Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1591 – Review of immunoglobulin use for secondary hypogammaglobulinaemia unrelated to haematological malignancies, or post-haemopoietic stem cell transplant (HSCT)

Applicant: National Blood Authority (NBA)

Date of MSAC consideration: MSAC 80th Meeting, 26-27 November 2020

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of application

This Post-market Review requested MSAC advice on the Government funded supply of replacement, human gamma immunoglobulin (IgG) therapy under the National Blood Arrangements for the treatment of secondary hypogammaglobulinaemia (SHGG) unrelated to haematological malignancies, or post-haemopoietic stem cell transplant (HSCT) – hereafter referred to as secondary hypogammaglobulinaemia (SHGG). The application (referral) was received by the Department of Health from the National Blood Authority (NBA).

2. MSAC's advice to the Minister

After considering the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC advised that funding of immunoglobulin (Ig) therapy for the treatment of SHGG should continue. MSAC considered that potential changes to BloodSTAR are required to improve data collection and reporting, and that further research could be scoped to address data gaps. There was insufficient evidence to evaluate the clinical and cost-effectiveness of Ig therapy for SHGG; however, MSAC noted that Ig is an accepted standard of care in this population and stakeholders were highly supportive of continued access to Ig therapy.

MSAC noted Ig use in this small patient population appears to be increasing disproportionately compared with the increase observed for alternative Ig indications. Ig product costs for the base case were projected to increase from about $15.3 million in 2018-2019 to about $41.3 million in 2023-2024. The financial estimates are highly uncertain as costs or changes in use are not considered. The cost of other medical services and the rate at which Ig use will continue in this population (overall population and subgroups) is also uncertain. MSAC considered that given the evidence presented in this review, that Ig use for this indication is highly likely to be cost-ineffective.

MSAC considered data collection could be optimised through BloodSTAR, and proposed further work be done to identify areas for improved data collection and reporting, or further research, which may inform any future evaluations of clinical and cost-effectiveness. This

could include better defining the eligibility requirements to access Ig therapy and reviewing current dosing recommendations. In addition, the use of the 'Other' criteria for access requires assessment to ensure that patients are not being prescribed Ig for indications that are otherwise precluded in the Criteria. MSAC was of a mind to review the application in 12 months' time, should additional data become available to inform the cost-effectiveness of Ig in SHGG.

Consumer summary
The National Blood Authority (NBA) sought advice from MSAC on the government-funded supply of human antibodies (immunoglobulin, or Ig) used to treat secondary hypogammaglobulinaemia (SHGG). The NBA is the statutory agency within the Australian Government Health portfolio that manages and coordinates arrangements for the supply of blood and blood products and services on behalf of the Australian Government and state and territory governments. This referral to review the use of Ig in SHGG is included as part of the Ig Reviews, which aim to ensure that government-funded Ig use within Australia is based on evidence of clinical safety, effectiveness and cost-effectiveness.   Hypogammaglobulinaemia (HGG) weakens the immune system. People with HGG do not have enough immunoglobulin (Ig) in their blood, which increases their risk of infection and complications. Secondary HGG can be caused by various conditions such as thymoma (a tumour originating from thymus cells) or by some treatments, such as organ transplant or immunosuppressant therapies such as B-cell depleting therapies (i.e. medicines or treatments that decrease this type of white blood cell). Management of the underlying cause of HGG may reverse the condition, but sometimes secondary HGG will persist and patients may require ongoing Ig replacement therapy. Ig is a standard treatment for patients with SHGG and clinicians and consumers submitted that continued access to Ig is important.   MSAC advised that Ig should continue to be available to treat people with SHGG but more evidence is required to confirm that it is clinically effective and cost effective. MSAC also noted that BloodSTAR data (https://www.blood.gov.au/bloodstar) i.e. data from the national government online system to manage access to the supply of government funded immunoglobulin products, could be further developed to inform future decisions about best use of Ig products.   MSAC noted that the use of Ig by this small patient population appears to be increasing at a higher rate compared with its use for other conditions. There is a lack of evidence overall to demonstrate whether Ig therapy is only being prescribed to people who obtain clear benefit. Cost projections based on current rates of usage of Ig products indicate Ig product costs could increase from about $15.3 million in 2018-2019 to about $41.3 million in 2023-2024. MSAC proposed that further research and work be done to identify areas for potential improvements in data collection to inform any future cost-effectiveness evaluations.

MSAC's advice to the National Blood Authority
MSAC advised it supports the continued funding of Ig for secondary hypogammaglobulinaemia (SHGG), noting Ig use for SHGG is an accepted standard of care. However, MSAC considered the published evidence and available BloodSTAR data

MSAC's advice to the National Blood Authority

to be insufficient to evaluate clinical effectiveness and cost-effectiveness of Ig therapy for the overall population with SHGG.

MSAC was concerned that Ig use in this small patient population appears to be increasing disproportionately compared with the increase observed for alternative Ig indications with very little evidence to support this use. MSAC understood that the increasing use of B cell depleting therapies (e.g. rituximab) may be contributing to the higher growth rate observed for this subgroup. MSAC remained concerned that patients classified as having "Other HGG" accounted for the majority of Ig use in the overall SHGG population, with no information collected on the underlying conditions within this subgroup.

MSAC accepted that further development of BloodSTAR data may provide more insights on treatment duration, trends and growth, noting that the Criteria V3 was introduced in October 2018. MSAC suggested that data collection through BloodSTAR could be improved in various ways. For example, improved granularity of the underlying conditions included in the "Other HGG" subgroup is required to ensure appropriateness of Ig use. MSAC also considered that collection of outcome data (pre and post- Ig treatment data) in BloodSTAR, and linkage of BloodSTAR data with other datasets such as registry, hospital, MBS and PBS data could also help address issues relating to poor quality evidence and uncertain outcomes.

MSAC proposed that a scoping exercise to explore the feasibility of conducting further research be undertaken. This would identify areas for potential research which may inform any future evaluations of clinical and cost-effectiveness and inform the decision whether to make an application to the Medical Research Future Fund (MRFF) or research funding available in other ways, including under the national blood arrangements. Considerations should include: better defining the eligibility requirements to access Ig therapy (thresholds for treatment commencement/continuation such as targeting particular Ig levels), reviewing current dosing recommendations (evaluation of the use of ideal body weight (IBW) as a way to optimise Ig use) or exploring dose-equivalence comparisons between SCIg and IVIg).

3. Summary of consideration and rationale for MSAC's advice

In Australia, Ig replacement therapy for the treatment of secondary hypogammaglobulinaemia (SHGG) is funded under the National Blood Supply Arrangements for subcutaneous (SC) and intravenous (IV) administration. MSAC noted that Ig therapy is an accepted treatment and standard care for patients with SHGG and agreed with the nominated comparator of no Ig (with or without antibiotics).

Patients with SHGG may be eligible for Ig treatment under the Criteria for the clinical use of immunoglobulin in Australia (version 3) (the Criteria) under the following specific conditions:

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

MSAC noted that patients must meet the qualifying criteria in order to access Ig therapy for SHGG. For continuation of Ig therapy, an initial review within six months of starting Ig is required, and ongoing reviews by a specialist are required at least annually to assess clinical benefit and whether cessation of Ig therapy should be considered. MSAC noted that documentation of clinical effectiveness (Ig levels and history of infection) is required for continued Ig therapy but thresholds for these measures are not specified. Therefore, the degree of HGG at which a decision is made to continue, cease or reduce the dose of Ig are not precisely defined. MSAC noted ESC advice that in England and Scotland, Ig use is restricted by the presence of recurrent or severe bacterial infections, and Ig treatment is reserved for patients in whom antibiotic prophylaxis proves to be ineffective. MSAC also noted pre-MSAC advice clarifying that the NHS (England) states that not all the criteria need to be fulfilled for an individual patient.

