



**Australian Government**

**Department of Health**

## **Application 1565:**

**Acquired hypogammaglobulinaemia  
secondary to haematological malignancies,  
or post-haemopoietic stem cell  
transplantation (HSCT)**

# **PICO Confirmation**

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

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*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 acquired hypogammaglobulinaemia secondary to haematological malignancies, or post-haemopoietic stem cell transplantation (HSCT) who are currently eligible for immunoglobulin (Ig) treatment in Australia according to version 3 of the <i>Criteria for the clinical use of immunoglobulin in Australia</i> .
Intervention	Replacement IgG therapy with or without antibiotics: <ul style="list-style-type: none"> <li>including IgG by intravenous administration (IVIg) or</li> <li>by subcutaneous administration (SCIg)</li> </ul>
Comparator	No IgG therapy with or without antibiotics
Outcomes	<p><b><i>The outcomes listed are those identified in the development of the PICO. Additional or more specific outcomes identified during the evaluation process that are considered relevant to the intervention or comparator treatment may be addressed in the evaluation report (Contracted Assessment). Broadly the outcomes identified pre assessment and considered in scope are:</i></b></p> <p><i>Safety Outcomes:</i></p> <ul style="list-style-type: none"> <li>Adverse events including development of disease or side effects</li> </ul> <p><i>Clinical effectiveness outcomes:</i></p> <ul style="list-style-type: none"> <li>Number of infections</li> <li>Change in quality of life, including anxiety</li> <li>Mortality</li> </ul> <p><i>Healthcare system resources utilisation</i></p> <ul style="list-style-type: none"> <li>Changes in health system resource utilisation associated with the intervention, for example <ul style="list-style-type: none"> <li>Ig products,</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 use of hospital resources)</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> </li> <li>Change in health system resource utilisation associated with the comparators, for example <ul style="list-style-type: none"> <li>Comparator products</li> <li>Resources to deliver the comparator</li> <li>Hospitalisation</li> <li>Management of adverse events</li> <li>Follow-up and/or monitoring visits</li> </ul> </li> </ul>

The National Blood Agreement provides for MSAC to undertake evidence-based evaluation of blood products funded under the national blood supply arrangements at the request of the Jurisdictional Blood Committee<sup>1</sup>. The Department of Health has convened an Ig Review Reference Group to provide advice for evaluation of IgG funded by the National Blood Authority (NBA). This application 1565 to MSAC is for use of human gamma immunoglobulin (IgG) as replacement therapy for “*Acquired hypogammaglobulinaemia secondary to haematological malignancies, or posthaemopoietic stem cell transplantation (HSCT)*”. IgG in this indication is presently funded under the national blood supply arrangements but cost-effectiveness of this use has not previously been established.

All IgG products approved by the Therapeutic Goods Administration (TGA) according to the current guidelines of the European Medicines Agency for IgG products are considered within scope for this application.

### PICO rationale for therapeutic medical services

#### **Population**

##### This indication

The population is patients with *Acquired hypogammaglobulinaemia secondary to haematological malignancies (HSCT)*. IgG replacement therapy, in this indication, is funded under the national blood arrangements as an “Established Therapeutic Role”. Clinical criteria for eligible patients to access subsidised IgG are specified by the National Blood Authority’s *Criteria for Immunoglobulin Use in Australia, Version 3*<sup>2</sup>(the *Criteria*). This indication is one of several ‘diagnostic groups’ of conditions eligible for funded IgG treatment under the *Criteria Version 3*.

According to the *Criteria Version 3*, the above indication covers hypogammaglobulinaemia, when it occurs, secondary to the following specific conditions (or associated treatment):

- Acute leukaemia
- Chronic lymphocytic leukaemia (CLL)
- Multiple myeloma (MM)
- Non-Hodgkin lymphoma (NHL)
- Other Haematological malignancy  
[Diagnosis of haematological malignancies should be according to the criteria of the current World Health Organization (WHO) classification<sup>3</sup>. ]
- Memory B cell deficiency secondary to HSCT

The target population is identified by symptoms but covers different underlying haematological malignancies each characterised by low IgG levels. Patients with each condition will differ in other clinical characteristics, treatments for underlying disease and prognosis. There are different baseline risks of infection (higher in acute leukaemia and post-HSCT patients) and consequently, a difference

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<sup>1</sup> <http://www.health.gov.au/internet/hta/publishing.nsf/Content/nba-1>

<sup>2</sup> National Blood Authority, 2018. Available at <https://www.blood.gov.au/igcriteria-version3>

<sup>3</sup> WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, IARC Revised 4<sup>th</sup> Edition 2017

in infection treatments among the above conditions. In addition, the baseline risk of intensive care admission is greater for post-HSCT patients than for the other specific conditions. The way in which hypogammaglobulinaemia is diagnosed and treated (with or without access to IgG) is common across the patients in this indication.

