Review of Immunoglobulin for Secondary Hypogammaglobulinaemia unrelated to haematological malignancies, or post-haemopoietic stem cell transplantation

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Assessment report

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The technical information in this document is used by the Medical Services Advisory Committee (MSAC) to inform its deliberations. MSAC is an independent committee which has been established to provide advice to the Minister for Health on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

MSAC's advice does not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

This report was prepared by Monash University. Clinical advice was provided by Erica Wood, Zoe McQuilten, and Alisa Higins. The report was commissioned by the Australian Government Department of Health.

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CONTENTS

TABLES

BOXES

FIGURES

EXECUTIVE SUMMARY

Main issues for MSAC consideration

- There is currently insufficient evidence to establish the clinical and cost-effectiveness of immunoglobulin G (Ig) replacement therapy (Ig-RT) in the population of secondary hypogammaglobulinaemia (HGG) unrelated to haematological malignancies, or post-haemopoietic stem cell transplantation (HSCT).

- Only three comparative studies were identified in the subpopulation of patients with secondary HGG following heart or lung transplant. There was no comparative evidence available for patients with HGG following B-cell depletion or Good Syndrome. In addition, patients classified as having "Other HGG unrelated to haematological malignancies or HSCT" in The Criteria V3 was estimated to account for 52% of Ig use for this condition in the calendar year 2019(unpublished NBA data).

- The quality of the comparative evidence was very low. Only one study (Lederer et al. 2014) with a small number of patients (n=11) was a randomised controlled trial (RCT). The other two non-randomised studies (Lichvar et al. 2018, Sarmiento et al. 2016) were at serious risk of bias due to selection bias, unbalanced baseline characteristics between the groups and lack of adjustment in their analyses.

- These studies provided insufficient information on Ig-RT (e.g. mean/median doses, initiation, duration, discontinuation), and antibiotic use was not fully described.

- One study conducted in heart transplant patients (Sarmiento et al. 2016) found significantly lower rates of severe infections in patients with secondary HGG treated with intravenous Ig (IVIG) compared to those who did not receive IVIG (25.0% vs. 76.9%), but this study was non-randomised, only included 25 patients and selection bias was a concern. There were no significant differences in any of the studies comparing Ig-RT to no Ig-RT for the other infection outcomes reported.

- There were insufficient data to develop an economic model:
    - Only very low quality evidence were available, and only for the subpopulation of patients with HGG following heart and lung transplantation, leading to a conclusion of uncertain effectiveness of Ig-RT.
    - None of the studies reported quality of life outcomes or cost data, and no further cost information or utilities were identified in the economic search.
    - There were insufficient healthcare utilisation data.

Main issues for MSAC consideration

- The lack of reliable inputs for transition probabilities and costs would result in unacceptable levels of uncertainty and any model developed may be misleading.

- It was not possible to estimate the full financial implications for Government Health Budgets due to lack of data. Only Ig product costs (excluding administration costs) could be estimated. The financial implications of Ig-RT in this population are very uncertain due to data gaps around treatment utilisation in the four HGG subpopulations, administration costs and the cost offsets associated with the reduction in infections. Of note is the recent increasing use of Ig related to B cell depletion therapy, which if this continues, may put considerable pressure on Ig budgets.

- Given the heterogeneous population and small numbers of patients in each treatment group it may be unlikely that sufficiently large randomised controlled trials will be conducted in the immediate future to inform an economic evaluation. However, studies assessing the effectiveness and cost-effectiveness of Ig use or optimising Ig use for HGG related to B cell depletion therapy may be considered if Ig use for this indication continues to grow.

- Further research may be useful in the following areas:

  - Linking patient level Ig use to hospitalisation, Medicare and mortality data is warranted to allow a better understanding of the healthcare use and outcomes for this population.
  - Analysis of patient-level data to understand Ig utilisation patterns in the separate HGG subpopulations and proportion of patients in each subpopulation using Ig.
  - Further data collection on the "Other" group to understand the clinical characteristics and outcomes in this subpopulation.
  - Observational studies and pragmatic trials in populations with HGG related to B cell depletion therapy may be of value if Ig use related to this indication continues to rise.

Secondary Hypogammaglobulinaemia unrelated to haematological malignancies, or post-haemopoietic stem cell transplantation

This contracted assessment examines the clinical effectiveness and cost-effectiveness evidence of immunoglobulin G (Ig for the treatment of Secondary Hypogammaglobulinaemia (HGG) unrelated to haematological malignancies, or post-haemopoietic stem cell transplantation (HSCT).

ALIGNMENT WITH AGREED PICO CONFIRMATION

This contracted assessment of Secondary HGG unrelated to haematological malignancies, or post-haemopoietic stem cell transplantation addresses some of the PICO[1] elements that were pre-specified in the PICO Confirmation that was ratified by the Ig Review Reference Group, which performed the function of the PICO Advisory Sub-Committee (PASC).

This application followed a fit-for-purpose pathway, in which the PICO Confirmation was presented to and approved by the Ig Review Reference Group, which was convened for the purpose of guiding the HTA reviews of Ig in Australia.

PROPOSED MEDICAL SERVICE

The intervention is Ig replacement therapy (Ig-RT), which may be given with or without antibiotics, and is currently funded by the National Blood Authority (NBA) for this indication under the National Blood Agreement. Ig products are purified from fractionated human donor plasma, formulated to contain the desired concentration of Ig as the active substance, and may be administered through intravenous (IV) or subcutaneous (SC) injection (IVIG and SCIG, respectively).

The 'Criteria for the clinical use of immunoglobulin in Australia' Version 3 (The Criteria V3) (NBA 2019a) describes the eligibility criteria that patients must meet to receive publicly-funded Ig. The current indication for Ig use is 'replacement therapy for recurrent or severe bacterial infections or disseminated enterovirus infection associated with HGG caused by a recognised disease process or B cell depletion therapy and/or immunosuppressant therapy'.

IVIG should be given at a maintenance dose of 0.4-0.6 g/kg every four weeks and SCIG at 0.1-0.15g/kg every week. Doses should be adjusted based on trough levels to achieve at least the lower limit of the age-related Ig reference range. The age-related reference range will vary between pathology laboratories. Ig for intramuscular (IM) injection is out of scope for this evaluation (NBA 2019a).

[1] Population, Intervention, Comparator, Outcomes

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

If the Ig therapy is delivered by IV infusion, patients will generally attend hospital for a day procedure to be infused by a nurse or doctor or they could receive it as an inpatient.

Patients or carers administering SCIG will require training and sufficient capability to administer the product at home. SCIG delivery also requires the appropriate infusion equipment for the product. SCIG programs are not available at all hospitals. This varies depending on the local jurisdiction's policy, and the local hospital's capacity.

Proposal for Public Funding

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 (NBA 2019a).

Population

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

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

HGG is defined as a serum Ig level <7 g/L (Florescu 2014). A susceptibility to infections may arise from acquired HGG that has diverse causes, including haematological malignancies and complications of its treatment (considered in the assessment of MSAC Application 1565 – Ig for acquired HGG related to haematological malignancy and post-HSCT).

The National Report on the Issue and Use of Immunoglobulin in 2015/2016 (NBA 2018) indicated that 4% (n=652) of patients treated with Ig in Australia were diagnosed with secondary HGG (excluding haematological malignancies). The updated 2017/2018 report indicated there has been a greater than 16% increase in Ig supplied for this indication since 2013/14, compared with an 11% increase over the same period for all medical conditions (NBA 2020c).

COMPARATOR DETAILS

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

CLINICAL MANAGEMENT ALGORITHM(S)

Ig is currently considered 'standard of care' for the population of interest. The clinical management algorithm is described in detail in Section A.5.

CLINICAL CLAIM

The proposed clinical claim is superior clinical effectiveness and safety of Ig-RT with antibiotics as required, compared to no Ig with antibiotics as required.

APPROACH TAKEN TO THE EVIDENCE ASSESSMENT

A systematic review of published literature was undertaken.

A search of medical literature was conducted on 28 November 2019 in the following electronic databases: Medline (PubMed), Embase, and Cochrane Central. No time limit was imposed. Search terms are described in Table 44 (Appendix B). Australian and international clinical trial registries were also searched. Attempts were also made to source unpublished or grey literature from published health technology assessment (HTA) agencies.

Key selection criteria in the PICO included:

- Population: Patients with secondary hypogammaglobulinaemia unrelated to haematological malignancy or HSCT
- Intervention: Ig-RT (IVIG or SCIG)
- Comparator:
    - No Ig therapy with or without antibiotics
    - If comparative studies are not identified, non-comparative evidence may be considered in this review
- Outcomes: infections, quality of life, mortality, transplant rejection rates, Ig trough levels, adverse events (AEs), healthcare utilisation (e.g. hospitalisation, ICU admission).