The evidence included in the contracted assessment report consisted of 15 studies, of which three provided comparative evidence (in heart and lung transplant patients only). MSAC noted that the available published evidence was of poor quality. No comparative evidence was identified for SHGG following B cell depletion therapy or Good syndrome. A lack of information on the underlying conditions for patients classified as having "Other HGG unrelated to haematological malignancies or haemopoietic stem cell transplantation (HSCT)" limited the ability to identify studies relevant to this population. The remaining 12 cohort studies mostly compared patients with SHGG to patients without SHGG and were determined to be at high or critical risk of bias.

With respect to safety, MSAC accepted the conclusion that Ig therapy is inferior to no Ig in patients with SHGG, but is well tolerated. Most adverse events (AEs) were mild and transient, with the exception of one recorded case of transfusion-related acute lung injury (TRALI).

MSAC accepted that Ig relative to no Ig in patients with SHGG has uncertain effectiveness based on the available evidence. MSAC noted that studies were small and of poor quality and outcomes were heterogeneous and poorly presented in the evidence. However, MSAC noted feedback from clinicians and stakeholders which was highly supportive of continuing use and access to Ig therapy. Consumers considered Ig therapy to be essential in the prevention and reduction of life-threatening infections, as well as improving the quality of life of patients.

An economic model was not presented in the contracted assessment report, due to there being insufficient data to inform a model. There was only very low-quality evidence available for patients with HGG following heart and lung transplantation, no quality-of-life outcomes or cost data and no utilities were identified for this population. MSAC noted that this decision was supported by the Ig Review Reference Group, which considered the results of economic modelling would be highly uncertain, may be misleading and have limited applicability to the population of interest, considering Ig treatment for 'HGG following solid organ transplant' accounts for 24% of all SHGG.

MSAC noted that patients receiving Ig for SHGG represents a small population (4% of all patients receiving Ig in Australia in 2015/16), but Ig use in this population appears to be growing disproportionately compared with the increase observed for alternative Ig indications. As noted by ESC, *the National Report on the Issue and Use of Immunoglobulin in 2017-18 indicated that there has been a greater than 16% increase in Ig supplied for SHGG since 2013/14, compared with an 11% increase over the same period for all medical conditions*. NBA data indicated that, in the period between June 2014 and March 2020, there

was an annual growth rate of approximately 19.3%, based on the monthly use of Ig (grams) for all SHGG (excl. haem malignancies) (see Figure 6).

Data provided by the NBA were used to estimate Ig product projected costs (excluding administration costs) for the treatment of SHGG from 2019-20 to 2023-24. An annual growth rate of 22% was applied to the 2018/19 estimates, based on the growth rate of Ig use for SHGG between July 2019-March 2020 when most of the transition from Version 2 to Version 3 of the Criteria had been completed. Ig costs for the base case were projected to increase from about $15.3 million in 2018-2019 to about $41.3 million in 2023-2024 (using an Ig cost per gram of $60.41). These financial estimates were considered highly uncertain as costs or changes in use and cost of other medical services are not considered. In addition, the growth rates of Ig use differed greatly across each subgroup during this time (e.g. a 61.8% growth rate was observed for "HGG following B cell depleting therapies" and 16.7% for "HGG following solid organ transplant" subgroups). Therefore, a sensitivity analysis was performed where respective growth rates were applied to each subgroup, rather than using 22% growth as in the base case. With respect to the sensitivity analysis, MSAC agreed with ESC advice that it is highly uncertain if the recent 61.8% growth rate observed for Ig use in "HGG following B cell depletion therapy" subgroup would continue; but considered that the increasing use of B cell depleting therapies is likely to be contributing to the higher growth rate observed for this subgroup.

MSAC noted that the requirement for downstream Ig therapy may not be an identified factor in the health technology assessment of applications for Pharmaceutical Benefits Scheme listing of B cell depleting medicines. MSAC considered it important that the Pharmaceutical Benefits Advisory Committee (PBAC) had visibility of this requirement and associated health care costs for potential inclusion in future cost-effectiveness evaluations of these medicines. In addition, off-label, unfunded, use of such therapies in clinical practice may be an additional driver of demand for Ig.

Overall, MSAC considered the published evidence and available data to be insufficient to make an assessment of the relative efficacy and cost-effectiveness of Ig in this population. MSAC agreed that the results of any economic model would be highly uncertain given this lack of evidence and the current price of Ig. MSAC considered that given the evidence presented in this review, that Ig use for this indication is highly likely to be cost-ineffective. In particular, MSAC expressed concern regarding the "Other HGG" subgroup, which accounted for over 50% of Ig use for all SHGG in 2018-19 and for which there is currently no information collected on the underlying conditions of these patients.

MSAC recommended that Ig therapy should continue to be funded for SHGG, with potential changes required with respect to improved data collection and the scoping of further research to address data gaps. MSAC advised that the "Other HGG" subgroup requires improved granularity on the underlying conditions to ensure appropriateness of Ig use. MSAC agreed that collection of outcome data (pre and post- Ig treatment data) in BloodSTAR, and linkage of BloodSTAR data with other datasets such as registry, hospital, MBS and PBS data could also help address issues relating to poor quality evidence and uncertain outcomes.

MSAC proposed a scoping exercise to explore the feasibility of conducting further research be undertaken. This would identify areas for potential research which may inform any future evaluations of clinical and cost-effectiveness and inform the decision whether to make an application to the Medical Research Future Fund (MRFF) or research funding available in other ways, including under the national blood arrangements. MSAC considered this could include better defining the eligibility requirements to access Ig therapy (thresholds for treatment commencement/continuation/cessation such as targeting particular Ig levels), and

reviewing current dosing recommendations (including the use of ideal body weight (IBW) as a way to optimise Ig use). MSAC also noted that stakeholders were supportive of SCIg uptake which may reduce barriers to Ig therapy, and considered that further research could explore dose-equivalence comparisons between SCIg and IVIg. MSAC was of a mind to review the application in 12 months' time, should additional data become available to inform the cost-effectiveness of Ig in this population.

4.   Background

All Australian Governments, through the Jurisdictional Blood Committee (JBC), have agreed to conduct robust Health Technology Assessments (HTAs) of immunoglobulin use (Ig Reviews) funded under the National Blood Agreement to ensure government-funded immunoglobulin use is based on strong evidence of clinical effectiveness and cost-effectiveness. 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 JBC.

The Ig Reviews are supported by a bespoke Reference Group, which oversees and provides advice on evaluation of all Ig HTA review applications. The PICO Confirmations for the Ig Reviews have been considered by the Reference Group instead of the PICO Advisory Sub-committee (PASC). Otherwise, the MSAC evaluation process remains the same as for applications for funding of items on the Medical Benefits Schedule (MBS).

Four reports from the Ig Reviews have been considered by MSAC so far:

- Application 1564 – Immunoglobulin for chronic inflammatory demyelinating polyneuropathy
- Application 1565 – Immunoglobulin for acquired hypogammaglobulinaemia secondary to haematological malignancies, or post-haemopoietic stem cell transplantation (HSCT)
- Application 1566 – Immunoglobulin for myasthenia gravis
- Application 1590 – Immunoglobulin for multifocal motor neuropathy

Application 1591 and 1592 are the next two reports from the Ig Reviews to proceed to MSAC.

5.   Prerequisites to implementation of any funding advice

All therapeutic products marketed in Australia require listing on the Australian Register of Therapeutic Goods (ARTG). Ig for this indication is already funded by the NBA. The purpose of this application is to consider the clinical effectiveness and cost-effectiveness of these products as currently funded under the Criteria V3. Ig products registered by the TGA for the potential treatment of SHGG in Australia are summarised in Table 1. The wording of the TGA approved indications varies widely between products, though most include wording such as "hypogammaglobulinaemia secondary to underlying disease or treatment" or similar.

