ul>
Comparator	No IgG therapy with or without antibiotics
Outcomes	The outcomes listed are those identified in the development of the PICO. Additional relevant outcomes may be identified during the evaluation process. The outcomes identified are: <p>Safety Outcomes:</p> <ul style="list-style-type: none"> <li>• Adverse events (AEs), including hypersensitivity reactions, anaphylaxis, veno-occlusive events</li> <li>• Antibiotic resistance</li> </ul> <p>Clinical effectiveness outcomes:</p> <ul style="list-style-type: none"> <li>• Infections</li> <li>• Quality of life</li> <li>• Mortality</li> <li>• Transplant rejection rates</li> <li>• IgG trough levels</li> </ul> <p>Healthcare system resource utilisation:</p> <ul style="list-style-type: none"> <li>• Ig products</li> <li>• Antibiotic use</li> <li>• Infusion equipment,</li> <li>• Administrative and clinician time (e.g. resources associated with requesting, and authorising, access to Ig),</li> <li>• Nursing time (for initiation and monitoring if IVIg)</li> <li>• Hospitalisation (including length of stay)</li> <li>• ICU admission (including length of stay)</li> <li>• Management of adverse events</li> <li>• Training of patient or carer to provide infusions (SCIg only),</li> <li>• Product dispensing and disposal of any unused product</li> <li>• Follow-up and/or monitoring visits</li> </ul>

### PICO rationale for therapeutic and investigative medical services only

Australian Governments, through the Jurisdictional Blood Committee (JBC), have agreed to conduct a robust Health Technology Assessment (HTA) review to ensure Government-funded immunoglobulin (Ig) use within Australia is based on strong evidence of clinical and cost effectiveness.

This HTA is being conducted through the Medical services Advisory Committee (MSAC) assessment process to review the evidence supporting IgG treatment for the indication of secondary hypogammaglobulinaemia unrelated to haematological malignancy or haematopoietic stem cell transplant (HSCT). The MSAC Immunoglobulin Review Reference Group will oversee all immunoglobulin HTA review applications. The review complements the National Blood Authority (NBA) Immunoglobulin Governance Program which aims to strengthen clinical governance and authorisation of Government funded immunoglobulin in Australia.

Public funding for immunoglobulins (IgG) for this indication is currently available under the National Blood Arrangements, as specified in the Criteria for the Clinical use of immunoglobulin (Ig) in Australia (The Criteria, Version 3) (1). The Criteria is a publication that describes the eligibility criteria that patients must meet to receive Ig that is funded by all Australian governments. The Criteria helps to ensure that Ig is accessed consistently across Australia for the treatment of patients whose health is likely to be improved with Ig therapy (2).

#### **Population**

The population is patients with secondary hypogammaglobulinaemia unrelated to haematological malignancy or HSCT. Specific conditions include:

- Hypogammaglobulinaemia following solid organ transplantation
- Hypogammaglobulinaemia following B cell depletion therapy
- Thymoma-associated hypogammaglobulinaemia (Goods Syndrome)
- Other hypogammaglobulinaemia unrelated to haematological malignancies or HSCT

Details on the clinical criteria to access initial and continuing treatment under this indication are presented in Table 3.

Hypogammaglobulinaemia is defined as a serum IgG level <7g/L (3). An abnormal susceptibility to bacterial infections may arise from acquired hypogammaglobulinaemia that has diverse causes, including haematological malignancies and complications of its treatment (considered in acquired hypogammaglobulinaemia related to haematological malignancy and post haemopoietic stem cell transplantation); protein losing states; malnutrition; thymoma, immunosuppressant therapy; and repeated cycles of B-cell depletion therapy (e.g. rituximab), especially when used with immunosuppressant therapy and in children.

In many cases, successful management of the underlying condition will reverse the hypogammaglobulinaemia. However, in some cases, hypogammaglobulinaemia persists and is complicated by recurrent or severe bacterial infections. Secondary hypogammaglobulinaemia may

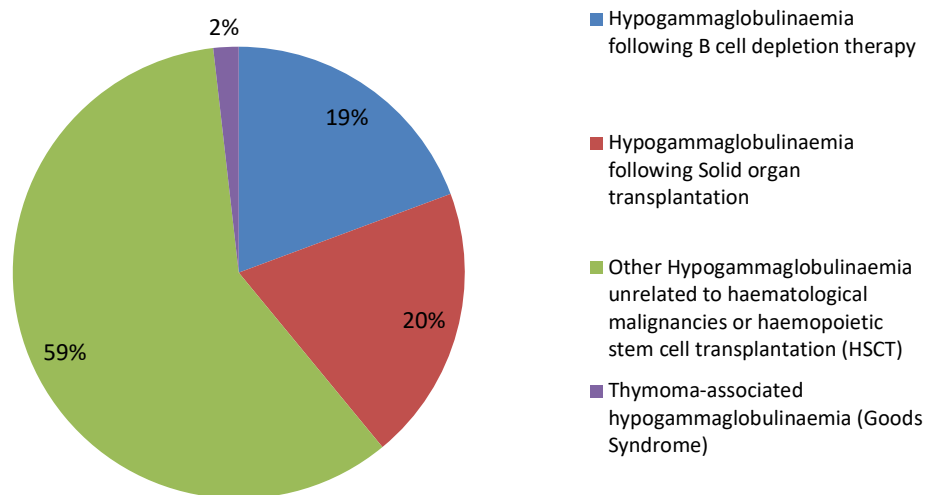
occasionally be complicated by a disseminated enterovirus infection, particularly in patients who have received B cell depletion therapy for a B cell lymphoproliferative disorder.