Additional pre-specified criteria for excluding studies included:

[2] Ig Review Reference Group Meeting 3 July 2019

- Fewer than 10 HGG patients: Non-comparative cohort studies were excluded under this criterion. These studies provided little evidence regarding clinical progression due to issues with low statistical power and thus their results may not be generalisable and are at high risk of patient selection bias. The comparative studies identified during the development of the PICO also indicated that a minimum of 10 patients were needed to evaluate the incidence of infections.
- Limited baseline and treatment data on HGG patients. These studies were excluded because it was difficult to interpret the outcomes without details of the population.
- Lack of outcome data. Studies that only included data on incidence of HGG but did not follow up HGG patients or included patient-relevant outcomes were excluded. In addition, studies with mixed cohorts where outcomes were not stratified by HGG status were excluded.
- Publication before year 2000. These studies were excluded due to significant changes in the clinical management of the underlying conditions over the last two decades, making such evidence outdated.
- Conference abstracts and posters were excluded due to the limited information provided.
- Cross-sectional studies, editorials, commentaries, narrative reviews and case reports were excluded.

A structured appraisal was performed to assess the quality of all included studies. Appraisal of the risk of bias within individual studies was done using the Cochrane risk of bias tool for cross-over trials (RoB2) [3] for the RCT (Lederer et al. 2014) included and the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I)[4] for the remaining studies (see Section **Error! Reference source not found.**). An overall appraisal of the evidence following GRADE methodology was done for the effectiveness outcomes across the three comparative studies (Appendix D Evidence Profile Tables).

CHARACTERISTICS OF THE EVIDENCE BASE

Fifteen studies were included in the clinical effectiveness review, including the following patient groups with secondary HGG:

- Lung transplant (Lederer et al. 2014; Lichvar et al. 2018; Claustre et al. 2015; Kawut et al. 2005; Noell, Dawson, and Seethamraju 2013; Shankar et al. 2013)

3 Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng H-Y, Corbett MS, Eldridge SM, Hernán MA, Hopewell S, Hróbjartsson A, Junqueira DR, Jüni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart LA, Tilling K, White IR, Whiting PF, Higgins JPT. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019; 366: l4898.

4 Current version of ROBINS-I, accessed on 6 January 2020

- Heart transplant (Sarmiento et al. 2016; Carbone et al. 2007; Carbone et al. 2012; Yamani et al. 2006)
- Intestinal transplant (Farmer et al. 2013)
- Infants undergoing cardiopulmonary bypass (CPB) (Rhodes et al. 2014)
- Rheumatoid arthritis (RA) treated with rituximab (Boleto et al. 2018)
- Good syndrome (Sun et al. 2015; Zaman et al. 2019).

Details of the studies are presented in 'Appendix C Studies included in the Systematic Review', and summaries are provided in Table 6 and Table 7, Section A.1B.4.

Only three of the studies included Ig-RT vs. no Ig-RT comparative evidence in the population of interest (Section **Error! Reference source not found.**, Table 6). These three studies included patients who developed secondary HGG after heart or lung transplantation, which is a small subpopulation within secondary HGG. Only one of these studies was a randomised controlled trial (RCT), but it had a very small number of patients (n=11) and moderate risk of bias. The two non-randomised studies were at serious risk of bias due to selection bias, unbalanced baseline characteristics between the groups and lack of adjustment in their analyses (though given their small sample sizes adjusting for baseline differences would have been difficult). Overall, these studies provided insufficient information on Ig-RT given e.g. mean/median doses, initiation, duration, discontinuation and antibiotic use was not appropriately described. Of interest, IVIG doses used in Sarmiento 2016 were lower than those recommended under The Criteria (0.4-0.6g/kg every 4 weeks); initially patients were administered two infusions of 0.2g/kg given two weeks apart, followed by up to 5 infusions of 0.3g/kg each given 4 weeks apart.

The remaining 12 studies were prospective and retrospective cohort studies that presented supportive non-comparative evidence. The aim of most of these studies was not to evaluate the effectiveness of Ig-RT in the secondary HGG population, but to compare outcomes in patients with HGG and those without HGG. The comparison of HGG to no-HGG falls beyond the scope of this review, and therefore only data from the population of interest was extracted. However, a top line summary of key outcome differences between HGG and non-HGG patients found in these studies has been included in Appendix F HGG vs No-HGG comparison for completeness.
Three cohort studies did not include a comparison group (Shankar et al. 2013; Sun et al. 2015; Zaman et al. 2019), and five studies did not mention whether or not the HGG cohort had received any Ig-RT (Kawut et al. 2005; Noell, Dawson, and Seethamraju 2013; Rhodes et al. 2014; Yamani et al. 2006; Boleto et al. 2018). The risk of bias in the non-randomised cohort studies (Table 5) was serious in most studies, and critical in studies that did not report details about Ig-RT

There was a high level of heterogeneity across the studies, with different populations, study designs, analyses, treatments, and follow-up, which prevented us from conducting a meta-analysis.

RESULTS

Safety

Three studies reporting on the safety of Ig-RT were identified in the systematic review (Lederer et al. 2014; Sarmiento et al. 2016; Shankar et al. 2013). Of them, only Lederer 2014 compared the occurrence of AEs in Ig-RT-treated and untreated patients, finding no significant differences in 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.

Overall, Ig-RT 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. Given the comparator was "no Ig-RT" and these patients would not have receive infusions, the safety of Ig-RT would be worse than the comparator due to the occurrence of infusion-related AEs

Effectiveness

The summary of key findings is shown in Table 1. There was a high level of heterogeneity across the studies in terms of populations, treatments and study designs. The risk of bias was serious in most studies and the overall quality of the available evidence was very low, which means that we are very uncertain about the effect estimate for all of the outcomes (Appendix D Evidence Profile Tables).

Only one study (Sarmiento 2016), conducted in heart transplant patients, found significantly lower rates of severe infections in patients with secondary HGG treated with IVIG compared to those who did not receive IVIG (25.0% vs. 76.9%), but this study only included 25 patients (12 in the treatment group) and selection bias was a concern. There were no significant differences in any of the studies comparing Ig-RT to no Ig-RT for the other infection outcomes reported.

There were no significant between-group differences for transplant rejection, except for a significantly lower grade 2 CLAD at 5 years in patients treated with on-demand IVIG compared to no IVIG (Lichvar et al. 2018). In the same study, 1-year, 2-year and 5-year survival was significantly worse in HGG patients treated with Ig-RT than in HGG patients who did not receive Ig-RT. However, HGG patients treated with Ig-RT had more severe HGG at baseline and underwent more bilateral lung transplants than those who did not receive Ig-RT, which could have biased survival outcomes against the Ig-RT group.

In the supportive studies, 5-year survival in another study of lung transplant recipients (Claustre et al. 2015) was higher than that reported by Lichvar 2018 (65% vs. 56.0%). Lichvar 2018 reported a longer time from transplant to Ig-RT initiation and shorter duration of Ig-RT than in Claustre 2015,

which could have also had an impact on poorer outcomes. Another cohort of lung transplant patients with HGG had a lower survival at 2 years (50%), but the study did not report any details on Ig-RT (Kawut et al. 2005).

For the outcome of 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-RT versus no Ig-RT. However, both studies included a very small number of patients and hospitalisations, limiting our confidence in any conclusions.

There were no available comparative data (Ig-RT vs. no Ig-RT) for patients with HGG following B-cell depletion.

Table 1 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	⊕⊙⊙⊙

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)
			56.0	67.2	11.2	P=0.006	5y	⨁⊙⊙⊙
Mortality rate								
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	⨁⊙⊙⊙

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.

On the basis of the evidence profile (summarised in Appendix D), it is suggested that, relative to no Ig-RT in patients with secondary HGG unrelated to haematological malignancies or HSCT, Ig-RT has inferior safety (though generally well tolerated with transient infusion-related AE and rare SAE) and uncertain effectiveness.

TRANSLATION ISSUES

There were some key issues that limit the translation of the evidence presented in Section B to the economic evaluation:

- Only three studies of patients with HGG following solid organ transplantation, two lung transplants studies (Lederer et al. 2014; Lichvar et al. 2018) and one heart transplant study (Sarmiento et al. 2016), included comparative data of patients treated with Ig-RT vs. no Ig-RT. This is a very specific subpopulation of patients with secondary HGG and clinical outcomes from these studies are not generalisable to the wider population of patients with secondary HGG excluding haematological malignancies or HSCT, in particular given their high risk of infection, transplant rejection and mortality. In addition, these studies were at very high risk of bias and our confidence in the effect estimates was very low.

- There is not enough available evidence that could be used to inform an economic evaluation for patients with HGG following B-cell depletion or Good Syndrome. In addition, patients in the group of "Other HGG unrelated to haematological malignancies or HSCT" was estimated to account for 52% of Ig use in Australia in 2018-19 according to NBA data(NBA 2020a), and given the lack of details on the underlying conditions it is not possible to know the effectiveness and cost-effectiveness of Ig-RT in this HGG subpopulation.