Table 1   Ig 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	Octaphama	IV	1g/10mL to 30g/300mL	No
Gamunex 10%	Grifols	IV and SC	1g/10mL to 20g/200mL	Yes
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
Octagam**	Octapharma	IV	1g/20mL to 20g/mL	No
Gammanorm	Octapharma	SC	1.65g/10mL or 3.3g/20mL	No

Source: Therapeutic Goods Administration

IV – intravenous, SC – subcutaneous, IM – intramuscular

* Indicates that Ig was funded for secondary hypogammaglobulinaemia under the National Blood Arrangements at 6 May 2020. Note that tendering arrangements may change products funded in the future. Refer to the NBA National Product List for current products, suppliers and prices

6.   Proposal for public funding

Ig therapy for SHGG is currently funded by the NBA under the national blood supply arrangements, but the cost-effectiveness of this use has not been evaluated in Australia. Version 3 of the Criteria categorises Ig use in this population as a "Condition for which Ig has an emerging therapeutic role", with a 'Level of evidence' Category 4A (insufficient data).

Applications for eligible patients to access funded Ig are made through the BloodSTAR online portal and assessed against the eligibility requirements specified in Version 3 of the Criteria[1]. Initial diagnosis must be made by a specialist and patients must meet the qualifying criteria in order to access Ig products. The Criteria, including eligibility criteria are periodically updated and may be refined according to recommendations of the relevant NBA working group and subsequent approval by the JBC.

7.   Summary of public consultation feedback/consumer Issues

In August 2019, the Referral was provided to a range of stakeholders nominated by the NBA and Ig Review Reference Group, which included clinicians, consumer groups and sponsors of immunoglobulin. In December 2019, the PICO confirmation was released to sponsor companies who were invited to provide any relevant input to the development of the Contracted Assessment. Four responses were received: from clinical groups (1); consumer groups (1); and sponsor companies (2). In August 2020, public consultation was undertaken on the Contracted Assessment. Three responses were received from the following: clinical groups (1); consumer groups (1); and sponsor companies (1).

Stakeholders were highly supportive of Ig therapy for secondary HGG unrelated to haematological malignancies, or post haemopoietic stem cell transplant. Ig therapy was considered essential in the prevention and reduction of life-threatening infections, as well as improvement in the quality of life of patients.

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[1] National Blood Authority, the Criteria (V3) and eligibility for *Secondary hypogammaglobulinaemia unrelated to Haematological malignancy or haemopoeitic stem cell transplant (HSCT)*

Noted disadvantages associated with Ig therapy included: possible adverse events, that it is time consuming for patients to attend hospital regularly to receive infusions, and other out-of-pocket costs (e.g. travel, parking). However, consumers considered that any side effects of Ig treatment are outweighed by its benefits. Stakeholders were supportive of SCIg use, noting it may offer better patient tolerability and convenience (reduced need to travel to hospital).

Stakeholders acknowledged that the population includes a heterogeneous group of conditions. Due to the heterogeneity of subgroups under this indication, it may be difficult to describe the appropriate comparator/s, and efficacy data (focused on solid organ transplant patients) may not be applicable to all conditions. One sponsor noted that while it is preferable to correct or remove the underlying cause of secondary HGG, this is not always possible and ongoing Ig therapy may be required.

8.   Proposed intervention's place in clinical management

Description of Proposed Intervention

The intervention is immunoglobulin (Ig) replacement therapy. Ig products are purified from fractionated human donor plasma, and may be administered through intravenous (IV) or subcutaneous (SC) injection (IVIg and SCIg, respectively). Access to government-funded Ig is through the national blood arrangements and determined by the NBA's Criteria for Clinical Use of Immunoglobulin in Australia (the Criteria).

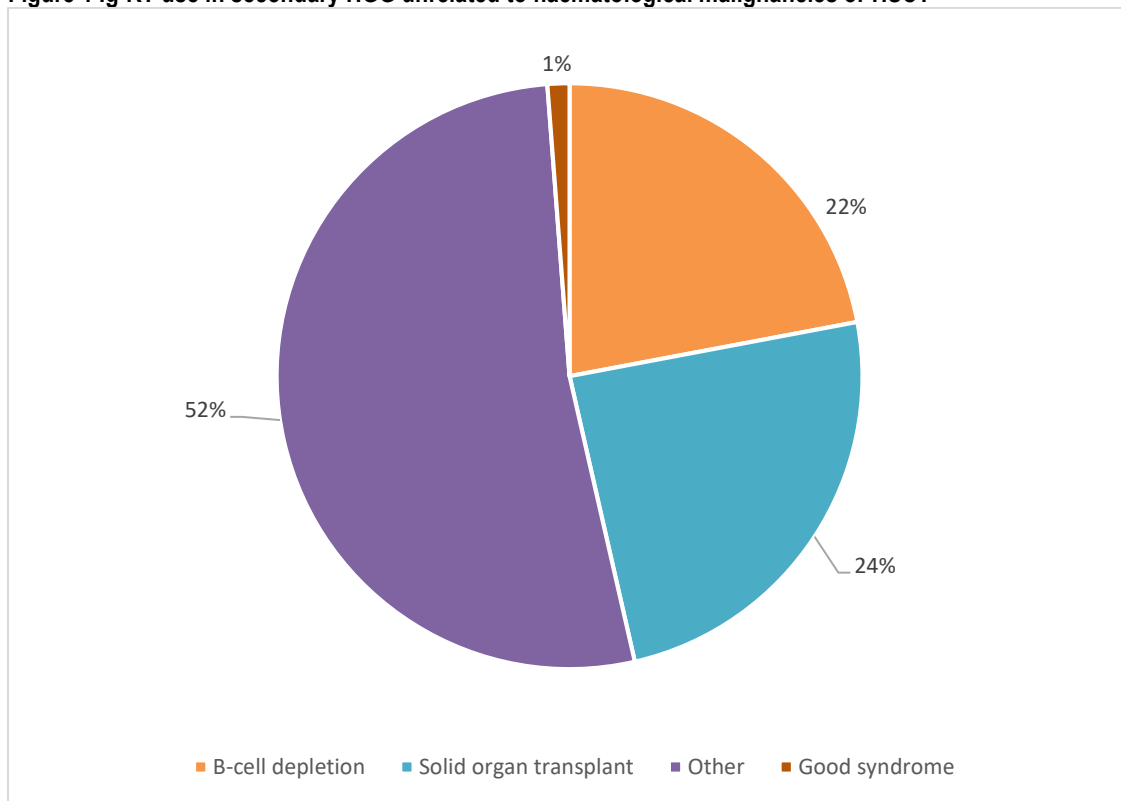**Description of Medical Condition(s)**
The indication for Ig use for this referral according to Version 3 of the Criteria is '*replacement therapy for recurrent or severe bacterial infections or disseminated enterovirus infection associated with hypogammaglobulinaemia caused by a recognised disease process or B cell depletion therapy and/or immunosuppressant therapy*'.

This includes patients with SHGG who are eligible according to Version 3 of the Criteria for the following conditions:
- Hypogammaglobulinaemia following solid organ transplantation
- Hypogammaglobulinaemia following B cell depletion therapy
- Thymoma-associated hypogammaglobulinaemia (Goods Syndrome)
- Other Hypogammaglobulinaemia unrelated to haematological malignancies or haemopoietic stem cell transplantation (HSCT)