#### Similar indications

This indication is similar, but funded separately to “Acquired hypogammaglobulinaemia secondary to haematological malignancies or post-haematopoietic stem cell transplantation (HSCT)”.

#### Prevalence and/or incidence

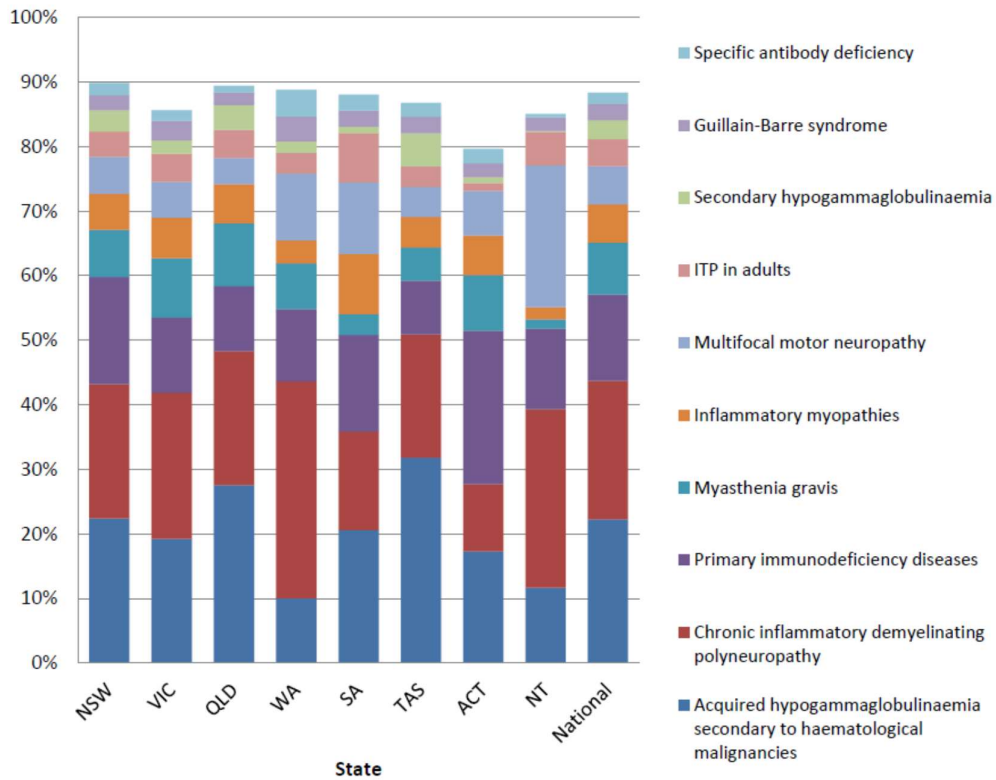
The prevalence of hypogammaglobulinaemia in the overall underlying medical conditions vary dependent on the cause. The wider use of therapies for autoimmune, inflammatory and malignant disease, especially those targeting B cells, is leading to an increase in secondary antibody deficiency (4). The incidence of hypogammaglobulinaemia in patients with thymoma is 6-11 percent (5). Approximately 15 percent of patients who have received a solid organ (heart, lung, kidney) transplant experience secondary hypogammaglobulinaemia with severe IgG deficiency (<4g/L) during the first year after transplantation (3). Figure 1 illustrates the main conditions included in secondary hypogammaglobulinaemia.



**Figure 1 Distribution of grams of Ig by specific condition in Secondary Hypogammaglobulinaemia**

Source: NBA internal data (provided by the applicant)

The National Report on the Issue and Use of Immunoglobulin (Ig) in 2015/2016 (2) indicated that 4% (n=652) of patients treated with Ig in Australia were diagnosed with secondary hypogammaglobulinaemia (excluding haematological malignancies). This indication falls into the top 10 diagnostic groups treated with Ig (Figure 2).



**Figure 2. Proportion of Ig used in the top 10 diagnostic groups**

Source: National report on the issue and use of Immunoglobulin (Ig). Annual Report 2015-16 (2)

The report highlights an increase in Ig grams used for this indication from 95,183g in 2011/12 to 145,497g in 2015/16 (2). The applicant provided unpublished numbers for 2017/2018; with an increase to a total number of patients of 1011 and 222,137 g. Table 1 presents the yearly increase by state.