- None of the studies included in Section B reported QoL data.

- The data from the three studies that compared Ig-RT to no Ig-RT in solid organ transplant patients (Sarmiento et al. 2016; Lederer et al. 2014; Lichvar et al. 2018) could be potentially used in the model, but Ig-RT use in these trials may be lower than the utilisation recommended in the Australian setting. The total number of doses in Lederer 2014 and Sarmiento 2016 were three and up to seven, respectively, while Lichvar 2018 reported a median of only two doses. No other utilisation data was found in the studies for patients with HGG following B-cell depletion or Good Syndrome.

- None of these studies (Sarmiento et al. 2016; Lederer et al. 2014; Lichvar et al. 2018) reported cost data. There was limited data on hospitalisations and length of hospital stay, and no data on the impact of infections on healthcare utilisation. BloodSTAR Ig utilisation data from 2017-18 and 2018-19 (NBA 2020a) was provided by the NBA and is presented in Section D and Section E.

ECONOMIC EVALUATION

There were insufficient data to develop an economic model. For most HGG subpopulations there were no usable data, and only very low-quality evidence was available for patients with HGG following heart and lung transplantation, leading to a conclusion of uncertain effectiveness of Ig-RT. No studies reported quality of life outcomes or cost data, and no further cost information or utilities were identified in the economic search for this population.

The Ig Review Reference Group agreed at the 25 March 2020 meeting that the results of any economic modelling would have limited applicability to the population of interest, would be highly uncertain and may be misleading. Further research is needed to inform an economic model to evaluate the value of Ig-RT in this population. Potential areas for research or collection of data are suggested under "Other Relevant Considerations".

ESTIMATED EXTENT OF USE AND FINANCIAL IMPLICATIONS

It was not possible to estimate the financial implications for Government Health Budgets due to lack of data. There was very limited evidence on the number of hospitalisations due to infections (see Section C and Section D) and no other health care resource utilisation data. There were no data available to calculate the cost offsets associated with a potential reduction in infections or transplant rejection.

Ig utilisation and cost data provided by the NBA (NBA 2020a) were used to estimate Ig projected costs (excluding administration costs) for the treatment of secondary HGG unrelated to haematological malignancies or HSCT (Table 2). As recommended by the Applicant and agreed with the Ig Review Reference 'Group, the base case Ig cost used were $60.41 per gram. This cost was provided by the Applicant 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. In addition, a recommended weighted average Ig cost across all indications was estimated to be $94.51 per gram and a highest $140.18 (maximum, i.e. domestic IVIg, including the cost of plasma fractionation) and lowest $44.94 (minimum, i.e. imported IVIg) cost per gram which was used to consider the implications of alternative Ig prices (NBA 2020c). For the base case, over the five years (2019-2020 to 2023-2024), the projected costs of Ig in this population are estimated to be $144,245,943.

Table 2 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

Assumed cost/gram	2018 - 2019[a]	2019 - 2020	2020-2021	2021 - 2022	2022 - 2023	2023 - 2024
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: (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 of 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.

A series of assumptions were made due to the lack of data:

- Ig (grams issued) average growth rate of 22% was applied to the 2018/19 estimates, this was similar to the growth rates observed both prior to and after the transition to Criteria V3 of Ig use. This is highly uncertain as over the last nine months, growth rates in Ig use by subgroups differed greatly.

- There were limited data available to establish robust trends in use for the different subpopulations of patients with HGG but if recent trends over the last 9 months continue the B cell depletion therapy subgroup will become a population using a significant amount of Ig in the future and thus impose a large future financial burden.

- It was not possible to estimate administration costs in our population due to the lack of data on treatment duration and treatment cycles per patient. The estimated cost per infusion used in the assessment MSAC 1565 (secondary HGG following haematological malignancies) was $253.42, estimated from Windegger 2019. The dataset only reported number of treatment episodes for the full secondary HGG (excl. haematological malignancies) population, but we do not know the number of infusions per patient for IVIG and SCIG.

- In addition, treatment patterns may differ in each of the four subpopulations included (e.g. patients undergoing solid organ transplantation might only receive with Ig-RT for a more limited period of time than those with Good syndrome or B-cell depletion therapy). The subgroup of patients classified as “Other” by the Criteria 3 had the highest use of Ig in the population of secondary HGG excluding haematological malignancies. The lack of knowledge of the underlying conditions in this patient subgroup prevent us from estimating their treatment needs and thus developing financial estimates in this population.

CONSUMER IMPACT SUMMARY

The draft Referral was released for targeted consultation in August 2019 to a range of stakeholders suggested by the Applicant which included clinicians, consumer groups and sponsors of immunoglobulin. In December 2019, the PICO Confirmation was released to sponsors of immunoglobulin who were invited to provide any relevant input to the development of the contracted assessment. A total of four responses were received from clinical groups (1), consumer groups (1) and sponsor companies (2).

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.

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).

One sponsor noted that while it is preferable to correct or remove the underlying cause of secondary HGG, this is not always possible and Ig therapy may be required. The sponsor also noted that due to the heterogeneity of subgroups under this indication, it may be difficult to describe the appropriate comparator/s.

OTHER RELEVANT CONSIDERATIONS

Further research may be useful in the following areas:

- Linking patient level Ig use to hospitalisation, Medicare and mortality data is warranted to allow a better understanding of the healthcare use and outcomes for this population.
- Analysis of patient-level data to understand Ig utilisation patterns in the separate HGG subpopulations and proportion of patients in each subpopulation using Ig.
- Data collection on the “Other” group to understand the clinical characteristics and outcomes in this subpopulation.

ACRONYMS AND ABBREVIATIONS

Acronym/abbreviation	Meaning
AE	Adverse event
ARTG	Australian Register of Therapeutic Goods
CI	Confidence interval
CLAD	Chronic lung allograft dysfunction
CMV	Cytomegalovirus
CUA	Cost utility analysis
HSCT	Haemopoietic stem cell transplant
HTA	Health technology assessment
Ig	Immunoglobulin G
Ig-RT	Immunoglobulin G replacement therapy
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IQR	Interquartile range
IVIG	Intravenous immunoglobulin G
MBS	Medicare Benefits Schedule
MSAC	Medical Services Advisory Committee
NBA	National Blood Authority
OR	Odds ratio
PASC	PICO Confirmation Advisory Sub-Committee of the MSAC
QALY	Quality adjusted life year
QoL	Quality of life
RA	Rheumatoid arthritis
RCT	Randomised controlled trial
RD	Risk difference
RR	Relative risk
SAE	Severe adverse event
SCIG	Subcutaneous immunoglobulin G
SD	Standard deviation
TGA	Therapeutic Goods Administration
TRALI	Transfusion-related acute lung injury
VAD	Ventricular assist device

SECTION A CONTEXT

This contracted assessment of immunoglobulin G replacement therapy (Ig-RT) for the treatment of secondary hypogammaglobulinaemia (HGG) unrelated to haematological malignancies, or post-haemopoietic stem cell transplantation (HSCT) is intended for the Medical Services Advisory Committee (MSAC). MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Schedule (MBS) in terms of their safety, effectiveness and cost-effectiveness, while considering other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

Ig-RT for this indication is currently funded by the National Blood Authority (NBA) under the national blood supply arrangements, but the cost-effectiveness of this use has not previously been established. As of 2017, 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 (JBC). All Australian Governments, through the JBC, have agreed to conduct robust Health Technology Assessments of immunoglobulin use (Ig Reviews) funded under the National Blood Agreement. The Department of Health has convened an Immunoglobulin Review Reference Group to provide advice to the Ig Reviews. The Population, Intervention, Comparator, Outcome (PICO) Confirmations for these products are being considered by the Ig Review 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).

Monash University has been commissioned by the Australian Government Department of Health to conduct a systematic literature review and economic evaluation of Ig-RT for the treatment of secondary HGG unrelated to haematological malignancies or HSCT. This assessment has been undertaken in order to inform MSAC's advice to the JBC regarding the clinical safety, effectiveness and cost-effectiveness of Ig-RT for this indication. This contracted assessment complements the NBA Immunoglobulin Governance Program, which aims to strengthen clinical governance and authorisation of government-funded Ig in Australia.

Appendix A1 Clinical Experts and Assessment Group provides a list of the people involved in the development of this assessment report, including clinical expertise.

The criteria for evaluation of Ig-RT as it is currently funded for this indication in Australia were outlined in a PICO Confirmation that was discussed at the Ig Review Reference Group meeting on 13 November 2019 and ratified on 11 December 2019.

A.1. ITEMS IN THE AGREED PICO CONFIRMATION

This contracted assessment of Ig-RT for secondary HGG unrelated to haematological malignancies or HSCT addresses some of the PICO elements that were pre-specified in the PICO Confirmation that was ratified by the Ig Review Reference Group. Proposed Medical Service

The intervention is Ig-RT, which may be given with or without antibiotics, and is currently considered 'standard of care' for the population of interest.