Figure 1 presents the proportional use of Ig in Australia stratified by the underlying cause of SHGG. Note that the data obtained for this chart is based on NBA data collected during the calendar year 2019 - after the Criteria V3 had been implemented; however, some patients continuing treatment in 2019 were still classified according to the Criteria V2 as they had not yet transitioned to V3.
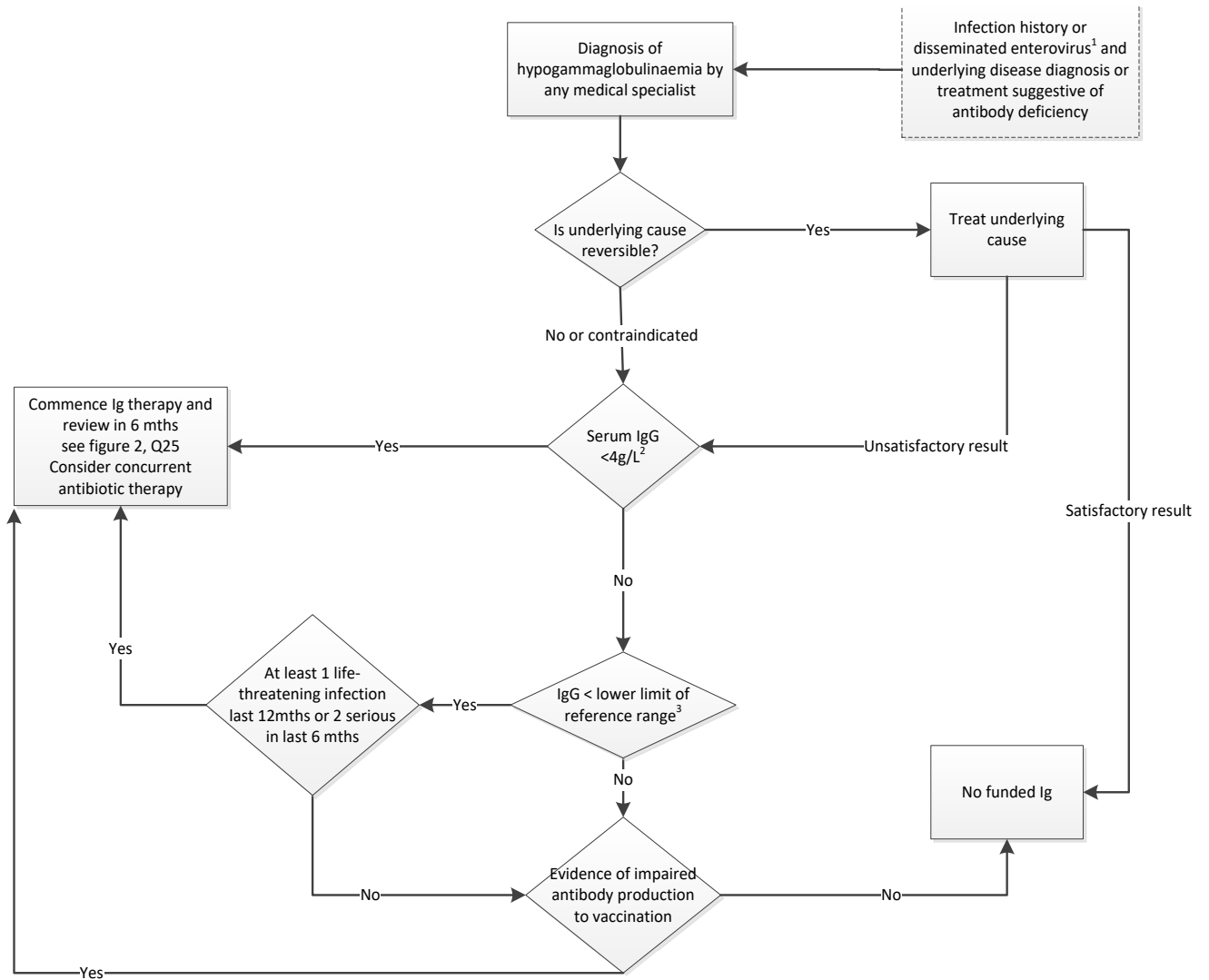
Figure 1 Ig-RT use in secondary HGG unrelated to haematological malignancies or HSCT

Source: Contracted Assessment Figure 1

Ig is currently considered 'standard of care' for the population of interest and may be given with or without antibiotics. Figure 2 and Figure 3 present the initial and continuing treatment algorithms as indicated in the Criteria V3.

Figure 2 Initial access to Ig for secondary HGG unrelated to haematological malignancies or HSCT, funded under the National Blood Agreement

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                                    ┌─────────────────────┐         ┌─────────────────────────┐
                                    │     Diagnosis of    │         │ Infection history or    │
                                    │ hypogammaglobulinaemia│◄───────│ disseminated enterovirus[1] and │
                                    │  by any medical     │         │ underlying disease      │
                                    │     specialist      │         │ diagnosis or treatment  │
                                    └─────────────────────┘         │ suggestive of antibody  │
                                              │                     │ deficiency              │
                                              ▼                     └─────────────────────────┘
                                    ◇ Is underlying cause ◇──Yes──► ┌──────────────────┐
                                    ◇    reversible?      ◇         │ Treat underlying │
                                              │                     │      cause       │
                                     No or contraindicated          └──────────────────┘
                                              ▼                              │
  ┌─────────────────────┐                                                    │
  │ Commence Ig therapy │◄──Yes──◇   Serum IgG   ◇◄──Unsatisfactory result───┤
  │ and review in 6 mths│        ◇    <4g/L[2]   ◇                           │
  │ see figure 2, Q25   │                │                         Satisfactory result
  │ Consider concurrent │               No                                   │
  │  antibiotic therapy │                ▼                                   │
  └─────────────────────┘                                                    │
         ▲      ▲                                                            │
         │      │Yes                                                         │
         │      │                                                            │
         │   ◇ At least 1 life- ◇──Yes──◇ IgG < lower limit of ◇            │
         │   ◇   threatening    ◇        ◇  reference range[3]  ◇           │
         │   ◇ infection last   ◇                │                          │
         │   ◇ 12mths or 2 serious◇             No                          │
         │   ◇  in last 6 mths  ◇                ▼                          ▼
         │              │                                          ┌──────────────┐
         │             No──────►◇ Evidence of impaired ◇──No─────►│ No funded Ig │
         │                      ◇ antibody production  ◇          └──────────────┘
         │                      ◇   to vaccination     ◇                 ▲
         │                              │                                │
         └──────Yes─────────────────────Yes
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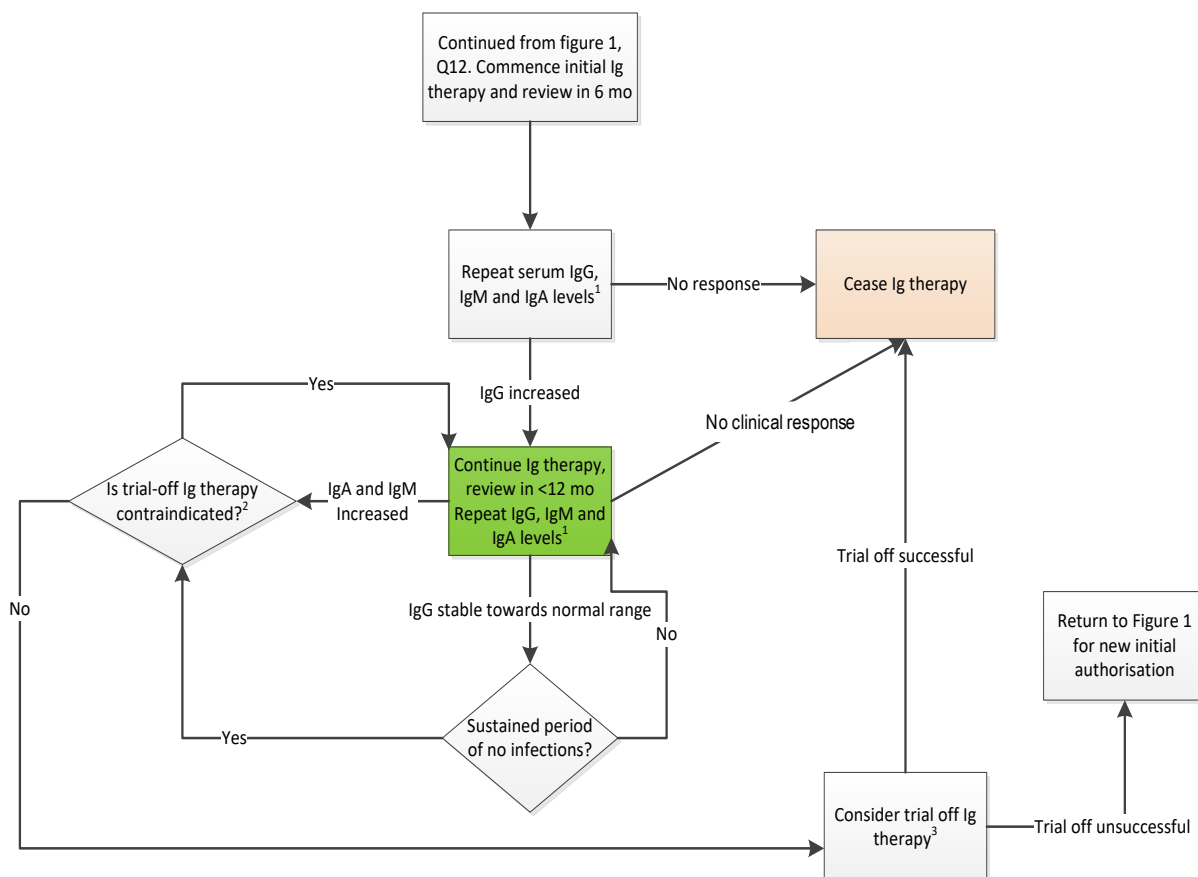
[1] Diagnosis of bronchiectasis and/or suppurative lung disease must be consistent with the Thoracic Society of Australia and New Zealand (Chang et al 2014).
[2] Serum Ig levels should be measured on two separate occasions, at least one hour apart and at least one sample taken when the patient does not have an active infection.
[3] Reference range should be age related.
Source: Contracted Assessment Figure 3 & Ratified PICO 1591