The *Criteria Version 3* provide for IgG supply as follows:

1. Patients with serum IgG less than 4g/L regardless of episodes of infection or antibiotic use.
2. Patients with serum IgG greater than 4g/L, IF serum IgG is less than the lower limit of the age-related reference range, AND the patient has had either (1) at least one life-threatening infection in the last 12 months, or (2) two serious infections in the last six months requiring more than standard courses of antibiotics.

[Serum IgG refers to values excluding paraprotein]

The Ig Review Reference Group noted that a literature search should include a broad definition of the population not constrained by these criteria for access (limited to the haematological malignancies above).

The applicant cites the UK's *Clinical Guidelines for Immunoglobulin Use (2011)* as clinical guidelines for this application.

#### Similar indications

According to the *Criteria Version 3*, the indication sought is separate to a similar indication "*Secondary hypogammaglobulinaemia unrelated to Haematological malignancy or HSCT*" (including patients with low plasma IgG due to B cell depletion or immunosuppressant therapies, or underlying health conditions such as thymoma). This and other uses of IgG (such as replacement therapy in patients with primary hypogammaglobulinaemia and immune-modulatory uses) are funded separately under the national blood supply arrangements.

#### Population prevalence and/or incidence

Of the conditions encompassed by this indication, hypogammaglobulinaemia will be present in 25% of patients at diagnosis and will occur in up to 85% during the disease course. The epidemiological literature does not permit much further refinement to estimate the patients meeting the specific criteria for this indication. However, the NBA has provided figures for IgG supplied to patients under the current funding arrangements which provide a reliable estimate of the patient population.

The 2015-16 NBA report on use of IgG in Australia shows that the indication for this application constituted the largest of the diagnostics groups in terms of grams supplied, at 22.2% of the total. The applicant notes the most significant leakage risk is associated with patients receiving ongoing Ig therapy after recovery of the immune system. Figures for the most recent available year (2015-16) broken down by condition are in Table 1. Totals for the indication since 2011-12 are in Table 2.

**Table 1: Numbers of patients receiving funded IgG for this indication (2015-16)**

Condition	Patients diagnosed (2015)	New IgG patients (2015-16)	Total patients (2015-16)	Grams Supplied (2015-16)	Average grams per patient
CLL	1,597	361	1380	350,066	254
MM	1,885	402	1177	275,685	234
NHL	5,031	369	1308	332,148	254
Post-HSCT	Unknown	206	345	48,266	140
Other Haem. Malignancy	Unknown	236	533	100,556	189
Totals (without AL)	–	1574	4743	1,106,721	233
Acute Leukaemia*	1431**	8	13	975	75

Abbreviations: CLL=Chronic lymphocytic leukaemia; MM=Multiple Myeloma; NHL=Non-Hodgkin lymphoma; HSCT=haemopoietic stem cell transplantation; AL=acute leukaemia; ALL=Acute Lymphoblastic Leukaemia; AML=Acute Myeloid Leukaemia; IgG=Immunoglobulin Gamma; NBA=National Blood Authority

\*For the year 2015-16 NBA funded IgG only for children with acute leukaemia, whereas patients including adults are now funded

\*\*Acute Lymphoblastic Leukaemia (ALL) and Acute Myeloid Leukaemia (AML) were used as a proxy for acute leukaemia since this is not reported in the ACIM books as a group; 1431 = 389 (ALL) + 1042 (AML)

Also included in Table 1 above are figures for incident patients diagnosed in Australia in the 2015 calendar year with CLL, MM, NHL and two types of acute leukaemia (from The Australian Cancer Incidence and Mortality (ACIM) books<sup>4</sup>). Proportions of patients that received IgG were not calculated as patients receiving IgG replacement therapy are drawn from the prevalent population (not at diagnosis) and prevalent patient numbers were not available from the ACIM books.