Immunoglobulin G (Ig) products are purified from fractionated human donor plasma, formulated to contain the desired concentration of Ig as the active substance, and may be administered through intravenous (IV) or subcutaneous (SC) injection (IVIG and SCIG, respectively). According to the 'Criteria for the clinical use of immunoglobulin in Australia' Version 3 (Criteria V3) (NBA 2019a), for this indication IVIG should be given at a maintenance dose of 0.4-0.6 g/kg every four weeks and SCIG at 0.1-0.15g/kg every week. Doses should be adjusted based on trough levels to achieve at least the lower limit of the age-related Ig reference range. The age-related reference range will vary between pathology laboratories. Ig for intramuscular (IM) injection is out of scope for this evaluation (NBA 2019a).

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

If the Ig therapy is delivered by IV infusion, patients will generally attend hospital for a day procedure to be infused by a nurse or doctor.

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

MARKETING STATUS OF TECHNOLOGY

All therapeutic products marketed in Australia require listing on the Australian Register of Therapeutic Goods (ARTG). A list of all Ig products currently approved in Australia by the Therapeutic Goods Administration (TGA) and registered on the ARTG is presented in Table 3. 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 3 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

Product name	Sponsor	Route of Administration	Strength	*NBA Funded
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

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.

OTHER INDICATIONS

Government-funded use of Ig is currently supported for a range of conditions as in indicated in the Criteria V3. The conditions are classified by the therapeutic role of Ig as 'established', 'emerging' or 'only in exceptional circumstances' (NBA 2019a).

CURRENT FUNDING ARRANGEMENTS

Public funding for Ig for this indication is currently available under the National Blood Agreement. The Criteria V3 (NBA 2019a) describes the eligibility criteria that patients must meet to receive publicly-funded Ig. The Criteria helps to ensure that Ig is able to be accessed consistently across Australia for the treatment of patients whose health is likely to be improved with Ig therapy (NBA 2018).

INTERNATIONAL COMPARISONS GUIDING THE USE OF IG IN SECONDARY HGG

Guidelines on the use of Ig for secondary HGG excluding haematological malignancies and HSCT were searched in countries with similar health systems to Australia; mainly, the UK and Canada (Alberta Ministry of Health 2018; NHS England 2018; NHS Scotland 2012; British Columbia Provincial Blood Coordinating Office 2019; Nova Scotia Provincial Blood Coordinating Team 2018; Ontario Regional Blood Coordinating Network 2018). Overall, these recommendations are largely based on expert opinion, given the paucity of evidence in this population. Table 42 in Appendix A2 provides a summary of how recommendations in these countries compared to those in Australia.

Recommendations in most of the selected countries do not differentiate by underlying condition in secondary HGG (excluding haematological malignancies), while some (Alberta, Manitoba, Satskachewan and Ontario in Canada) have separate recommendations for HGG following solid organ transplantation.

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, they are required to record the number of infections and days in hospital pre-treatment and 6-monthly thereafter. New Zealand follows the indications and dosage of each approved Ig product, but there are no overall criteria for Ig use (New Zealand Blood Service 2016).

A.2. PROPOSAL FOR PUBLIC FUNDING

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.

A.3. PROPOSED POPULATION

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

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

Figure 1 presents the proportional use of Ig-RT in Australia stratified by the underlying cause of secondary HGG unrelated to haematological malignancies or HSCT. 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.

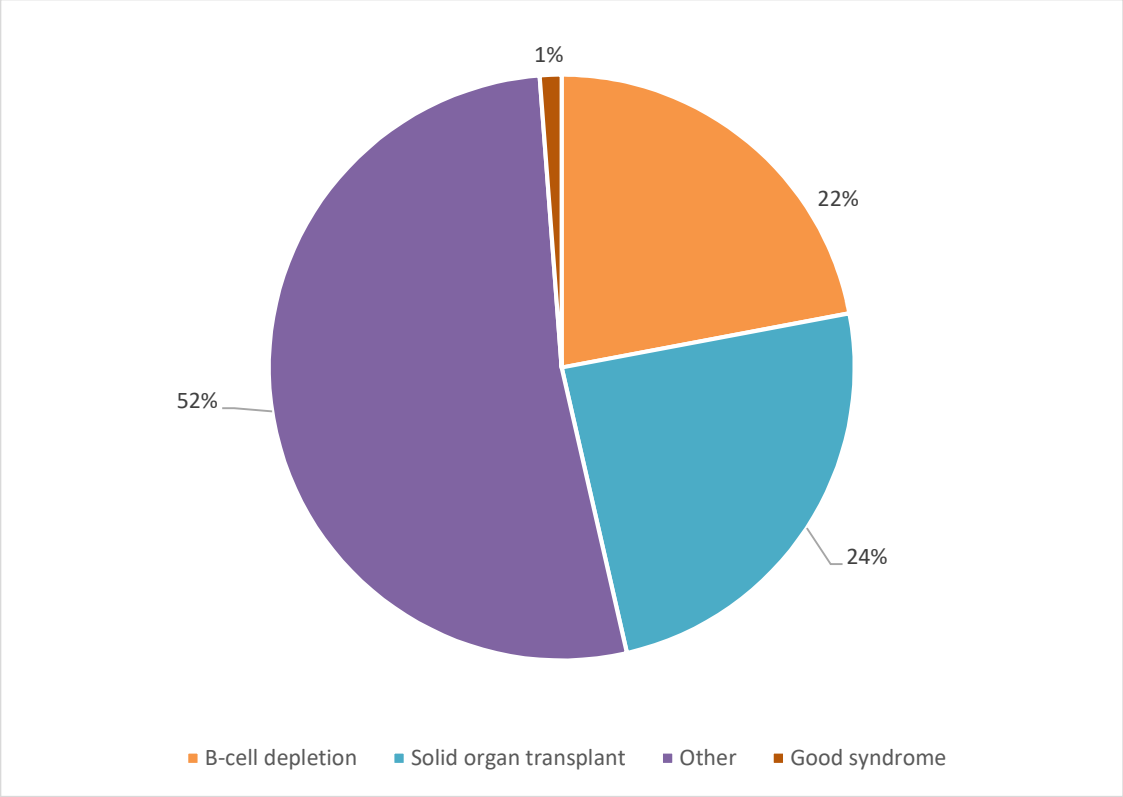

Figure 1 Ig-RT use in secondary HGG unrelated to haematological malignancies or HSCT
Source: NBA unpublished data on Ig-RT use

HGG is defined as a serum Ig level <7 g/L (Florescu 2014). An abnormal susceptibility to bacterial infections may arise from acquired HGG that has diverse causes, including haematological malignancies and complications of its treatment (considered in the assessment of MSAC Application 1565 – Ig for acquired HGG related to haematological malignancy and post-HSCT); protein losing states; malnutrition; thymoma; immunosuppressant therapy; and repeated cycles of B-cell depletion therapy (e.g. rituximab), especially when used with immunosuppressant therapy and in children.

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

The prevalence of HGG in the overall underlying medical conditions varies dependent on the cause. The wider use of therapies for autoimmune, inflammatory and malignant disease, especially those targeting B cells, is leading to an increase in secondary antibody deficiency (Patel, Carbone, and Jolles 2019). The incidence of HGG in patients with thymoma is 6-11% (Kelesidis and Yang 2010). Approximately 15% of patients who have received a solid organ (heart, lung, kidney) transplant experience secondary HGG with severe Ig deficiency (<4g/L) during the first year after transplantation (Florescu 2014).

The 'National Report on the Issue and Use of Immunoglobulin (Ig) in 2015/2016' (NBA 2018) indicated that 4% (n=652) of patients treated with Ig in Australia were diagnosed with secondary HGG (excluding haematological malignancies). The updated 2017/2018 report indicated there has

been a greater than 16% increase in Ig issued for this indication since 2013/14, compared with an 11% increase over the same period for all medical conditions (NBA 2020c).

This indication falls into the top 10 diagnostic groups treated with Ig (Figure 2).