Figure 3 Continuing access to Ig for secondary HGG unrelated to haematological malignancies or HSCT, funded under the National Blood Agreement

[1] If serum IgM and IgA levels are trending upwards and near normal, Ig is also likely to be trending towards normality. This may suggest recovery of the immune system and a trial-off Ig therapy might be considered.

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

[3] 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.

Source: Contracted Assessment Figure 4 & Ratified PICO 1591

9.   Comparator

Noting that this is a heterogeneous patient group, the comparator to Ig therapy for SHGG is 'no Ig'. Best practice standard of care for specific conditions within SHGG may or may not include antibiotic treatment, prophylactic antibiotics or thymectomy.

10.   Comparative safety

One randomised controlled trial (RCT) (Lederer et al. 2014) and two prospective studies (Sarmiento et al. 2016; Shankar et al. 2013) were identified in the literature review of Ig use for SHGG.

Of these, only Lederer 2014 reported comparative evidence in patients (with SHGG post lung transplant) treated with IVIG vs. placebo, finding no significant differences in adverse events (AEs) between the two treatment groups. However, this study included a very short treatment period and follow up (12 weeks) and small number of patients (n=11), and therefore was not powered to detect small or moderate differences in AEs.

Sarmiento 2016 reported a high number of severe AEs in patients (with SHGG post-heart transplant) receiving treatment with IVIg over four months (66%), but AEs in the control

group were not reported. Therefore, it is unclear if the AEs are associated with IVIg or the underlying condition.

Overall, the safety profile of Ig was considered to be inferior versus no Ig, although Ig was well tolerated with few infusion-related adverse events (AEs were mainly mild and transient) with the exception of one recorded incident of transfusion-related acute lung injury (TRALI) in Shankar 2013.

11.   Comparative effectiveness

The DCAR suggested that relative to no Ig in patients with secondary HGG unrelated to haematological malignancies or HSCT, Ig has uncertain effectiveness.

The summary of key findings is shown in Table 2. One RCT (Lederer 2014), and two cohort studies (Sarmiento 2016, Lichvar 2018) presented comparative evidence of Ig vs. no Ig in patients with SHGG. These studies included patients who developed SHGG after heart or lung transplantation, which represents approximately 24% of Ig use (grams) in all patients accessing Ig for SHGG. These studies provided insufficient information on the mean/median doses, initiation, duration and discontinuation of Ig therapy given, and antibiotic use was not adequately described. The quality of the available evidence was very low for all the effectiveness outcomes; therefore, the HTA evaluators considered the effectiveness of Ig in this population to be very uncertain. Twelve cohort studies were also included as supportive non-comparative evidence. Most of these studies aimed to compare outcomes of patients with HGG and without HGG (outside the scope of this review), rather than evaluating the effectiveness of Ig therapy in patients with HGG. Only data relevant to the population of interest was extracted to provide information on whether patients with HGG may benefit from Ig therapy. All of the supportive studies were considered to be at serious or critical risk of bias.

Infections

One study (Sarmiento 2016, n=25) in heart transplant patients, found significantly lower rates of severe infections in patients with SHGG treated with IVIg compared to those who did not receive IVIg (25.0% vs. 76.9%; RR 0.33 (0.12, 0.91)). A severe infection was defined as any infection requiring at least one dose of IV antimicrobial therapy (catheter-related infections and surgical wound infections were excluded). There were no significant differences in the other studies comparing Ig to no Ig for the other infection outcomes reported.

Transplant rejection

There were no significant differences between treatment groups for the outcome of acute rejection. However, there was significantly lower grade 2 Chronic Lung Allograft Dysfunction (CLAD) at 5 years in patients treated with on-demand IVIg compared to no IVIg (RR 0.51 (0.28, 0.94))(Lichvar et al. 2018), but there were no significant differences in grade 3 CLAD rates.

Survival Outcomes

In the study by Lichvar (2018), 1-year, 2-year and 5-year survival was significantly worse in HGG patients treated with Ig than in HGG patients receiving no Ig. However, HGG patients in the Ig-treated group had more severe HGG at baseline and more underwent bilateral lung transplants than those who did not receive Ig, which could have biased survival outcomes against the Ig group.

In Claustre et al. 2015, one of the supportive studies, 5-year survival in IVIg-treated lung transplant patients with HGG was higher than that reported by Lichvar 2018 (65% vs.

56.0%). Lichvar 2018 reported a longer time from transplant to Ig initiation and shorter duration of Ig therapy than in Claustre 2015, which could have also had an impact on poorer outcomes.

Hospitalisations

With regard to hospitalisations, Sarmiento 2016 indicated a trend towards increased number of readmissions in heart transplant patients not treated with IVIg, whereas Lederer 2014 found no significant differences for hospitalisations for patients treated with Ig versus no Ig. However, both studies included a very small number of patients and hospitalisations, so results should be interpreted with caution.

Table 2   Clinical benefits of Ig-RT, relative to no-Ig-RT, and as measured by the critical patient-relevant outcomes in the key studies

Study ID	Cause of secondary HGG	Risk of bias	Ig-RT n with event/N (%)	No Ig-RT n with event/N (%)	Absolute difference (RD 95% CI)	Relative difference OR/RR (95%CI)	Follow up	Quality of evidence (GRADE)
Any infections								
Lederer 2014	Lung transplant	Moderate	7/11 (63.6)	3/11 (27.3)	0.36 (-0.02, 0.75)	OR 2.7 (0.95, 7.6)	12w (2.7m)	⊕⊙⊙⊙
Lichvar 2018	Lung transplant	Serious	139/216 (64.3)	139/192 (72.4)	-0.08 (-0.17, 0.01)	OR 0.69 (0.45, 1.05) RR 0.89 (0.78, 1.01)	5y	
Severe infections[c]								
Sarmiento 2016	Heart transplant	Serious	3/12 (25.0)	10/13 (76.9)	**-0.52 (-0.85, -0.18)**	**RR 0.33 (0.12, 0.91)**	6m	⊕⊙⊙⊙
CMV disease								
Sarmiento 2016	Heart transplant	Serious	0/12 (0)	5/13 (38.5)	**-0.38 (-0.66, -0.11)**	RR 0.10 (0.01, 1.60)	6m	⊕⊙⊙⊙
Viral infection								
Lederer 2014	Lung transplant	Moderate	2/11 (18.2)	2/11 (18.2)	0.00 (-0.32, 0.32)	OR 0.8 (0.1, 5.9)	12w (2.7m)	⊕⊙⊙⊙
Bacterial infection								
Lederer 2014	Lung transplant	Moderate	3/11 (27.3)	1/11 (9.1)	0.18 (-0.13, 0.50)	OR 3.5 (0.4-27.6)	12w (2.7m)	⊕⊙⊙⊙
Sarmiento 2016	Heart transplant	Serious	3/12 (25)	9/13 (69.2)	**-0.44 (-0.79, -0.09)**	RR 0.36 (0.13, 1.03)	6m	
Acute transplant rejection								
Lederer 2014	Lung transplant	Moderate	0/11 (0)	0/11 (0)	NA	NA	12w (2.7m)	⊕⊙⊙⊙
Sarmiento 2016	Heart transplant	Serious	1/12 (8.3)	1/13 (7.7)	0.01 (-0.21, 0.22)	RR 1.08 (0.08, 15.46)	6m	⊕⊙⊙⊙
A-grade rejection score*, median (IQR)								
Lichvar 2018	Lung transplant	Serious	0.50 (0.33-1.00)	0.50 (0.33-0.75)	NR	NR	1y	⊕⊙⊙⊙
			0.50 (0.29-0.83)	0.50 (0.33-0.75)	NR	NR	2y	⊕⊙⊙⊙
			0.50 (0.30-0.83)	0.38 (0.25-0.60)	NR	NR	5y	⊕⊙⊙⊙
Overall survival								
Lichvar 2018	Lung transplant	Serious	75.0	88.0	13	P=0.006	1y	⊕⊙⊙⊙
			64.8	81.3	16.5	p<0.001	2y	⊕⊙⊙⊙
			56.0	67.2	11.2	P=0.006	5y	⊕⊙⊙⊙
Mortality rate								