**Table 1 Difference in grams issued for secondary hypogammaglobulinaemia (%)**

	2009-10	2010-11	2011-12	2012-13	2013-14	2014-15	2015-16
<b>NSW</b>	51%	31%	37%	31%	8%	20%	15%
<b>VIC</b>	17%	35%	30%	4%	-7%	11%	20%
<b>QLD</b>	-6%	13%	12%	1%	7%	15%	16%
<b>WA</b>	-14%	-20%	45%	10%	-24%	6%	38%
<b>SA</b>	88%	0%	-4%	45%	15%	-9%	-20%
<b>TAS</b>	16%	41%	-4%	-8%	-2%	-3%	-7%
<b>ACT</b>	29%	-16%	-66%	-51%	41%	454%	22%
<b>NT</b>	-	1100%	-67%	330%	-73%	119%	-81%
<b>Total</b>	<b>11%</b>	<b>21%</b>	<b>20%</b>	<b>12%</b>	<b>3%</b>	<b>15%</b>	<b>15%</b>

Source: National report on the issue and use of Immunoglobulin (Ig). Annual Report 2015-16 (2)

### **Intervention**

The intervention is IgG replacement therapy, which is given in combination with or without antibiotics, and is currently considered ‘standard of care’ for the population of interest.

IgG products may be administered through intravenous (IV) or subcutaneous (SC) injection (IVIg and SCIg, respectively). According to the Criteria V3, IVIg should be given at a maintenance dose of 0.4g/kg every four weeks and SCIg at 0.1g/kg every week. Doses should be adjusted based on trough levels to achieve at least the lower limit of the age-related IgG reference range. The age-related reference range will vary between pathology laboratories. IgG for intramuscular (IM) injection is out of scope for this evaluation (1).

The Criteria requires initial review within six months and ongoing reviews by a specialist at least annually to assess clinical benefit and whether cessation of Ig therapy should be considered. It is recommended that any cessation of the therapy occurs in September/October, with repeat clinical and/or immunological evaluation to consider the need for recommencement of therapy.

If the Ig therapy is delivered by intravenous infusion, patients will attend hospital for a day procedure to be infused by a nurse or doctor. Depending on the dose, which may be split over several days, they may (or may not) be required to attend for a ‘day procedure’ on a number of days (usually consecutive) each month. The NBA understands that in very rare circumstances, IVIg has been administered by the patient or by a ‘hospital in the home’ nurse.

Patients receiving (or carers administering) SCIg will require training and sufficient aptitude and capability to administer the product at home. SCIg also requires the appropriate infusion equipment as appropriate for the particular product. SCIg programs are not available at all hospitals. This varies depending on the local jurisdiction’s policy, and the local hospital’s capacity.

## List of products

IgG products (IVIg and SCIg) are purified from fractionated human donor plasma, formulated to contain the desired concentration of IgG as the active substance. A list of all IgG products currently approved in Australia by the Therapeutic Goods Administration (TGA) and registered on the Australian Register of Therapeutic Goods (ARTG) is in Table 2. The wording of the TGA approved indications vary widely between each product, though most include wording such as “hypogammaglobulinaemia secondary to underlying disease or treatment” or similar. The TGA approved Product Information was checked to confirm that each product in Table 2 was manufactured from normal donor plasma and not hyperimmune plasma.

**Table 2 IgG products registered on the ARTG for use in Australia for secondary hypogammaglobulinaemia**

Product name	Sponsor	Route of Administration	Strength	*NBA Funded
Privigen	CSL Behring	IV	5g/50mL to 40g/400mL	Yes
Hizentra	CSL Behring	SC	1g/5mL to 10g/50mL	Yes
Flebogamma 10%	Grifols	IV	5g/50mL to 20g/200mL	Yes
Evogam 16%	CSL Behring	SC	0.8g/5mL or 3.2g/20mL	Yes
Intragam 10	CSL Behring	IV	2.5g/25mL to 20g/200mL	Yes
Flebogamma 5%	Grifols	IV	0.5g/10mL to 20g/400mL	Yes
Cuvitru 20%	Shire	SC	1g/5mL to 8g/40mL	No
Panzyga	Octapharma	IV	1g/10mL to 30g/300mL	No
Gamunex 10%	Grifols	IV and SC	1g/10mL to 20g/200mL	No
Hyqvia	Shire	SC	2.5g/25mL to 30g/300mL	No
Intratect	Pfizer	IV	1g/10mL to 20g/200mL	No
Intratect 5%	Pfizer	IV	1g/20mL to 10g/200mL	No
Kiovig	Shire	IV and SC	1g/10mL to 20g/200mL	No
<i>Octagam**</i>	<i>Octapharma</i>	<i>IV</i>	<i>1g/20mL to 20g/mL</i>	<i>No</i>
<i>Gammanorm</i>	<i>Octapharma</i>	<i>SC</i>	<i>1.65g/10mL or 3.3g/20mL</i>	<i>No</i>

\* Indicates that Ig is currently funded for secondary hypogammaglobulinaemia under the National Blood Arrangements. Note that tendering arrangements may change products funded in the future. The current [National Product List](#) with suppliers and prices.