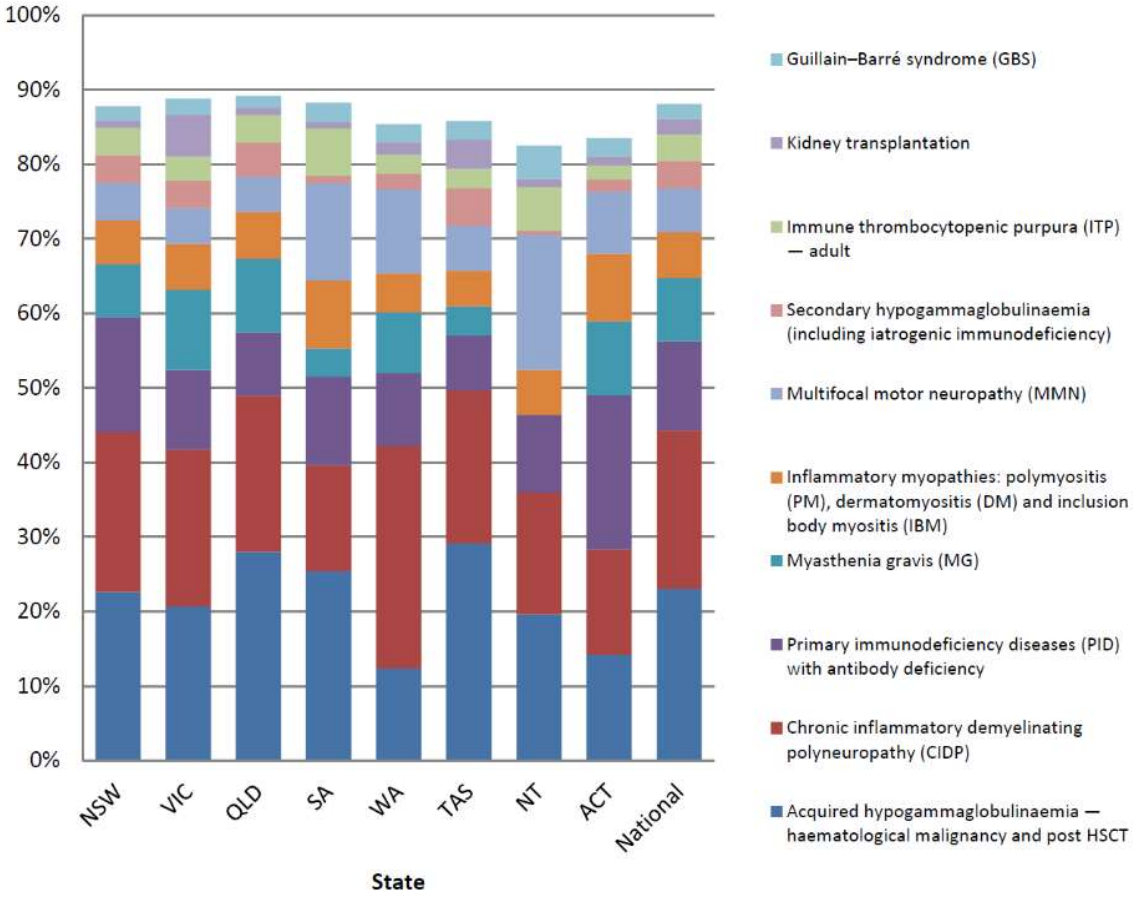

Figure 2 Proportion of Ig used in the top 10 diagnostic groups
Source: National report on the issue and use of Immunoglobulin (Ig). Annual Report 2017-18 (NBA 2020c).

A.4. COMPARATOR DETAILS

The Ig Review Reference Group[5] agreed that, given the heterogeneous patient group, 'no Ig' should be the comparator to Ig therapy for secondary HGG. Best practice standard of care for certain specific conditions may or may not include antibiotic treatment, prophylactic antibiotics or thymectomy.

[5] Ig Review Reference Group Meeting 3 July 2019

A.5. CLINICAL MANAGEMENT ALGORITHM(S)

Figure 3 and Figure 4 present the initial and continuing treatment algorithms as indicated in the Criteria V3 (NBA 2019a).

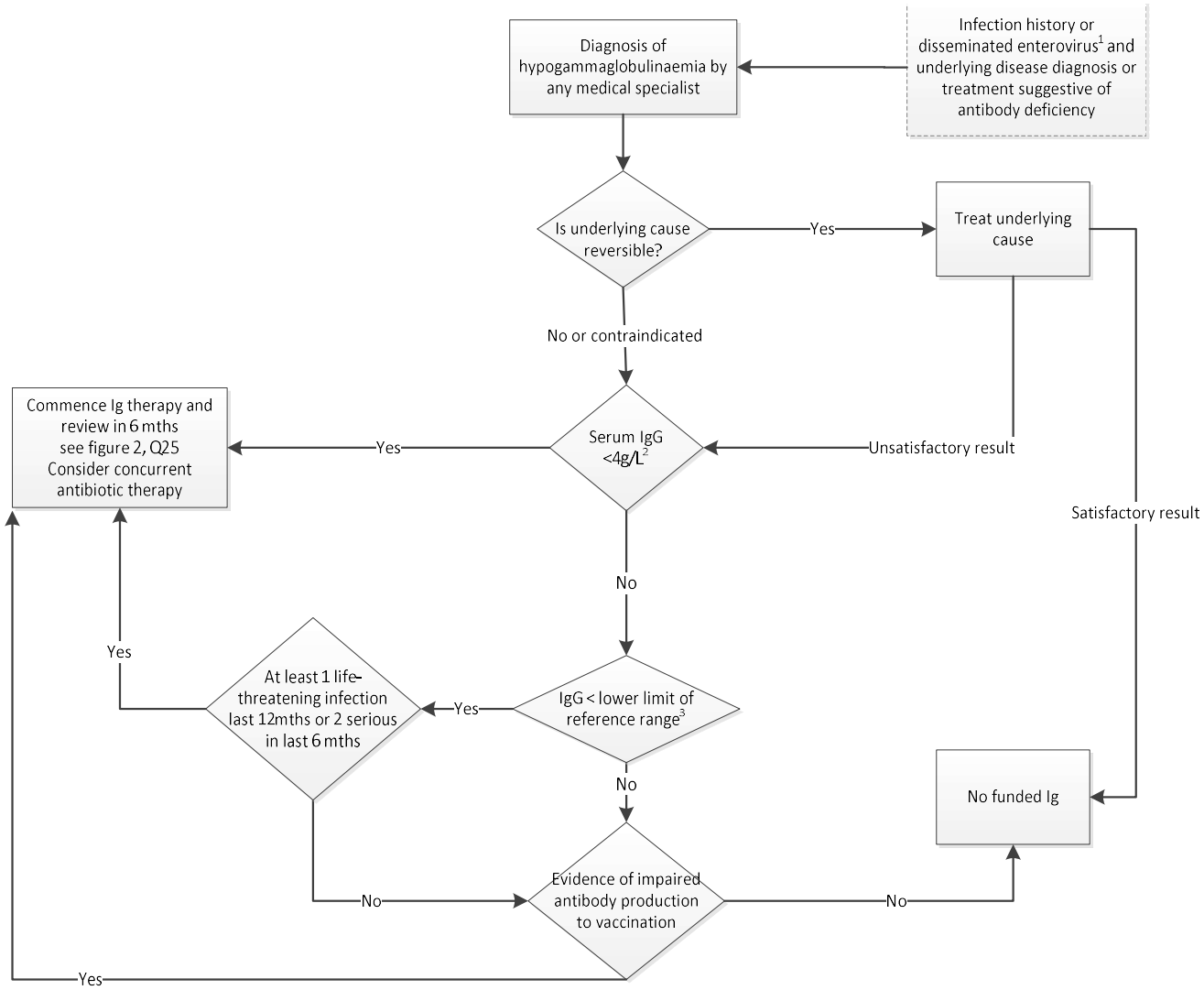

Figure 3 Initial access to Ig for secondary HGG unrelated to haematological malignancies or HSCT, funded under the National Blood Agreement