**Table 2: Numbers of patients receiving funded IgG for this indication (2011/12 – 2015/16)\***

Financial Year	New patients	Total patients	Growth, patients (%)	Grams	Growth, IgG Use (%)	Average grams per patient
2011-12	1,174	3,296	–	694,641	–	211
2012-13	1,238	3,584	8.74%	771,072	11.0%	215
2013-14	1,393	3,922	9.43%	862,899	11.9%	220
2014-15	1,460	4,326	10.30%	982,774	13.9%	227
2015-16	1,574	4,743	9.64%	1,106,721	12.6%	233

\*Not including acute leukaemia in children

Since 2011-12, the numbers of patients receiving funded IgG for this indication have increased by around 9-10% per year and the total grams supplied by 11-14% per year (Table 2).

## Intervention

The intervention is IgG replacement therapy, which is given in combination with or without antibiotics. This is 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 Version 3*, 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

<sup>4</sup> <https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/acim-books>

vary between pathology laboratories. IgG for intramuscular (IM) injection is out of scope for this evaluation.

### Overview

*When undertaking an evaluation of an intervention X that is not currently funded, ‘standard of care’ is usually taken to mean ‘no intervention X’. However, IgG replacement therapy has been funded for this indication for more than ten years, so the current standard of care in Australia is ‘IgG replacement therapy; with or without antibiotics’. Thus, the standard of care is the intervention under evaluation (and the comparator would be ‘No IgG access; with or without antibiotics’).*

*IgG replacement and antibiotics are used for slightly different purposes. Antibiotics are prescribed per episode and treatment aims to resolve the current infection. Antibiotic use may be prophylactic (in the absence of clinical signs of infection) or on demand (prn). IgG is indicated in patients with hypogammaglobulinaemia and a history of infections and aims to reduce the incidence of infections.*

### List of products

IgG products (IVIg and SCIg) are purified from fractionated human donor plasma, formulated to contain the desired concentration of IgG as 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 3. This does not include products manufactured from hyperimmune plasma.<sup>5\*</sup>

**Table 3: IgG products registered on the ARTG for use in Australia**

Product	Sponsor	Route of Administration	NBA Funded*
Intragam 10	CSL Behring	IV	Yes
Privigen 10%	CSL Behring	IV	Yes
Hizentra	CSL Behring	SC	Yes
Gamunex 10%	Grifols	IV and SC	No
Flebogamma 10%	Grifols	IV	Yes
Flebogamma 5%	Grifols	IV	Yes
<i>Intragam P</i>	<i>CSL Behring</i>	<i>IV</i>	<i>Yes – out of scope**</i>
Evogam	CSL Behring	SC	Yes
Panzyga	Octapharma	IV	No
Hyqvia	Shire	SC	No
Intratect	Pfizer	IV	No
Intratect 5%	Pfizer	IV	No
Octagam	Octapharma	IV	No
Kiovig	Shire	IV and SC	No
Gammanorm	Octapharma	SC (and IM)	No
Cuvitru	Shire	SC	No
<i>CSL Normal Immunoglobulin VF</i>	<i>CSL Behring</i>	<i>IM</i>	<i>Not stated – out of scope</i>

\* Indicates that Ig is currently funded for the indication sought in this application, though this may change in the future.

\*\*With the introduction of Intragam 10, Intragam P manufacturing ceased in 2017. Inventories of Intragam P were expected to be exhausted by between mid-March and mid-April 2017 and it is expected to be discontinued by the time this evaluation is completed. IV – intravenous; SC – subcutaneous; IM – intramuscular.

<sup>5</sup> NBA disagree with statement ‘CSL Normal Immunoglobulin VF is manufactured from hyperimmune plasma

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 Ig Review Reference Group indicated that the two products in italics above should be out of scope for this evaluation: Intragam P and CSL Normal Immunoglobulin VF.*

*The NBA distinguishes between IVIg/SCIg products on the one hand and ‘normal human immunoglobulin’ on the other. The NBA describes ‘normal human immunoglobulin’ as having been fractionated from hyperimmune plasma<sup>6</sup> (plasma from donors selected due to their high titre to a specific antigen). However, the TGA (and the ARTG approved documentation) describes all IgG products relevant to the indication for this application as containing ‘normal immunoglobulin’. The TGA approved Product Information was checked to confirm that each product in Table 3 was manufactured from normal donor plasma and not hyperimmune plasma.*

The sub-set of approved IgG products funded under the current National Blood Supply Arrangements for this indication is in Table 4, including prices per pack strength.