\*\* In September 2010, Octapharma Australia Pty Ltd conducted a voluntary recall of all batches of Octagam 5% and 10%. This recall was initiated after an increased incidence of thromboembolic complications associated with the use of this product in Europe and the USA. The TGA allowed the [resupply in Australia of Octagam 5%](#) since 8 August 2011 and is implementing additional monitoring activities.

IV – intravenous, SC – subcutaneous, IM – intramuscular

Italics: items added during PICO development following recommendations from the consultation

NBA advised the applicant that in 2017-18, around 8.3 percent of treatment episodes of Ig therapy used SCIg, of which around 4.9 percent was for secondary hypogammaglobulinaemia. In the same year, approximately 3.3 percent of total Ig grams were for SCIg of which 6.3 percent was for secondary hypogammaglobulinaemia. While the initial infusions are administered in the public hospital outpatient setting to train the patient or the carer, SCIg is subsequently administered in the patient’s home.

There could be differences in response rates between IVIg and SCIg for some of the selected outcomes (adverse events, disability, venous damage), and likely to be differences in health service consumption (e.g. outpatient, day- admission, hospital care v self-care). However, the applicant

recommends that IgG is considered the intervention and IVIg and SClg different routes of administration.

Provider and treatment setting

The National Ig Governance Program was introduced in 2014 to achieve Governments’ objectives for Ig products funded and supplied under the national blood arrangements. All sites that administer blood or blood products should be accredited under the National Safety and Quality Health Service Standard for Blood Management (6).

Medical officers need to be registered as a specialist with the Australian Health Practitioner Regulation Agency (AHPRA) to diagnose and review a patient with secondary hypogammaglobulinaemia (6). Under the Criteria V3, any specialist may diagnose and review a patient with secondary hypogammaglobulinaemia, although the majority are transplantation specialists, immunologists, haematologists and paediatricians. Applications for IgG are made through the BloodSTAR online portal and assessed against the Criteria V3 (1).

IVIg administration requires a hospital or clinic with IV infusion facilities. For access to SClg (in addition to requirements applicable for access to IVIg), the patient must be being treated by a clinical specialist within a hospital participating in the National SClg Program (7). A qualified nurse to deliver SClg in an out of hospital setting would be responsible for training the patient/carer in the procedure and follow-up to assess ongoing competency for self-administered treatment (6).

Criteria V3. Initial and continuing treatment

The qualifying criteria for initial and continuing treatment with IgG for this indication is presented in Table 3.

**Table 3 Initial and continuing treatment according to The Criteria V3**

<b>Initial treatment</b>
<ul style="list-style-type: none"> <li>• Significant hypogammaglobulinaemia with serum IgG less than 4g/L (excluding paraprotein) regardless of the frequency and severity of infections OR</li> <li>• Serum IgG (excluding paraprotein) greater than 4g/L but less than the lower limit of the age related reference range and at least one life-threatening infection in the last 12 months OR</li> <li>• Serum IgG (excluding paraprotein) greater than 4g/L but less the lower limit of the age related reference range with at least two serious infections in the last six months requiring more than standard courses of antibiotics (e.g. Hospitalisation, intravenous or prolonged antibiotic therapy) OR</li> <li>• Evidence of impaired antibody production to vaccination in the context of persistent infections affecting long term function such as persistent purulent suppurative otitis media threatening long term hearing</li> </ul> <p>AND</p> <ul style="list-style-type: none"> <li>• Underlying cause of hypogammaglobulinaemia cannot be reversed OR</li> <li>• Underlying cause of hypogammaglobulinaemia is reversible but reversal is contraindicated</li> </ul>
<b>Continuing treatment</b>
<u>On review of the initial authorisation period</u>



<b>Initial treatment</b>
<p>Monitoring of serum immunoglobulin levels (IgG, IgM and IgA) and infection history AND A trial period of cessation of Ig for the purposes of immunological evaluation will commence in September or October or is medically contraindicated on safety grounds (such as neutropenia, immunosuppressant medication, active bronchiectasis and/or suppurative lung disease or severe hypogammaglobulinaemia) persists where no significant improvement has occurred in the underlying condition</p> <p><u>On review of a continuing authorisation period</u></p> <p>Monitoring of trough or serum immunoglobulin levels (IgG, IgA and IgM) and any history of infection AND A trial period of cessation of IVIg for the purposes of immunological evaluation will commence in September or October or is medically contraindicated on safety grounds (for example neutropenia, immunosuppressant medication, active bronchiectasis and/or suppurative lung disease or severe hypogammaglobulinemia persists) where no significant improvement has occurred in the underlying condition</p>

Source: Criteria for Clinical Use of Immunoglobulin in Australia (1)

Serum IgG should be 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). Baseline serum levels of IgA and IgM should be provided to allow assessment of immune recovery at review.