[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: Ratified PICO 1591

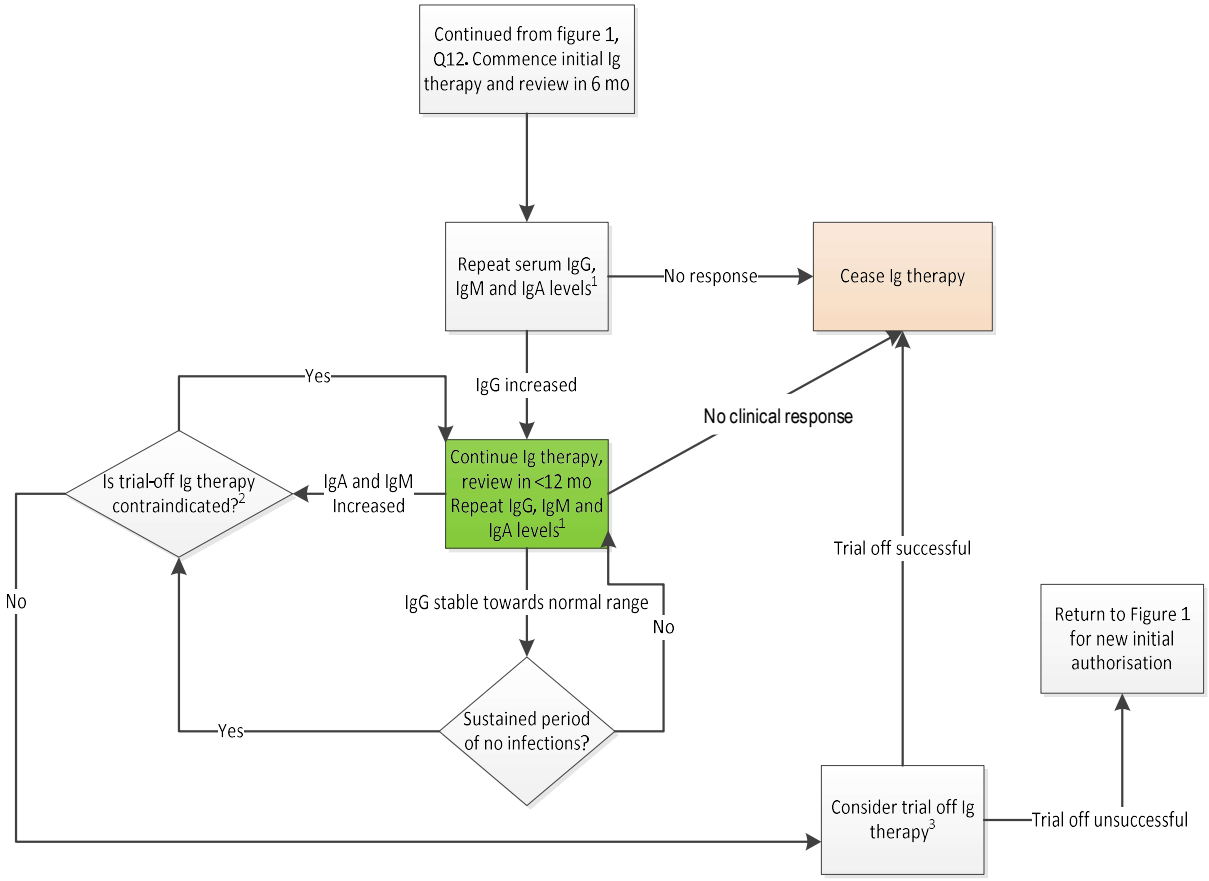

Figure 4 Continuing access to Ig for secondary HGG unrelated to haematological malignancies or HSCT, funded under the National Blood Agreement

[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: Ratified PICO 1591

A.6. CLINICAL CLAIM

The Applicant proposed clinical claim, as specified in the PICO, is superior clinical effectiveness and safety of Ig-RT with antibiotics as required, compared to no Ig with antibiotics as required.

A.7. SUMMARY OF THE PICO

The guiding framework of a PICO Confirmation is recommended by MSAC for each assessment. The PICO Confirmation describes current clinical practice and reflects the likely future practice with the proposed medical service.

The PICO that were pre-specified to guide the systematic literature review are presented in Box 1 and Box 2.

Box 1 Criteria for identifying and selecting studies to determine the safety of Ig-RT in patients with secondary HGG unrelated to haematological malignancies or HSCT

Selection criteria	Description
Population	Patients with secondary hypogammaglobulinaemia unrelated to haematological malignancy or haemopoietic stem cell transplant (HSCT)
Intervention	Ig-RT (IVIG or SCIG)
Comparator	Step 1: No Ig therapy with or without antibiotics Step 2: if high quality comparative studies are not identified, lower quality non-comparative evidence may be considered in this review
Outcomes	• Adverse events (AEs), including hypersensitivity reactions, anaphylaxis, veno-occlusive events • Antibiotic resistance
Systematic review question	What is the safety of Ig-RT in patients with secondary HGG unrelated to haematological malignancies or HSCT?

Box 2 Criteria for identifying and selecting studies to determine the safety of Ig-RT in patients with secondary HGG unrelated to haematological malignancies or HSCT

Selection criteria	Description
Population	Patients with secondary hypogammaglobulinaemia unrelated to haematological malignancy or haemopoietic stem cell transplant (HSCT)
Intervention	Ig-RT (IVIG or SCIG)
Comparator	Step 1: No Ig therapy with or without antibiotics Step 2: if high quality comparative studies are not identified, lower quality non-comparative evidence may be considered in this review
Outcomes	Clinical effectiveness outcomes: • Infections • Quality of life • Mortality • Transplant rejection rates • Ig trough levels Healthcare system resource utilisation: • Ig products • Antibiotic use • Infusion equipment, • Administrative and clinician time • 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
Systematic review question	Is Ig-RT effective in the treatment of secondary HGG unrelated to haematological malignancies or HSCT?

A.8. CONSUMER IMPACT STATEMENT

The draft Referral was released for targeted consultation in August 2019 to a range of stakeholders suggested by the Applicant which included clinicians, consumer groups and sponsors of immunoglobulin. In December 2019, the PICO Confirmation was released to sponsors of immunoglobulin who were invited to provide any relevant input to the development of the

contracted assessment. A total of four responses were received from clinical groups (1), consumer groups (1) and sponsor companies (2).

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.

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).

One sponsor noted that while it is preferable to correct or remove the underlying cause of secondary HGG, this is not always possible and Ig therapy may be required. The sponsor also noted that due to the heterogeneity of subgroups under this indication, it may be difficult to describe the appropriate comparator/s.

SECTION B CLINICAL EVALUATION

The systematic search conducted during the PICO development identified only three small studies comparing Ig-RT vs no Ig-RT in specific subpopulations of patients within the wider population with secondary HGG excluding haematological malignancies (hereafter referred to as "secondary HGG" for simplicity). As a result, the Ig Review Reference Group suggested a pragmatic stepped approach to review weaker forms of evidence such as non-comparative evidence in this population. The PICO was widened to include non-comparative cohort studies and single arm studies in the population of interest to provide more context on the natural history of the disease, in addition to the three comparative studies identified. Only higher quality non-comparative studies were included as supportive evidence.

B.1. LITERATURE SOURCES AND SEARCH STRATEGIES

The medical literature was searched on 28 November 2019 to identify relevant studies with no date limits. Searches were conducted of the databases, Australian and international clinical trial registries, and other sources described in

Appendix A2 International comparisons Ig use

Table 42 International comparisons Ig use recommendations

	Australia1	England3	Scotland4	Atlantic Provinces (Canada)[5]	Alberta, Manitoba, Satskachewan (Canada)[6]	British Columbia (Canada)[7]	Ontario (Canada)
Condition Indication	Secondary HGG unrelated to Haematological malignancy or haematopoietic stem cell transplant (HSCT) Indication for Ig Use: Replacement therapy for recurrent or severe bacterial infections or disseminated enterovirus infection associated with HGG caused by a recognised disease process or B cell depletion therapy and/or immunosuppressant therapy. Specific Conditions: HGG following Solid organ transplantation HGG following B cell depletion therapy Thymoma-associated HGG (Good Syndrome) Other HGG unrelated to haematological malignancies or HSCT	Secondary antibody deficiency – long term use	Secondary antibody deficiency (any cause)	Secondary Immunodeficiency	HGG, secondary: Ig replacement is recommended for preventing recurrent, severe infection due to HGG (excl paraprotein) related to other diseases or medical therapy Separate recommendations for: - Acquired HGG secondary to haematological malignancies (incl. HSCT) - Kidney, active antibody-mediated rejection (ABMR) prevention and management - Solid organ (other than kidney) ABMR (see Table below for further details on solid organ transplantation)	Secondary immune deficiency	Secondary immune deficiency Separate recommendations for solid organ transplantation: - Kidney transplant from living donor to whom the patient is sensitized - Pre-transplant (heart) - Peri-transplant (heart, lung, kidney, pancreas) - Post-transplant (see Table below for further details on solid organ transplantation)
Criteria	A diagnosis must be made by any specialist. Serum IgG to be measured on two separate occasions (at least one hour apart and at least one sample taken when the patient does not have an active infection). Baseline serum levels of IgA and IgM should be provided to allow assessment of immune recovery at review. Significant HGG with serum IgG less than 4g/L (excluding paraprotein) regardless of the frequency and severity of infections; OR Serum IgG (excluding paraprotein) greater than 4g/L but less than the lower limit of the age-related reference range and at least one life-threatening infection in the last 12 months; OR Serum IgG (excluding paraprotein) greater than 4g/L but less the lower limit of the age-related reference range with at least two serious infections in the last six months requiring more than standard courses of	Underlying cause of HGG cannot be reversed or reversal is contraindicated; OR HGG associated with drugs, therapeutic monoclonals targeted at B cells and plasma cells (rituximab and other anti-CD20,CD19 agents, daratumumab etc) post-HSCT, NHL, CLL, MM or other relevant B-cell malignancy confirmed by haematologist; AND Recurrent or severe bacterial infection despite continuous oral antibiotic therapy for 6 months IgG < 4g/L (excl paraprotein) Documented failure of serum antibody response to unconjugated pneumococcal	Underlying cause of HGG cannot be reversed or reversal is contraindicated; OR HGG associated with NHL, CLL, MM or other relevant B-cell malignancy confirmed by haematologist; AND Recurrent or severe bacterial infection despite continuous oral antibiotic therapy for 3 months IgG < 5 g/L (excl paraprotein) Documented failure of serum antibody response to unconjugated	Adult: Patient has/had recent life threatening or recurrent clinically significant infection(s) related to low levels of polyclonal immunoglobulin Paediatric: Order must be in consultation with an Immunologist	HGG secondary to underlying disease or medical therapy (incl HCST) with all of the following: Serum IgG less than the lower limit of the reference range on two separate occasions; AND At least one of the following: One invasive or life-threatening bacterial infection (e.g., pneumonia, meningitis, sepsis) in the previous year; Recurrent, severe bacterial infections; Clinically active bronchiectasis confirmed by radiology; Assessment by a physician specializing in immunodeficiency indicating a significant antibody defect that would benefit from Ig replacement.	HGG (reduced total IgG or IgG subclasses) with recurrent bacterial infection Monitor IgG trough level as appropriate to achieve desired clinical outcome	Hypogammaglobulinemia (reduced total IgG or IgG subclasses) with recurrent bacterial infection