Study ID	Cause of secondary HGG	Risk of bias	Ig-RT n with event/N (%)	No Ig-RT n with event/N (%)	Absolute difference (RD 95% CI)	Relative difference OR/RR (95%CI)	Follow up	Quality of evidence (GRADE)
Sarmiento 2016	Heart transplant	Serious	3/11 (25)	3/12 (23)	-0.01 (-0.20, 0.18)	RR 0.92 (0.21, 4.11), p=0.91	6m	⊕⊙⊙⊙
Hospitalisation during the treatment period								
Lederer 2014	Lung transplant	Moderate	3/11 (27.3)	1/11 (9.1)	0.18 (-0.13, 0.50)	OR 3.5 (0.2, 51.2)	12w (2.7m)	⊕⊙⊙⊙
Hospitalisation readmission after discharge (due to infection)								
Sarmiento 2016	Heart transplant	Serious	32 (16-200)	48 (12-191)	16	p=0.57	6m	⊕⊙⊙⊙

Source: Contracted Assessment Table 1

Abbreviations: CMV=cytomegalovirus, HGG=hypogammaglobulinaemia, Ig-RT=immunoglobulin G replacement therapy, m=months, OR=odds ratio, RD=risk difference, RR=relative risk, w=weeks, y=years

* Defined as rejection requiring intensified immunosuppression

GRADE Working Group grades of evidence (Guyatt et al., 2013)

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.

⊕⊕⊕⊙ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

⊕⊕⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
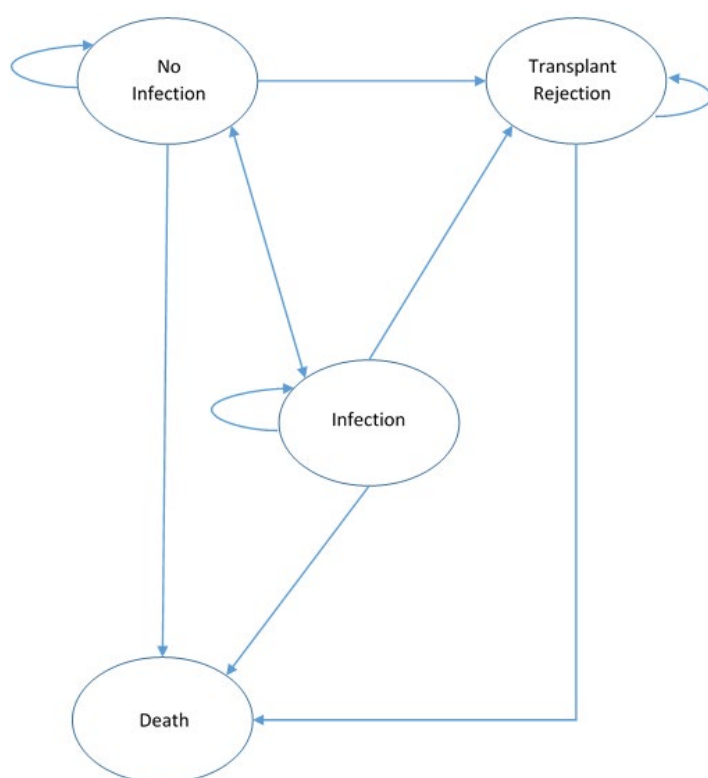
⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

12.   Economic evaluation

An economic evaluation was not presented in this contracted assessment report due to there being insufficient data to inform a model. Only very low-quality evidence was available for patients with SHGG following heart and lung transplantation, and no suitable data was identified for other SHGG subpopulations, leading to a conclusion of uncertain effectiveness of Ig for these conditions. No studies reported quality of life outcomes or cost data, and no further cost information or utilities were identified in the searches for economic data.

A potential simplified model structure for the solid organ transplant subpopulation (representing approximately 24% of Ig use in the SHGG population of interest) is discussed in Section D.3 of the assessment report, but it was not possible to populate the model due to lack of reliable inputs. Outside of the solid organ transplant group, information was lacking on the other three subpopulations of patients with SHGG (i.e. Good syndrome, HGG following B cell depletion therapy, and other SHGG unrelated to haematological malignancies or HSCT).

Figure 4 Proposed Simplified Economic Evaluation Model for solid organ transplant patients only

Source: Contracted Assessment Figure 6

Section D.4 and D.5 of the assessment report describe the data gaps and inputs required to populate an economic model. Broadly, the identified data gaps for a simplified economic model included; transition probabilities, utilities for all health states, and healthcare utilisation and cost information (see Table 3).

Table 3   Healthcare utilisation and Cost Data Gaps

Other Inputs	Healthcare utilisation
Duration of treatment (for each subpopulation of interest) Trends in patient count for different subpopulations Growth in Ig use by subpopulation Trends in number of treatment episodes by subpopulation Up to date data on Ig usage per patient Concomitant medication use (e.g. antibiotic use)	Antibiotic use Infusion equipment, Administrative and clinician time (e.g. resources associated with requesting, and authorising, access to Ig), Nursing time (for initiation and monitoring if IVIG) Hospitalisation (including length of stay) ICU admission (including length of stay) Management of adverse events Training of patient or carer to provide infusions (SCIG only), Product dispensing and disposal of any unused product Follow-up and/or monitoring visits

13.   Financial/budgetary impacts

The financial implications and predicted use of Ig in patients with SHGG were estimated for a 5-year period from 2019-20 to 2023-24, using a market-based approach.

The cost per gram of Ig used in the base case analysis is $60.41. This cost was provided by the NBA to inform the economic and financial analyses and had been estimated retrospectively based on the reported total domestic product cost in 2017/18 ($195 million) minus domestic SCIg product costs ($4 million) in that same year, divided by the number of IVIg domestic grams issued (3,161,673) as published in the National Report on the Issues and Use of Ig in 2017/18 (NBA 2019b). Additional estimates are presented assuming:

- The highest (maximum) cost of Ig (i.e. domestic IVIG, including the cost of plasma fractionation), $140.18 per gram
- The lowest (minimum) cost of Ig (i.e. imported IVIG), $44.94 per gram
- The weighted average cost of Ig across all indications, $94.51 per gram

In the base case, Ig costs are projected to increase from about $15.3 million in 2018-2019 to about $41.3 million in 2023-2024. Over five years (2019-2020 to 2023-2024), the projected costs of Ig in this population are estimated to be $144,245,943.