Initial review is required within six months and ongoing reviews by a specialist 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 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 cessation period of Ig therapy may be undertaken. Ig therapy should be extended as required to enable the trial cessation of therapy to take place in September/October, with repeat clinical and/or immunological evaluation before recommencement of therapy if needed.

The applicant reported the usual length of an authorisation for maintenance therapy is one year, although continuing therapy can exceed one year and can be ongoing. The average duration of Ig therapy for secondary hypogammaglobulinaemia is unknown and is likely to vary between specific conditions due to varying specific conditions and underlying causes. Clinical experts<sup>1</sup> advised that patients with secondary hypogammaglobulinaemia are usually treated for 12-24 months while their immune system recovers. However, this recovery time doesn't apply to all patients as the underlying conditions of this group are heterogenous and the treatments used to manage the conditions have varying durations. Whilst most patients are likely to improve from Ig therapy, there are patients that do not respond to Ig therapy but who may continue to be treated with Ig therapy under another condition.

It is important to note the level of evidence underlying the Criteria is "Category 4a" (insufficient data) and Ig replacement therapy treatment is considered to have an "emerging therapeutic role" in this indication.

<sup>1</sup> Ig Reference Group Meeting 3, July 2019

## Dosing

The aim of treatment with IgG should be to use the lowest dose possible to achieve the appropriate clinical outcome for each patient. The Criteria V3 (1) recommends the following dosing regimen for IVIg:

- Loading Dose - One loading dose of 0.4 g/kg in the first month of therapy (in addition to the maintenance dose) is permitted if the serum IgG level is <4 g/L.
- Maintenance Dose - 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. More frequent dosing to achieve IgG trough level of up to 9 g/L is 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. A total dose of up to 1 g/kg may be given over any four week period.

Subcutaneous administration of immunoglobulins is a suitable alternative to IVIg in this condition, at a dose of 0.1 g/kg every week, modified to achieve a serum IgG level of at least the lower limit of the age specific serum IgG reference range.

## **Comparator**

The Ig Reference Group<sup>2</sup> agreed that, given the heterogeneous patient group, 'no Ig' should be the comparator to Ig therapy for secondary hypogammaglobulinaemia. Best practice standard of care for certain specific conditions may or may not include antibiotic treatment, prophylactic antibiotics and thymectomy.

Patients may require different concurrent therapies for secondary hypogammaglobulinaemia depending on the initial cause. For example, a patient with Good's syndrome is likely to require a thymectomy to treat a thymoma.

## **Outcomes**

### Effectiveness

The applicant proposes that mortality, morbidity, infections (decrease in infection rate), hospitalisations and quality of life are the effectiveness outcomes that should be included in the evaluation.

The United Kingdom's Clinical Guidelines for Immunoglobulin Use (8) require reporting the number of infections and number of days in hospital as efficacy outcomes for secondary hypogammaglobulinaemia of any cause. Additionally, they require the measurement of antibody-mediated rejection (AMR), antibody incompatible transplant (AIT), and viral pneumonitis in patients treated with Ig following solid organ transplantation.

The European Medicines Agency (EMA) Guidelines for IgG products recommend the number of serious bacterial infections as the primary endpoint for clinical evaluation of IVIg and SCIg in primary

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<sup>2</sup> Ig Reference Group Meeting 3, July 2019

and secondary immunodeficiencies, with the aim to achieve less than 1.0 infection/subject/year. Recommended secondary endpoints include IgG trough levels, any infections, antibiotic treatment, hospitalisations and fever episodes (9, 10). Although IgG trough levels are surrogate outcomes, they would be informative as a measure of how well serum IgG levels are recovering. Given that the applicable studies involve small patient numbers, pre-dose trough levels could provide valuable context for the interpretation of the patient relevant outcomes.

### Safety

The applicant proposes that serious adverse events (e.g. antibiotic allergy, anaphylaxis, veno-occlusive events) and antibiotic resistance should be included as safety outcomes for the evaluation.

### Current and proposed clinical management algorithm for identified population

IgG for this indication is already funded by the NBA. The purpose of this application is to consider the clinical and cost-effectiveness of these products as currently funded.

The applicant's treatment algorithms for initial and continuing Ig treatment are presented in Appendix 1.

### Proposed economic evaluation

The applicant proposed clinical claim is superiority of IgG with antibiotics as required to only antibiotics as required. The proposed economic evaluation would therefore be a cost-effectiveness analysis (CEA) or cost-utility analysis (CUA), noting that this will be subject to whether the studies found in the literature search support this approach. Table A1 in the Appendix is included to guide the requirements for an economic evaluation based on the findings of the clinical review.

Resources that could be considered for inclusion in the analysis would be acquisition costs (IgG and/or antibiotics), IV infusion administration (outpatient setting), health resource use (number of specialist visits, hospital days, ICU admission) and cost of managing adverse outcomes or events such as severe infections or severe infusion reactions. Drug costs should include dispensing fees and wastage where applicable.