**Table 4: Ig products funded for this indication**

Product	Sponsor	Route of Administration	Strength	NBA price
Intragam 10	CSL Behring	IV	2.5g/25mL 10g/100mL 20g/200mL	\$146.23 \$584.93 \$1,169.86
Privigen 10%	CSL Behring	IV	5g/50mL 10g/100mL 20g/200mL 40g/400mL	\$225.00 \$450.00 \$900.00 \$1,800.00
Hizentra	CSL Behring	SC	1g/5mL 2g/10mL 4g/20mL 10g/50mL	\$59.15 \$118.31 \$236.61 \$591.53
Flebogamma 5%	Grifols	IV	0.5g/10mL 2.5g/50mL 5g/100mL 10g/200mL 20g/400mL	\$22.50 \$112.50 \$225.00 \$450.00 \$900.00
Flebogamma 10%	Grifols	IV	5g/50mL 10g/100mL 20g/200mL	\$225.00 \$450.00 \$900.00
<i>Intragam P*</i>	<i>CSL Behring</i>	<i>IV</i>	<i>3g/50mL</i>	<i>\$175.48</i>
Evogam	CSL Behring	SC	16% 0.8g/5mL 16% 3.2g/20mL	\$46.79 \$187.18

\* Intragam P is out of scope – see Table 1.

IV=intravenous; SC=subcutaneous; IM=intramuscular

Source: Table 2 MSAC Application 1565 Referral form; NBA National Product List (<https://www.blood.gov.au/national-product-list>)

<sup>6</sup> National report on the issue and use of immunoglobulin (Ig). Annual Report 2015-16. NBA.

The Ig Review Reference Group considered whether SCIg should be considered a different intervention to IVIg given that response rates between IVIg and SCIg for some of the selected outcomes (adverse events, number of infections, venous damage), and health service consumption (such as outpatient day-admission hospital care versus self-care) are likely to be different. However, differences also apply across the conditions included in the indication such as baseline risk of infections, mortality, rates and types of adverse events and other factors due to underlying disease. The clinical and regulatory rationale for using SCIg is predicated on the principles of IVIg use – even if these are considered different interventions, a systematic review to evaluate SCIg products would need to include evidence from IVIg administration to draw any meaningful conclusion.

#### Provider and treatment setting

In order to qualify for supply of IgG, a diagnosis must be made by an immunologist, haematologist, paediatrician, general medicine physician or an oncologist. Management and review of the patient and prescribing of continuing treatment should also be undertaken by one of these specialists. Applications for IgG are made through the BloodSTAR online portal and assessed against the *Criteria Version 3*.

IVIg administration requires a hospital or clinic with IV infusion facilities. For access to SCIg (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 SCIg Program<sup>7</sup>. The patient/carer must be trained in the procedure by a qualified nurse or technician to deliver SCIg in an out of hospital setting.

#### Criteria for initial treatment

According to the *Criteria Version 3*, treating specialists should report the following clinical parameters (for review by the BloodSTAR reviewing officer):

- Serum IgG level (results of two readings at least an hour apart, one taken when the patient does not have active infection)
- Serum IgM level (as a baseline for monitoring)
- Serum IgA level (as a baseline for monitoring)
- The number of acute episodes of bacterial infection requiring antibiotics in last 6 months (the most severe infection(s) that have occurred within the last 6 months)
- Description of the bacterial infections and antibiotic or other treatment required

#### Criteria for continuing treatment

According to the *Criteria Version 3*, initial review is required within six months at which time only those patients showing ‘demonstrated clinical benefit’ should be considered for continuing treatment. Thereafter, review should be annual at which time number of infections should be reviewed. The *Criteria Version 3* do not define clinical benefit but the following factors ‘inform a decision to trial a cessation of therapy’ by the reviewing medical officer:

- An increase in IgG levels (increase compared with baseline or stabilisation towards normal)

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<sup>7</sup> <https://www.blood.gov.au/SCIg>

- An improvement in IgM levels (an indicator of humoral immune function)
- An improvement in IgA levels (an indicator of humoral immune function)
- An improvement in the number of acute episodes of bacterial infections followed by a sustained period with no infections in subsequent review periods

A trial cessation of IgG would be contraindicated on safety grounds (if the patient is receiving immunosuppressant medication or has neutropenia, active bronchiectasis, or suppurative lung disease) or if severe hypogammaglobulinemia persists where no significant improvement has occurred in the underlying condition. Where bronchiectasis and/or suppurative lung disease is cited as the reason for continuing IgG treatment, the diagnosis must be consistent with the guideline of the Thoracic Society of Australia and New Zealand.