Table 4 Ig use projected costs

Assumed cost/gram	2018 - 2019[a]	2019 - 2020	2020-2021	2021 - 2022	2022 - 2023	2023 - 2024
Base $60.41/g	$15,276,583	$18,637,432	$22,737,667	$27,739,954	$33,842,743	$41,288,147
Minimum $44.94/g	$11,364,504	$13,864,694	$16,914,927	$20,636,211	$25,176,178	$30,714,937
Weighted Average $94.51/g	$23,899,849	$29,157,816	$35,572,536	$43,398,494	$52,946,163	$64,594,318
Maximum $140.18/g	$35,448,957	$43,247,727	$52,762,227	$64,369,917	$78,531,299	$95,808,185

Source: Contracted Assessment, Table 2 (NBA 2020b)
IVIG: intravenous immunoglobulin, SCIG: subcutaneous immunoglobulin, HGG: hypogammaglobulinaemia, HM: haematological malignancies, HSCT: haemopoietic stem cell transplantation
*All Secondary HGG (excluding haematological malignancies) includes all the subgroup patients. Note that due to the very different growth rates within subpopulations and the limited data available to estimate these trends we do not break down the extrapolation into subpopulations.
** Based on actual use.

These projected costs consider the Ig product only (excluding administration costs). The estimates do not consider costs or changes in use and cost of other medical services, as there was insufficient information to make such predictions; therefore the financial implications are highly uncertain. Treatment patterns may differ in each of the four subpopulations included (e.g. patients undergoing solid organ transplantation might only receive Ig for a more limited period of time compared with those with Good syndrome or B-cell depletion therapy, for which treatment might be lifelong).

Where new B-cell depleting therapies are considered for government reimbursement, the impact of the additional cost of Ig therapy must be included in any assessment of cost-effectiveness.

The cumulative need for Ig following organ transplant is likely to be proportional to the number of transplants occurring. Between 2009 and 2019, there was an increase in transplantation of 81%, but the rate of increase has plateaued- see Figure 5.
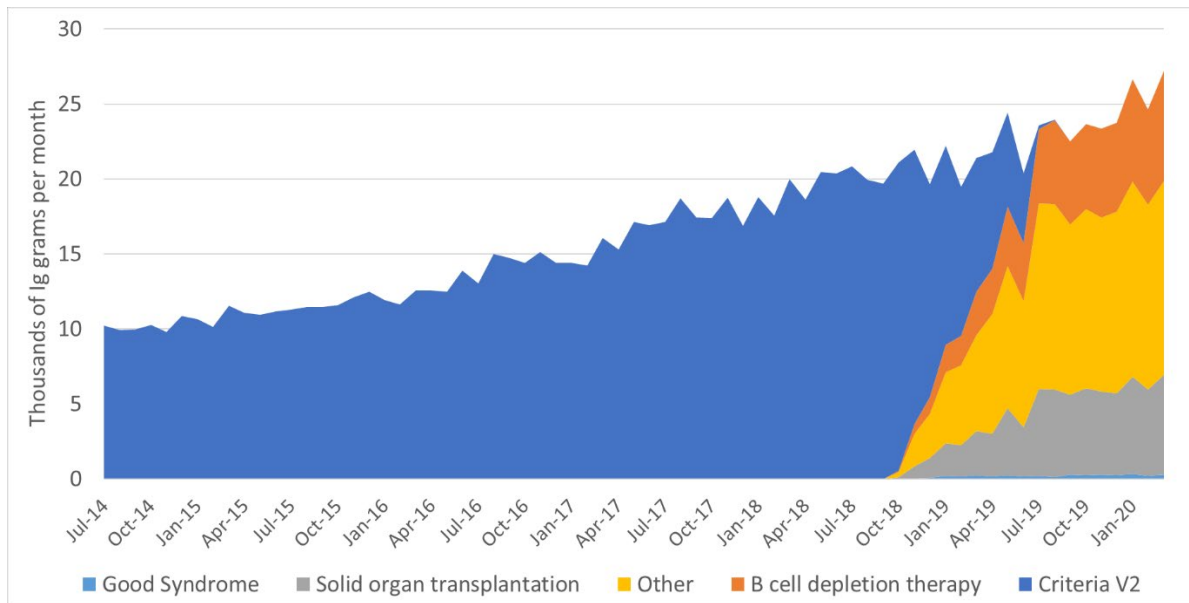
Figure 5 Deceased organ and transplant recipients 2009-2019 (source https://transplant.org.au/statistics/)

The subgroup of patients classified as "Other" by the Criteria V3 had the highest use of Ig (52%) in the population of SHGG. The lack of knowledge of the underlying conditions in this patient subgroup means that the treatment needs of these patients and the associated costs could not be predicted. Furthermore, it would be critical to identify the diagnoses in this 'Other' group to ensure that this classification is not being used to circumvent the restriction on conditions for which Ig are 'not supported' per the Criteria.

From June 2014 to March 2020 there was an annual growth rate of approximately 19.3%, based on the monthly use of Ig (grams) for all SHGG (excl. haem malignancies). A 22% annual growth in Ig use was applied to the 2018/19 estimates for the financial implications, based on the growth rate of Ig use for SHGG between July 2019-March 2020 when most of the transition from Version 2 to Version 3 of the Criteria had been completed (Figure 6). This is highly uncertain as growth rates in Ig use by subgroups differed greatly over these nine months. Therefore, a sensitivity analysis was also presented, extrapolating each subpopulation by their corresponding recent growth rate. In particular, the assessment report noted the recent increasing use of Ig related to B cell depletion therapy, which if this continues, may put considerable pressure on Ig budgets in the future.

Figure 6 Monthly recorded Ig use (IVIG and SCIG) under each criterion and by subpopulation in V3

Source: Contracted Assessment Figure 7(NBA 2020b)

14.   Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
Details of the "Other hypogammaglobulinaemia (HGG)" subgroup	The "Other HGG" subgroup represented the majority of Ig use for all secondary hypogammaglobulinaemia (SHGG) in the 2019 calendar year. Data collection for this currently un-defined subgroup is required to understand the clinical diagnoses and outcomes for this population. More knowledge of the diagnoses in this subgroup will allow a better understanding of the applicability of Ig treatment for these patients and the associated costs.
Consider data linkage to address issues relating to poor quality evidence and uncertain outcomes.	ESC noted it is unlikely that high quality randomised controlled trial (RCT) or more comparative clinical trial evidence of clinical effectiveness will be forthcoming given this practice is now the standard of care in patients with SHGG. ESC supports the consideration of linked data, e.g. linking of patient-level data on Ig use (from BloodSTAR) to hospitalisation, on- & off-label B-cell depleting therapy, Medicare and mortality data to allow a better understanding of the healthcare use and outcomes in this population.
BloodSTAR collection of more detailed data	It may be appropriate for BloodSTAR to collect more detailed data for Ig-treated patients as is done in other countries. Analysis of on-treatment data (treatment cycles) or linkage of BloodSTAR data to PBS/hospitalisation data may help to estimate administration costs.
Ideal body weight (IBW) as a means to calculate immunoglobulin (Ig) dose	ESC considered that standardising the use of IBW results in an appropriately lower dose given to a patient if they are above their 'ideal' weight, thereby optimising Ig use. This approach is already available on the BloodSTAR website, but adherence to this dosing calculation is not monitored, and outcomes are not reported separately based on the bodyweight used. More evidence is sought on using this calculation.
The impact of other therapies on future Ig use (e.g. B-cell depleting therapies)	Consider the impact of new therapies, or new indications of existing therapies, which lead to the increase in use of Ig. Are these therapies still cost-effective, given the need for further treatments in the future (e.g. Ig therapy) and is this considered in the financial impact?

ESC discussion

Application 1591 requests MSAC advice on the supply of Ig therapy under the national blood arrangements for the treatment of secondary hypogammaglobulinaemia unrelated to haematological malignancies, or post-HSCT, hereafter referred to as SHGG. In line with the PICO confirmation, the DCAR reviews the available evidence on safety and clinical effectiveness of Ig replacement therapy in this population. MSAC is asked to consider the evidence presented, and provide advice on a range of strategies to manage the cost-effectiveness of Ig use in this population.