The supply of IgG to patients meeting the eligibility criteria involves no direct cost to the patient.

The application provided the five references (Table A2 in the Appendix) included in The Criteria (1), but none of these studies would meet the specified PICO criteria. A systematic scoping search and additional bibliographic searches conducted during the preparation of this PICO identified only three small studies comparing IgG replacement treatment with no-IgG in patients with secondary hypogammaglobulinaemia following solid organ transplantation (Table 4). Other potential studies identified did not meet the inclusion criteria specified in this PICO, mainly due to the study design (e.g. cohort study with no comparator group or incorrect comparator) or population (e.g. patient with secondary hypogammaglobulinaemia due to haematological malignancies).

**Table 4 Evidence identified during the development of the PICO**

Reference	Description
Sarmiento E, Diez P, Arraya M, Jaramillo M, Calahorra L, Fernandez-Yañez J, Palomo J, Sousa I, Hortal J, Barrio J, Alonso R, Muñoz P, Navarro J, Vicario J, Fernandez-Cruz E, Carbone J. Early intravenous immunoglobulin replacement in hypogammaglobulinemic heart transplant recipients: results of a clinical trial. <i>Transpl Infect Dis.</i> 2016 Dec;18(6):832-843.	Retrospective study including 25 heart transplant patients with HGG. Of these, 12 were treated with IVIg and 13 patients were not treated with IVIg. The primary outcome was severe infections during the 6-month study period. Secondary outcomes included specific infections, adverse reactions, and Ig trough levels.
Lederer DJ, Philip N, Rybak D, Arcasoy SM, Kawut SM. Intravenous immunoglobulin for hypogammaglobulinaemia after lung transplantation: a randomized crossover trial. <i>PLoS One.</i> 2014 Aug 4;9(8):e103908	Randomised double-blind placebo-controlled two-period crossover trial in 11 lung transplant patients. Participants were randomised to three doses of IVIg or placebo given 4 weeks apart followed by a 12-week washout period and then 3 doses of the opposite treatment received initially every 4 weeks. The primary outcome was bacterial infections during each period. Secondary outcomes included non-bacterial infections, trough Ig levels, rejections and mortality.
Lichvar AB, Ensor CR, Zeevi A, Morrell MR, Pilewski JM, Hayanga JWA, D'Cunha J, McDyer JF, Petrov AA. Detrimental Association of Hypogammaglobulinaemia With Chronic Lung Allograft Dysfunction and Death Is Not Mitigated by On-Demand Immunoglobulin G Replacement After Lung Transplantation. <i>Prog Transplant.</i> 2018 Dec 11:1526924818817028.	Retrospective study including 484 lung transplant patients: 76 without HGG, 216 HGG patients treated with IVIg, and 192 HGG patients not treated with IVIg. Primary outcome was freedom from allograft dysfunction during the 5-year period. Secondary outcomes included rejection, infections and mortality.

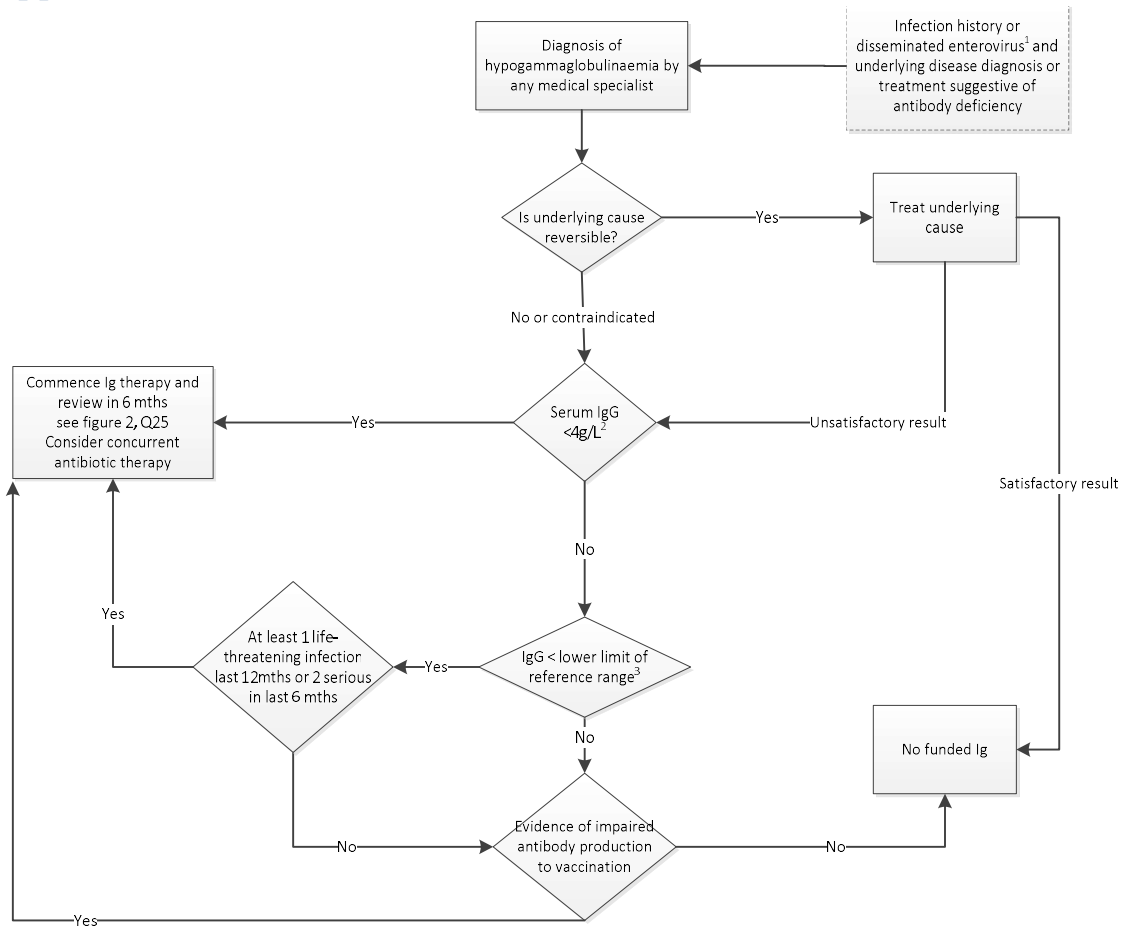
Abbreviations: HGG, hypogammaglobulinaemia; IVIg, intravenous immunoglobulin G