	Australia1	England3	Scotland4	Atlantic Provinces (Canada)[5]	Alberta, Manitoba, Satskachewan (Canada)[6]	British Columbia (Canada)[7]	Ontario (Canada)
	antibiotics (e.g. Hospitalisation, intravenous or prolonged antibiotic therapy); OR Evidence of impaired antibody production to vaccination in the context of persistent infections affecting long term function such as persistent purulent suppurative otitis media threatening long term hearing; AND Underlying cause of HGG cannot be reversed; OR Underlying cause of HGG is reversible but reversal is contraindicated A diagnosis of bronchiectasis and/or suppurative lung disease must be consistent with the Thoracic Society of Australia and New Zealand (Chang AB et al. 2014). Initial review is required within six months and ongoing reviews by a specialist at least annually to assess clinical benefit. Documentation of clinical effectiveness is necessary for continuation of Ig therapy. Cessation of Ig therapy should be considered at least after each 12 months of treatment. If serum IgM and IgA levels are trending upwards and near normal, this may suggest recovery of the immune system and a trial might be considered if the patient is well. Once the patient has normal IgA and IgM levels, the IgG is also likely to be normal and a trial off Ig therapy may be undertaken. Ig therapy should be extended as required to enable cessation of therapy in September/October, with repeat clinical and/or immunological evaluation before recommencement of therapy.	or other polysaccharide vaccine challenge In these circumstances vaccine challenge may be omitted if it is considered inappropriate clinically. It is acknowledged that not all of the above criteria will need to be fulfilled for an individual patient. In patients developing HGG associated with B-cell aplasia as a consequence of Chimeric Antigen Receptor – T cell therapy (CAR-T cells) targeted against B cell antigens, the prophylactic use of Ig in the absence of a burden of severe infections and vaccine challenge may be appropriate. There is controversy regarding Ig replacement in adult patients with HGG post-HSCT for haematological malignancy. The American Society for Blood and Marrow transplantation and the Canadian Blood and Marrow Transplant group have recently stated as follows: Don't routinely give Ig replacement to adult HSCT recipients in the absence of recurrent infections regardless of the IgG level (Bhella et al. Choosing Wisely BMT. Biol Blood Marrow Transplant 2018;24:909-13)	pneumococcal or other polysaccharide vaccine challenge				
Dosing	The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.	0.4-0.6g/kg/month modified to achieve an IgG trough level of at least the lower limit of the	0.4 g/kg/month modified to achieve an IgG trough level of at least the lower limit	Adult: 0.4-0.6 g/kg every 4 weeks	Aim to use the dose that achieves a significant reduction in the number of bacterial infections.	Adult: 0.4-0.6 g/kg every 3-4 weeks Paediatric: 0.3-0.6 g/kg every 4 weeks	Adult: 0.4-0 .6 g/kg every 3-4 weeks Paediatric: 0.3-0 .6 g/kg every 3-4 weeks

	Australia1	England3	Scotland4	Atlantic Provinces (Canada)[5]	Alberta, Manitoba, Satskachewan (Canada)[6]	British Columbia (Canada)[7]	Ontario (Canada)
	Loading Dose (IVIG) - One loading dose of 0.4 g/kg in the first month of therapy (in addition to the maintenance dose) is permitted if the serum IgG level is <4 g/L. Disseminated Enterovirus Dose (IVIg) - One dose of 2g/kg at any stage is permitted (in addition to the maintenance dose) in the management of disseminated enterovirus infection. Maintenance Dose (IVIg) - 0.4–0.6g/kg every four weeks or more frequently, to achieve IgG trough level of at least the lower limit of the age-specific serum IgG reference range. More frequent dosing to achieve IgG trough level of up to 9 g/L is permitted if chronic suppurative lung disease is not adequately controlled at an IgG trough level at the lower limit of the age-specific serum IgG reference range. A total dose of up to 1 g/kg may be given over any 4-week period. Supplementary Dose (IVIg) - One additional dose of 0.4 g/kg is permitted at any stage (in addition to the maintenance dose) if the serum IgG level is <4 g/L. Loading Dose (SCIg) - One loading dose of 0.4 g/kg in the first month of therapy (in addition to the maintenance dose) is permitted if the serum IgG level is <4 g/L. Disseminated Enterovirus Dose (SCIg) - One dose of 2g/kg at any stage is permitted (in addition to the maintenance dose) in the management of disseminated enterovirus infection. Maintenance Dose (SCIg) - 0.1-0.15g/kg every week or more frequently, to achieve IgG trough level of at least the lower limit of the age-specific serum IgG reference range. More frequent dosing to achieve IgG trough level of up to 9 g/L is permitted if chronic suppurative lung disease is not adequately controlled at an IgG trough level at the lower limit of the age-specific serum IgG reference range. A	age-specific serum IgG reference range	of the age-specific serum IgG reference range	Paediatric: 0.3-0.6 g/kg every 4 weeks	Maintenance: 0.4 to 0.6 g/kg adjusted body weight IVIg every 4 weeks, or SCIg 0.1 to 0.5 g/kg adjusted body weight weekly, modified to achieve an IgG trough level of at least the lower limit of the age-specific serum IgG reference range, or as needed to achieve clinical effectiveness. Loading: One additional dose of 0.4 g/kg adjusted body weight may be given in the first month of therapy if the serum IgG level is markedly reduced. Chronic suppurative lung disease: 0.4 to 0.8 g/kg adjusted body weight IVIg or equivalent SCIg dose may be given if chronic suppurative lung disease is not adequately controlled at an IgG trough level at the lower limit of the age-specific serum IgG reference range.		Doses or frequency to be adjusted by experts according to desired trough level (more than 500 mg/dL and ideally 700 mg/dL) and according to individual patient clinical needs.

	Australia1	England3	Scotland4	Atlantic Provinces (Canada)[5]	Alberta, Manitoba, Satskachewan (Canada)[6]	British Columbia (Canada)[7]	Ontario (Canada)
	total dose of up to 1 g/kg may be given over any 4-week period. Supplementary Dose (SCIg) - One additional dose of 0.4 g/kg is permitted at any stage (in addition to the maintenance dose) if the serum IgG level is <4 g/L.						
Review / Clinical Outcome Measures	Initial review is required within six months and ongoing reviews by a specialist at least annually to assess clinical benefit. Documentation of clinical effectiveness is necessary for continuation of Ig therapy. Cessation of Ig therapy should be considered at least after each 12 months of treatment. If serum IgM and IgA levels are trending upwards and near normal, this may suggest recovery of the immune system and a trial might be considered if the patient is well. Once the patient has normal IgA and IgM levels, the IgG is also likely to be normal and a trial off Ig therapy may be undertaken. Ig therapy should be extended as required to enable cessation of therapy in September/October, with repeat clinical and/or immunological evaluation before recommencement of therapy On review of the initial authorisation period: Monitoring of serum immunoglobulin levels (IgG, IgM and IgA) and infection history; AND There should be regular consideration of a trial period of cessation of Ig for the purposes of immunological evaluation unless medically contraindicated on safety grounds (for example active bronchiectasis and/or suppurative lung disease, neutropenia, or ongoing immunosuppressant medication) or where there is persistence of the underlying condition that would result in severe HGG in the absence of Ig replacement therapy. Trial cessation is best commenced in September or October. When IgA and IgM are trending upwards and close to normal and the patient is well, a trial	Reduction in number of infections and days in hospital (Database parameters will include entry of number of infections and days in hospital pre-treatment and 6 monthly thereafter)	Reduction in number of infections and days in hospital. Database parameters will include entry of number of infections and days in hospital pre-treatment and 6 monthly thereafter.	n/a	Continued use of Ig should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of treatment and at least annually thereafter by a physician specializing in immunodeficiency disorders. If clinical effectiveness has not been achieved, Ig treatment should be discontinued. Cessation of Ig treatment may be possible depending on the status of the underlying disease.	n/a	n/a