### Dosing

Standard doses are 0.2-0.4 g/kg every three to four weeks. The majority of documentation reviewed cites a maintenance dose for IVIg of 0.4g/kg every four weeks, however, doses lower than 0.4g/kg may be used during titration. A maximum IgG dose of up to 1g/kg may be given. Dosing may be divided to give two or more infusions within the month. Dosing for SCIg is 0.1g/kg per week (based on patient's lean or ideal body weight).

The applicant states that the usual length of an authorisation for maintenance therapy is one year, though they can be as short as one month. Continuing therapy is allowed so treatment duration can exceed one year. The majority of patients have more than one authorisation.

Specialists may prescribe an initial loading dose of 0.4g/kg (on top of monthly maintenance supply) and a one-off dose of 2g/kg is for disseminated enterovirus infection. Treatment of disseminated enterovirus infection, currently provided for under *the Criteria Version 3*, would not be included in an evaluation that antibiotics as part of both intervention and comparator.

### Monitoring

Cessation of Ig therapy should be considered at least after each twelve 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 may be undertaken. Monitoring of IgG trough levels enables dose adjustment as described above though no frequency is defined by *the Criteria Version 3*.

### **Comparator**

The applicant advises that standard practice in haematological malignancies is to treat infections as they arise. The comparator is defined as 'No IgG access; with or without antibiotics', given that the intervention is defined as 'IgG access; with or without antibiotics' (discussed above). The utilisation of antibiotics is expected to be higher in the comparator arm.

The haematology expert on the Ig Review Reference Group advised oral trimethoprim + sulfamethoxazole would be the first line antibiotic. This has a broad TGA indication and is available on the Pharmaceutical Benefits Scheme (PBS) (Table 5).

**Table 5: Relevant trimethoprim + sulfamethoxazole listings on the PBS**

Strengths	Brands	Dosage form	Pack size	Max Qty	Repeats	Item #	PBS Benefit Type
trimethoprim 160mg + sulfamethoxazole 800mg	Resprim Forte Septrin Forte Bactrim DS	Tablets	10 tablets	1 pack	1	2951H	Unrestricted
trimethoprim 40mg/5mL + sulfamethoxazole 200mg/5mL	Bactrim Septrin	Oral liquid	100mL	1 bottle	1	3103H	Unrestricted

Note: the tablet brands are 'a' flagged as Schedule equivalent, but the oral liquids are not.

Patients already on chemotherapy for MM or CLL would likely be offered prophylactic antibiotics, however those not receiving chemotherapy are unlikely to be offered prophylaxis. The IgG Review Reference Group considered that around 10% of MM or CLL patients would receive antibiotic prophylaxis.

The applicant advises that some patients with hypogammaglobulinaemia (likely less than 20%) are commenced on chemotherapy because the patient is getting infections. The clinical signs to commence chemotherapy are the same regardless of IgG access, but this is likely to be required more frequently without IgG replacement therapy.

*The IgG Review Reference Group considered that antibiotic use in the current treatment algorithm could be either prophylactic (based on high risk of infection) or prn (in response to clinical signs of infection). Chemotherapy was not considered to be a secondary comparator for the evaluation.*

## 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.

*Mortality and morbidity are likely to be confounded by divergent baseline risk and life expectancy due to differences in underlying disease and given the modest size of clinical studies in this indication. The definition of morbidity is also likely to vary widely and is better captured as individual outcomes such as hospitalisations or severe infections. Mortality could be considered a secondary outcome. The key outcome should be infections, including severe and/or recurrent infections (or infections requiring hospitalisation), total infections, and antibiotic use (noting whether as prophylaxis). Hospitalisations (all cause) and QoL (and anxiety, if reported) are appropriate patient-relevant outcomes – if duration of hospital stay or time to discharge is available, this could also be included.*