Extending the PICO to consider non-comparative cohort studies (i.e. separate cohort studies for patients with secondary hypogammaglobulinaemia treated and untreated with IgG) would require widening the systematic search to include untreated cohorts. This would lead to a considerable increase in the number of references found and further restrictions to the search strategy may need to be applied to make such a strategy feasible. Furthermore, the inclusion of non-comparative studies would not allow to generate any robust estimates of effectiveness and safety compared to placebo that we can trust to be the true effect of the intervention. This is a highly heterogeneous population and the identified studies are at high risk of bias.

One Australian cost-utility analysis (CUA) comparing IVIg with SCIg in the wider population of patients with secondary immunodeficiency (due to any cause) was identified<sup>3</sup>. Inputs from this study could be used to inform a model, but it may not be directly applicable to the PICO population. It is important to note that high quality randomised controlled trials are unlikely to be identified in a wider systematic literature review, and the quality of any economic evaluation is likely to reflect the limited evidence of effectiveness in the PICO populations.

<sup>3</sup> Windegger TM, Nghiem S, Nguyen KH, Fung YL, Scuffham PA. Cost-utility analysis comparing hospital-based intravenous immunoglobulin with home-based subcutaneous immunoglobulin in patients with secondary immunodeficiency. *Vox Sang.* 2019 Apr;114(3):237-246. doi: 10.1111/vox.12760