The clinical criteria for subsidised access to IVIg for SHGG is set out under version 3 of the *Criteria for the clinical use of immunoglobulin in Australia*[2] (the Criteria). There are currently four specific conditions for which patients with SHGG may be eligible for Ig therapy according to the Criteria. ESC noted that in the 2019 calendar year, the majority (52%) of Ig use for SHGG was for patients in the subgroup 'Other HGG unrelated to haematological malignancies or haemopoietic stem cell transplantation (HSCT)'. The remaining sub-conditions are: HGG following solid organ transplantation (24%), HGG following B cell depletion therapy (22%) and thymoma-associated HGG (Goods Syndrome) (1%).

ESC noted that despite the poor quality of evidence, Ig therapy is considered the standard of care in patients with SHGG and therefore it is unlikely that additional clinical trial evidence will be forthcoming. A comparison of international clinical guidelines presented in the DCAR noted that recommendations are largely based on expert opinion given the paucity of evidence in this population. ESC noted that some comparable guidelines are more stringent than others, for example, in England and Scotland, Ig use is restricted by the presence of recurrent or severe bacterial infections, and Ig treatment is reserved for those patients in whom antibiotic prophylaxis proves to be ineffective. In addition, there is a requirement to record the number of infections and days in hospital pre-treatment and 6-monthly thereafter. ESC noted that utilisation of Ig in Australia appears to be higher than other countries, although the reasons for this are not yet clear.

The Criteria Version 3 requires patients to meet the qualifying criteria in order to access Ig therapy for SHGG. For continuation of Ig therapy, an initial review within six months of starting Ig is required, and ongoing reviews by a specialist are required at least annually to assess clinical benefit and whether cessation of Ig therapy should be considered. The Criteria states that if serum IgM and IgA levels are trending upwards and near normal, this may suggest recovery of the immune system and a trial off Ig therapy might be considered if the patient is well. ESC noted that the degree of HGG at which a decision would be made to continue, cease or reduce the dose of Ig, requires clinical judgement and are not precisely defined, but there is potential to do so. With regards to dosing, ESC noted that the BloodSTAR dose calculator provides an option to dose Ig according to ideal body weight (IBW) which results in a lower dose given to a patient compared to using the actual bodyweight (used only if the patient is overweight). ESC considered that more evidence is required to establish whether dosing according to IBW results in non-inferior outcomes, and that this information could be obtained prospectively in the form of a pragmatic trial where data is collected in BloodSTAR.

There are indications for the use of Ig in solid organ transplantation to prevent or treat antibody-mediated rejection, or desensitisation to improve the likelihood of transplantation, that are separate from the indication to treat secondary hypogammaglobulinaemia addressed herein.

Fifteen studies were included in the clinical effectiveness review, with only three of these studies providing comparative evidence for Ig versus No Ig. Based on the evidence presented, ESC agreed that Ig has uncertain effectiveness relative to no Ig in patients with SHGG unrelated to haematological malignancies or HSCT. The studies that provided comparative evidence (one RCT and two cohort studies) of Ig vs. No Ig in patients with SHGG included heart and lung transplant patients which accounts for approximately 24% of Ig use for SHGG. ESC noted that owing to the heterogeneous population and paucity of available evidence, only some of the SHGG sub-groups for which Ig therapy is subsidised, were

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[2] National Blood Authority, 2018, *Criteria for the clinical use of immunoglobulin in Australia* (version 3).

presented. No comparative evidence was identified for SHGG following B cell depletion or Good syndrome, and the lack of details of the underlying conditions for patients classified as having "Other HGG unrelated to haematological malignancies or HSCT" limited the ability to identify studies relevant to this population. ESC noted that the outcomes of interest such as infection rates, hospitalisations and survival, were not adequately presented in the studies, and overall the quality of the trials were poor (mostly small, non-randomised and with a high risk of bias).

Overall, ESC agreed that the safety of Ig is inferior to no Ig because infusion events associated with Ig therapy would not be experienced with the comparator. ESC considered Ig to be generally well tolerated, and adverse events (AEs) were usually mild and transient, with the exception of one recorded incidence of transfusion-related acute lung injury (TRALI).

ESC noted that an economic evaluation was not presented in the contracted assessment report due to there being insufficient data to inform a model. None of the studies reported quality of life (QoL) outcomes or cost data, and no further cost information or utilities were identified in the economic search. ESC considered that QoL data would be difficult to collect and that potential future models may consider cost per effect (e.g. reduced AEs, or reduced hospital admissions). ESC agreed that any economic evaluation model would require additional data but noted that since the clinical effectiveness is inconclusive, this would be based on expert opinion. Furthermore, ESC considered the lack of information associated with the "Other HGG" group to be substantial and requiring attention. ESC agreed that collection of data in this subgroup is required to understand the clinical characteristics and outcomes in this population. More knowledge of the underlying conditions in this subgroup will allow a better understanding of the treatment needs of these patients and the associated costs. In addition, characterisation of the conditions in this 'Other HGG' group should be identified, to ensure that this indication is not being used to circumvent contraindicated uses.

Regarding the financial impacts, ESC considered that the assumptions in growth (22%) applied to Ig usage in this population appeared reasonable. The total Ig product costs are projected to increase from $15.3 million in 2018-19 to approximately $41.3 million in 2023-2024. However, ESC noted that the projected costs are uncertain as it was not possible to calculate the cost offsets associated with the changes in use and costs of other medical services. ESC also noted the sensitivity analysis presented in the DCAR, which was extrapolated using recent (July 2019 to March 2020) growth rates by each subpopulation, instead of the 22% growth rate for all SHGG used in the base case. ESC noted that it is highly uncertain if the recent 61.8% growth rate observed for Ig use in SHGG following B cell depleting therapies would continue, or at what time point this would plateau, impacting these projections. The incidence of solid organ transplantation has stabilised over the last 5 years, and is unlikely to be a source of growth in demand for Ig.

ESC noted consultation feedback indicating that consumers were very supportive of Ig therapy. Perceived benefits included the prevention of life threatening infections and improvements in QoL. Disadvantages included the cost of travelling to and attending hospital for infusions, loss of work time, and other out-of-pocket expenses such as parking fees.

ESC agreed with the considerations for future research discussed in the DCAR, particularly linking of patient-level data on Ig use (from BloodSTAR) to hospitalisation, PBS, Medicare and mortality data to allow a better understanding of the healthcare use and outcomes in this population. The National Report on the Issue and Use of Immunoglobulin in 2017-18 indicated that there has been a greater than 16% increase in Ig supplied for SHGG since 2013/14, compared with an 11% increase over the same period for all medical

conditions. ESC considered that a possible reason for this higher growth could be the increasing number of B cell depleting therapies used in the treatment of non-malignant diseases which can result in hypogammaglobulinaemia, and may require patients to be treated with Ig replacement therapy. ESC considered that the current and future use of B cell depleting therapies should consider whether there are implications for the use of Ig and if these are accounted for in future projections.

15. Other significant factors

Nil

16. Applicant comments on MSAC's Public Summary Document

The National Blood Authority appreciates MSAC's recommendations and will consider and discuss with experts the suggestion of undertaking a scoping exercise to explore the feasibility of conducting further research. The NBA has previously been in contact with the MRFF to discuss the possibility of further funding for Ig research. The ability of BloodSTAR, or other sources, to capture more detailed outcomes in this group will be considered, with a view to providing a balance between the capture of enough information to inform future criteria and burden on prescribers. The NBA will also follow its existing processes to consider a requirement to provide further information in BloodSTAR for the 'other' subgroup. The NBA notes MSAC's intention to review the application again in 12 months with updated data. Prescriber compliance to the V3 Criteria will continue to be monitored through the Ig Governance Program. This review followed the transition from Version 2 to Version 3 of the Criteria for Clinical Use of Immunoglobulin in Australia. The Criteria will continue to be reviewed on both a reactive and proactive basis, based on available evidence and clinical expert advice, to ensure the supply of Ig continues for those patients who benefit from it the most. This will include thresholds for continuing use, and dosing. Furthermore, the NBA plans to continue to undertake and support research into the effectiveness and utilisation of Ig, of which these recommendations will assist to prioritise. The NBA negotiates prices of Ig through tendering processes and will continue to strive to achieve the best prices for governments within existing limitations.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website:
visit the MSAC website