*Although IgG trough levels are not patient-relevant, 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 to interpretation of the patient relevant outcomes, especially for studies including SClg products.*

The United Kingdom's *Clinical Guidelines for Immunoglobulin Use* (2011) require reporting number of infections and number of days in hospital as efficacy outcomes for this indication, to be measured every six months. The EMA Guideline which applies to TGA review of IgG products recommends the number of serious bacterial infections as the primary endpoint for clinical evaluation of IVIg in primary and secondary immunodeficiencies. The EMA guideline defines an acceptable level as less than 1.0 infection/subject/year. Recommended secondary endpoints include IgG trough levels, any other infections, antibiotic treatment, hospitalisations and fever episodes.

### Safety

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

*Anaphylaxis should be expanded to include any serious infusion reactions, although total number of reactions are relatively common for these products and may not be as informative.*

*Thrombotic (veno-occlusive) events are known adverse events of IgG products. Other known serious adverse effects such as renal insufficiency, haemolytic anaemia and aseptic meningitis should be reported where known, acknowledging that patient numbers in most studies will render these infrequent at most. Venous damage is also mentioned as relevant for IVIg use. The Ig Review Reference Group suggested including graft versus host disease (GVHD), noting that it would be expected IgG would enable a full course chemotherapy to prevent this.*

*Antibiotic allergy and antibiotic resistance are adverse events specific to antibiotic use and should be reported for both intervention and comparator, depending on how these are defined.*

### Current clinical management algorithm for identified population

The applicant's treatment algorithms are presented in Appendix Figure 1. The main algorithm in Figure 1 (A) is considered appropriate.

### 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.

### Proposed economic evaluation

The applicant proposed clinical claim is superiority of IgG to antibiotics as required (defined in this draft PICO Confirmation as 'IgG with antibiotics as required' versus 'no IgG with antibiotics as required'). The proposed economic evaluation is therefore a cost-effectiveness or cost-utility analysis, noting that this will be subject to whether the studies found in the literature search support this approach. The table in Appendix Table 1 is included to guide the requirements for economic evaluation based on the findings of the clinical review.

*Resources for inclusion in the analysis are to be confirmed by the Department of Health.* 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 events such as severe infusion reactions. Drug costs should include dispensing fees and wastage where applicable.

The supply of IgG to patients meeting eligibility criteria involves no direct cost to the patient. It is assumed there are no dispensing fees that are met by the health system.

*For the contracted assessment, the applicant should provide the following, where available:*