## Appendix 1

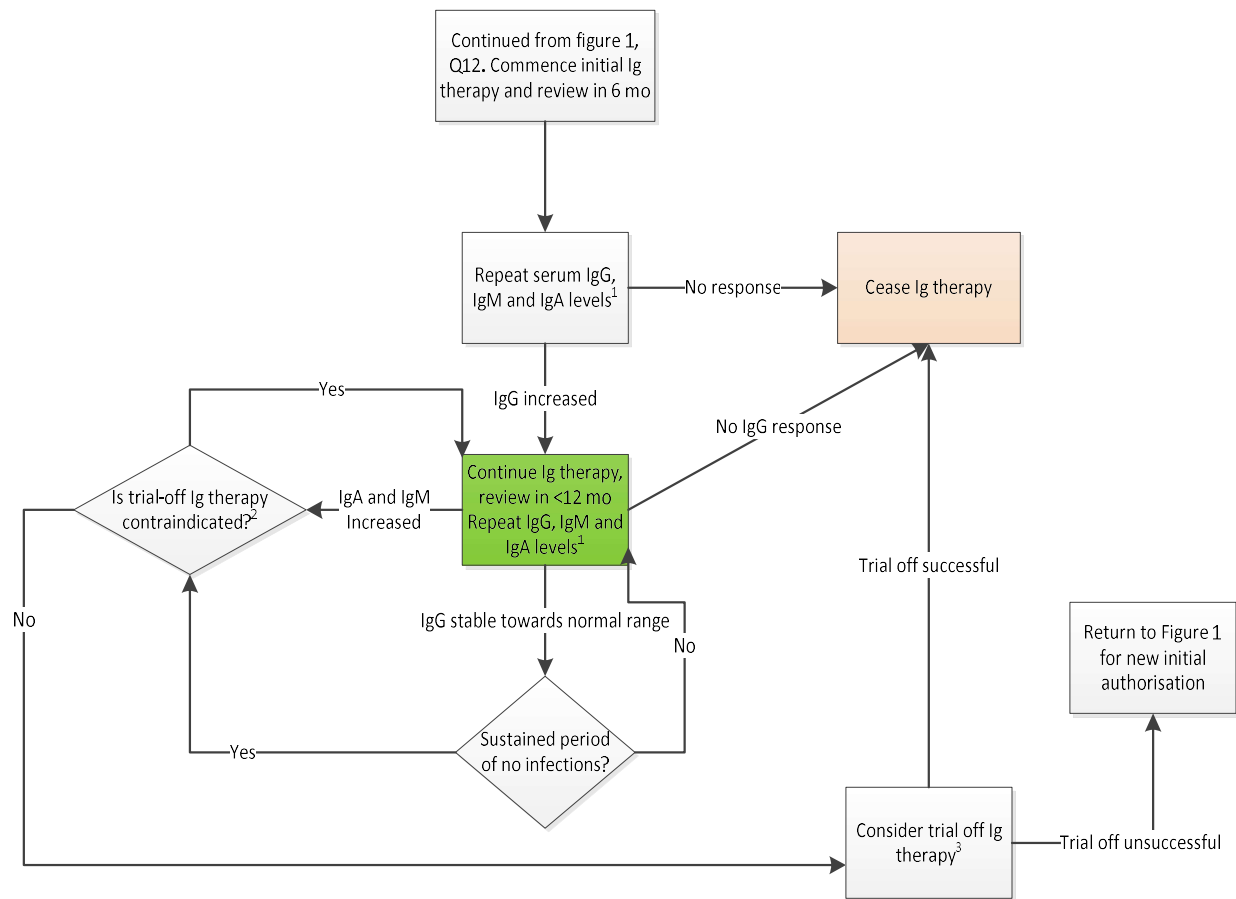


**Figure A1 Initial access to Ig funded under the National Blood Arrangements as per this Referral**

<sup>1</sup> Diagnosis of bronchiectasis and/or suppurative lung disease must be consistent with the Thoracic Society of Australia and New Zealand (Chang et al 2014)

<sup>2</sup> Serum IgG levels should be 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.

<sup>3</sup> Reference range should be age related.



**Figure A2 Continuing access to Ig funded under the National Blood Arrangements as per this Referral**

<sup>1</sup> If serum IgM and IgA levels are trending upwards and near normal, IgG is also likely to be normal, this may suggest recovery of the immune system and a trial-off Ig therapy might be considered

<sup>2</sup> Contraindication reasons for a trial-off Ig therapy include neutropenia, immunosuppressant medication, active bronchiectasis and/or suppurative lung disease or severe hypogammaglobulinaemia persists where no significant improvement has occurred in the underlying condition.

<sup>3</sup> 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

**Table A1. Classification of a service under MSAC consideration/Classification of the effectiveness of the proposed medical service over its main comparator and guide to the suitable type of economic evaluation**

Comparative safety	Comparative effectiveness			
	Inferior	Uncertain <sup>a</sup>	Non-	Superior
<b>Inferior</b>	Health foregone: need other supportive factors	Health foregone possible: need other supportive factors	Health foregone: need other supportive factors	? Likely CUA
<b>Uncertain <sup>a</sup></b>	Health foregone possible: need other supportive factors	?	?	? Likely CEA/CUA
<b>Non-</b>	Health foregone: need other supportive factors	?	CMA	CEA/CUA
<b>Superior</b>	? Likely CUA	? Likely CUA	? Likely CEA/CUA	CEA/CUA

CEA = cost-effectiveness analysis; CMA = cost-minimisation analysis; CUA = cost-utility analysis

? = reflects uncertainties and any identified health trade-offs in the economic evaluation, as a minimum in a cost-consequences analysis

<sup>a</sup> 'Uncertainty' covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or the comparative safety considerations (e.g. where the safety profiles of the compared medical services differ, with some aspects worse for the proposed medical service and some aspects better for the proposed medical service).

<sup>b</sup> An adequate assessment on 'non-inferiority' is the preferred basis for demonstrating equivalence

Source: [MSAC Therapeutic Technical Guidelines version 2](#).

**Table A2. Evidence identified in the application**

Reference	Description
Chang AB, Bell SC, Torzillo PJ, et al 2014, Thoracic Society of Australia and New Zealand Chronic Suppurative Lung Disease and Bronchiectasis in children and adults in Australia and New Zealand – Clinical Practice Guideline.	Guidelines for managing chronic suppurative lung disease (CSLD) and bronchiectasis in Australian and New Zealand children and adults
Florescu DF. Solid organ transplantation: hypogammaglobulinaemia and infectious complications after solid organ transplantation. Clin Exp Immunol. 2014 Dec;178 Suppl 1:54-6.	Meta-analysis of 18 studies incorporating 1756 patients to evaluate prevalence of hypogammaglobulinaemia after solid organ transplantation and its impact on the rate of opportunistic infections during the first year
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