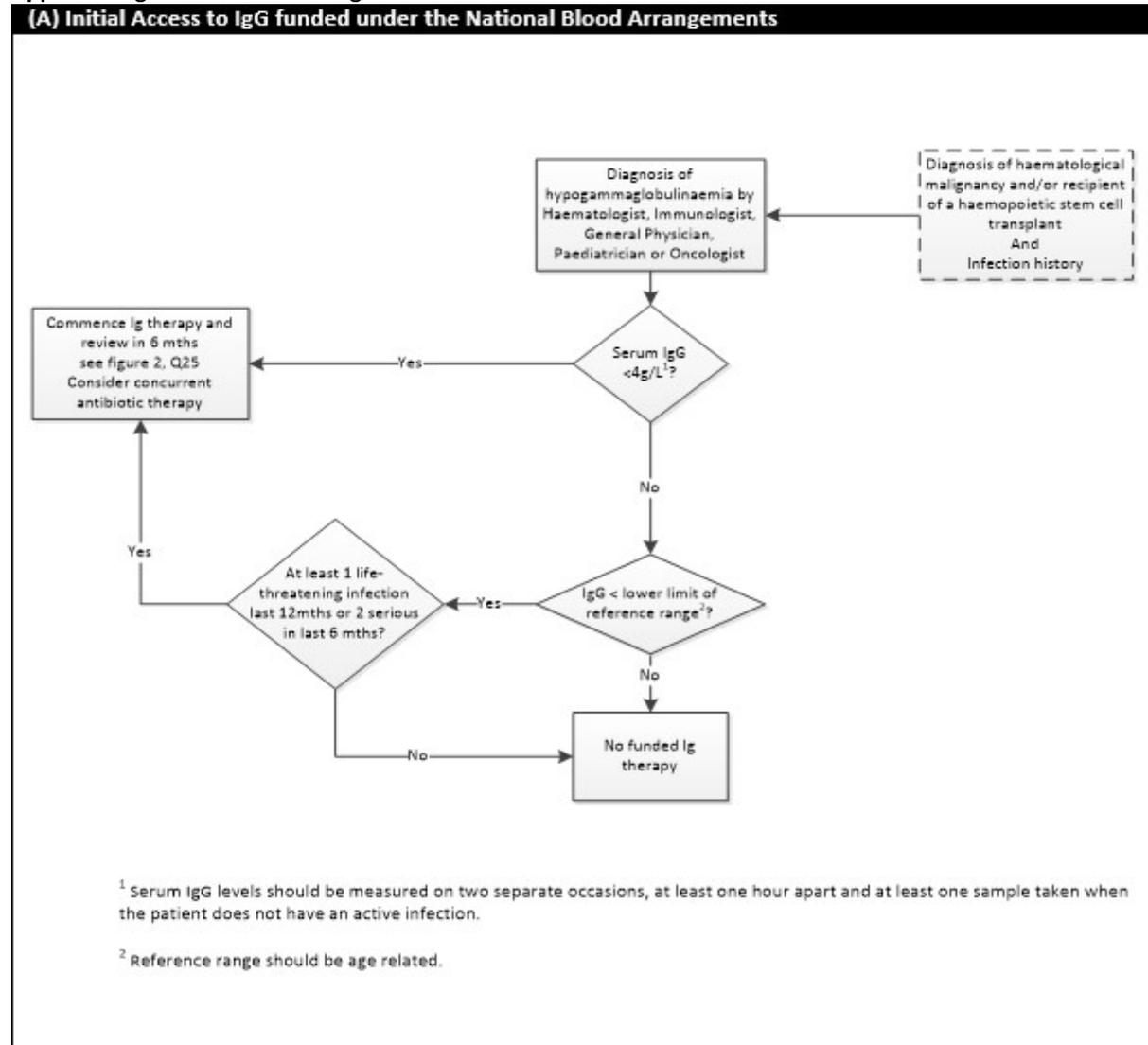
- *Typical monthly dose and/or dose range per patient*
- *Typical dose duration and/or range per patient*

*This should permit a calculation of cost per month and cost per course. The applicant should ideally separate estimates by the conditions included in this indication as patients with different underlying diseases are likely to require different dose duration and intensity to achieve the same outcomes.*

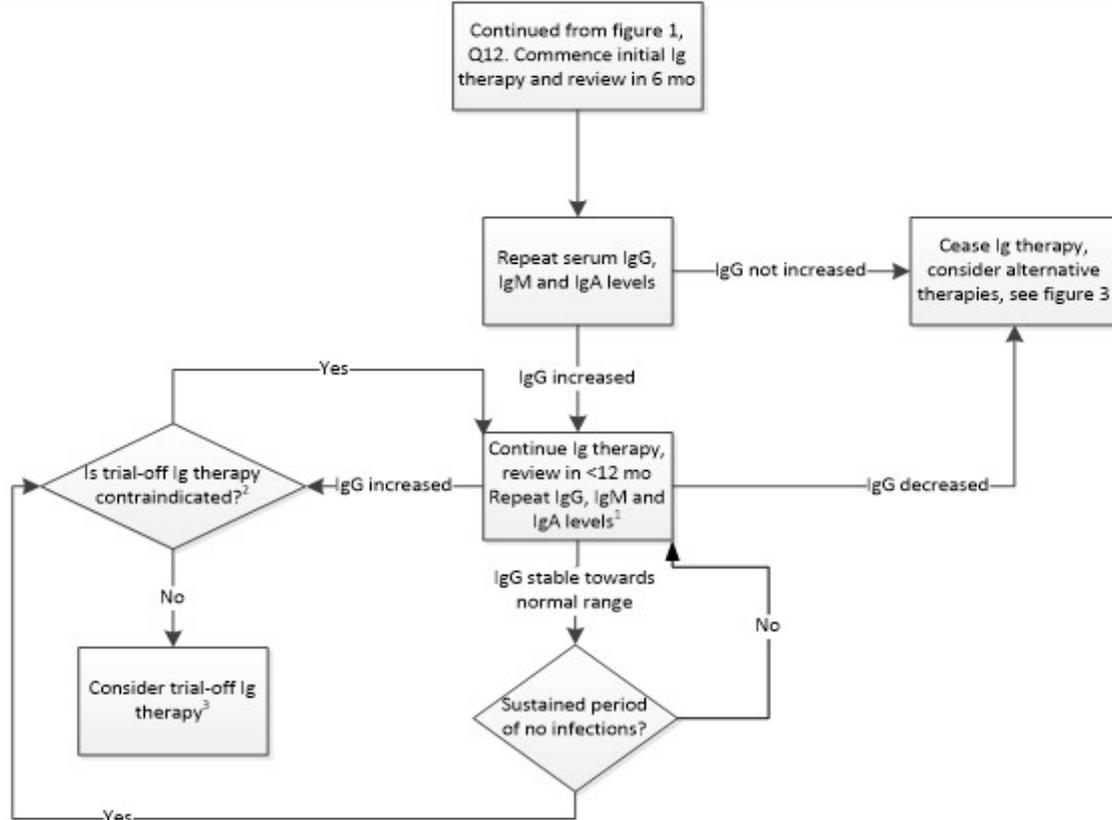
*The Department of Health advises that the NBA price structure is not within scope for this review, though the economic evaluation may need to consider local versus imported pricing. Pricing of IgG products may be amended by the NBA in future.*

## Appendix

Appendix Figure 1: Treatment algorithm



### (B) Monitoring response to IgG therapy

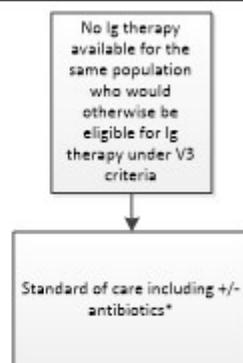


<sup>1</sup> If serum IgM and IgA levels are trending upwards and near normal, IgG is also likely to be normal, this may suggest recovery of the immune system and a trial-off Ig therapy might be considered.

<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.

### (C) Treatment pathway when IgG is not an option



**Appendix Table 1 - Decision algorithm for undertaking an economic evaluation in the setting of the Ig Review. (Schubert, C and Merlin T, Adelaide Health Technology Assessment, 2018)**

Comparative safety of Ig	Comparative effectiveness of Ig				
	Inferior		Uncertain	Non-inferior	Superior
	No active comparator	Active comparator			
Inferior	X	F	?	F <sup>b</sup>	F <sup>a</sup>
Uncertain	X	F <sup>a</sup>	?	?	F <sup>a</sup>
Non-inferior	X <sup>c</sup>	F	?	\$	F
Superior	X <sup>c</sup>	F <sup>a</sup>	?	F <sup>b</sup>	F

X = health forgone (at cost). An economic evaluation is not warranted and continued use of Ig should not occur in this circumstance unless there are other supportive factors.

F = undertake a full economic evaluation. These may take the form of cost-utility analyses (preferred if adequate data are available) or cost effectiveness analyses in terms of clinically relevant outcome(s).

? = high levels of uncertainty will occur in an economic evaluation (if it is feasible to construct one). A cost analysis (partial economic evaluation) could be performed.

\$ = cost minimisation analysis (partial economic evaluation that explicitly assumes no significant differences in health outcomes, associated with either effectiveness or safety, and analyses cost-differences only).

<sup>a</sup> where the conclusions with respect to effectiveness and safety are not congruent, then analyses identifying all relevant health consequences (i.e. effectiveness and safety outcomes in opposing directions of benefit) need to be presented. If a CUA is presented, this should capture effectiveness and safety collectively. If a CUA is not possible, then a single CEA may not capture all health consequences adequately and so a CCA is likely to be required. Where possible, the CCA should be quantitative, but in the absence of adequate data, a minimum qualitative identification of consequences should be presented.

<sup>b</sup> where effectiveness is assessed as non-inferior but safety differences exist, and in the absence of a CUA being possible, the outcomes component of the analysis should include a clinically relevant outcome which reflects the safety differences between Ig and the comparator.

<sup>c</sup> The small but unavoidable potential risks associated with administering a blood product means that a conclusion of non-inferior or superior Ig safety relative to no active comparator, should never arise.