	Australia1	England3	Scotland4	Atlantic Provinces (Canada)[5]	Alberta, Manitoba, Satskachewan (Canada)[6]	British Columbia (Canada)[7]	Ontario (Canada)
	off therapy (in September or October) is considered to allow immunological re-evaluation, or is unless medically contraindicated. On review of a continuing authorisation period: Monitoring of trough or serum immunoglobulin levels (IgG, IgA and IgM) and any history of infection; AND There should be regular consideration of a trial period of cessation of Ig for the purposes of immunological evaluation unless medically contraindicated on safety grounds (for example active bronchiectasis and/or suppurative lung disease, neutropenia, or ongoing immunosuppressant medication) or where there is persistence of the underlying condition that would result in severe HGG in the absence of Ig replacement therapy. Trial cessation is best commenced in September or October. When IgA and IgM are trending upwards and close to normal and the patient is well, a trial off therapy (in September or October) is considered to allow immunological re-evaluation, or is medically contraindicated. A diagnosis of bronchiectasis and/or suppurative lung disease must be consistent the guideline of the Thoracic Society of Australia and New Zealand (Chang AB et al. 2014).						
Alternative treatments	Antibiotic therapy may be indicated in addition to Immunoglobulin therapy.	Many patients with secondary antibody deficiency will achieve protection from bacterial infections with prolonged antibiotic prophylaxis. Ig is reserved for those patients in whom antibiotic prophylaxis proves to be ineffective. Since infection susceptibility in patients with haematological malignancies is frequently	n/a	n/a	n/a	n/a	

	Australia1	England3	Scotland4	Atlantic Provinces (Canada)[5]	Alberta, Manitoba, Satskachewan (Canada)[6]	British Columbia (Canada)[7]	Ontario (Canada)
		multifactorial, the reduction in overall burden of infections with long term Ig replacement may be variable. For this reason annual reviews of treatment are recommended. In patients with seasonal preponderance of infections, it may be appropriate to consider temporary cessation of Ig in the summer.					

Abbreviations: CLL= Chronic lymphocytic leukaemia, HGG=hypogammaglobulianemia, HSCT=haematopoietic stem cell transplantation, Ig=immunoglobulin,IVIG=intravenous immunoglobulin, MM=multiple myeloma, NHL=non-Hodgkin lymphoma, SCIG=subcutaneous immunoglobulin
Sources: (Alberta Ministry of Health 2018; European Medicines Agency 2018; New Zealand Blood Service 2016; NHS England 2018; NHS Scotland 2012; British Columbia Provincial Blood Coordinating Office 2019; Nova Scotia Provincial Blood Coordinating Team 2018; NBA 2019a; Ontario Regional Blood Coordinating Network 2018).

Table 43 Separate Ig use recommendations for solid organ transplantation

Country/region	Solid organ transplantation	Recommendations	Dose
Ontario	Kidney transplant from living donor to whom the patient is sensitized	IVIG is recommended to decrease donor-specific sensitization.	2 g/kg/month for 4 months.
	Pre-Transplant (heart)	For desensitization in selected heart transplant recipients who are highly sensitized, medically urgent and unlikely to receive a transplant otherwise – this should be preceded by discussion at the transplant program level.	Suggested dose is up to 1 g/kg/month until transplant.
	Peri-Transplant (heart, lung, kidney, pancreas)	Solid-organ transplant recipient with donor-specific antibodies identified at time of transplant surgery (heart, lung, kidney, pancreas) on virtual crossmatch –first-line agent.	Suggested dose 1 g/kg, can give as divided doses if in association with a course of plasmapheresis.
	Post-Transplant	Acute antibody-mediated rejection in a solid-organ transplant recipient – first-line agent. Chronic antibody-mediated rejection in a solid-organ transplant recipient.	1 g/kg/dose, can give as divided doses if in association with a course of plasmapheresis. 1 g/kg/month.
Alberta, Manitoba, Satskachewan	Kidney, active antibody-mediated rejection (ABMR) prevention and management	Pre-transplant: IVIG is recommended when an antibody or antibodies might preclude transplantation (e.g., donor specific anti-human leukocyte antigen (HLA) antibody or anti-blood group	IVIG with plasma exchange: 0.1 g/kg adjusted body weight after each plasma exchange, to a maximum total dose of 2 g/kg.

Country/region	Solid organ transplantation	Recommendations	Dose
		antibody). IVIG may be continued for up to 3 months post-transplant. Post-transplant: IVIG may be used to treat active ABMR1 when other therapies are ineffective. Patient response to each treatment cycle should be documented according to objective measures of effectiveness established at the outset of treatment.	IVIG alone: 2 g/kg adjusted body weight divided over 2 to 5 days. When IVIG is used alone, further doses may be indicated every 4 weeks for a further 3 cycles, depending on clinical response or biopsy findings. Thereafter, additional treatment cycles (often together with other treatment modalities) may be indicated, but only when biopsy findings and/or clinical response demonstrate ongoing/recurrent active ABMR or chronic active ABMR.1 Demonstration of ongoing/recurrent active ABMR or chronic active ABMR should precede each treatment cycle. Note: Some sucrose-stabilized formulations of IVIG have shown nephrotoxicity and are best avoided in patients with pre-existing kidney impairment.2 Some nephrologists recommend that IVIG infusions be capped at 140 g/day to reduce the risk of nephrotoxicity.
	Solid organ (other than kidney) ABMR	IVIG is recommended in addition to plasma exchange. Where appropriate, biopsy evidence of rejection should be sought. Patient response should be documented according to objective measures of effectiveness established at the outset of treatment.	0.1 g/kg adjusted body weight after each plasma exchange, to a maximum dose of 2 g/kg total.

Source: (Ontario Regional Blood Coordinating Network 2018; Alberta Ministry of Health 2018)

Appendix B Search strategies. Attempts were also made to source unpublished or grey literature from published health technology assessment (HTA) agencies. Search terms are described in Table 44 (Appendix B).

As the PICO inclusion criteria was expanded, no filters for study design or outcome were included, but filters to exclude patients with HGG due to haematological malignancies or HSCT were added. The appropriateness of this filter was explored and further bibliographic searches were conducted, but no evidence of important studies being excluded was found. The intervention search terms included "exp immunoglobulin" to capture studies that did not explicitly mention Ig-RT, but included the population of interest, Ig-treated or untreated.

B.2. RESULTS OF LITERATURE SEARCH

Three studies (Lederer et al. 2014; Lichvar et al. 2018; Sarmiento et al. 2016) comparing IVIG vs. placebo in patients with secondary HGG were identified. Supportive evidence from 12 cohort studies in the population of interest, which did not include comparative data on Ig-RT vs. placebo, were also included (Claustre et al. 2015; Kawut et al. 2005; Noell, Dawson, and Seethamraju 2013; Carbone et al. 2007; Carbone et al. 2012; Farmer et al. 2013; Rhodes et al. 2014; Yamani et al. 2006; Boleto et al. 2018; Shankar et al. 2013; Sun et al. 2015; Zaman et al. 2019).
A PRISMA flowchart (Figure 5) provides a graphic depiction of the results of the literature search and the application of the study selection criteria (listed in Box 1 and Box 2).

Studies were selected independently by a single reviewer with a random sample receiving independent assessment by a second reviewer.

Additional pre-specified criteria for excluding studies included:

- Fewer than 10 HGG patients. Non-comparative cohort studies were excluded under this criterion. These studies provided little evidence regarding clinical progression due to issues with low statistical power and thus their results may not be generalisable and are at high risk of patient selection bias. The comparative studies identified during the development of the PICO also indicated that a minimum of 10 patients were needed to evaluate the incidence of infections.
- Limited baseline and treatment data on HGG patients. These studies were excluded because it was difficult to interpret the outcomes without details of the population.
- Lack of outcome data. Studies that only included data on incidence of HGG but did not follow up HGG patients or included patient-relevant outcomes were excluded. In addition, studies with mixed cohorts where outcomes were not stratified by HGG status were excluded.
- Publication before year 2000. These studies were excluded due to significant changes in the clinical management of the underlying conditions over the last two decades, making such evidence outdated.

- Conference abstracts and posters were excluded due to the limited information provided.
- Cross-sectional studies, editorials, commentaries, narrative reviews and case reports were excluded.

While the inclusion criteria did consider supportive evidence from cohort studies on secondary HGG patients who did not receive Ig-RT, we did not find any cohort studies where it was explicitly reported that they did not receive Ig-RT. The exclusion criteria "intervention" included studies with secondary HGG patients treated with the wrong intervention (e.g. CMV-specific Ig).

Studies that could not be retrieved or that were excluded based on the pre-specified criteria are listed in Appendix E Excluded Studies. All other studies that met the inclusion criteria are listed in Appendix C Studies included in the Systematic Review.

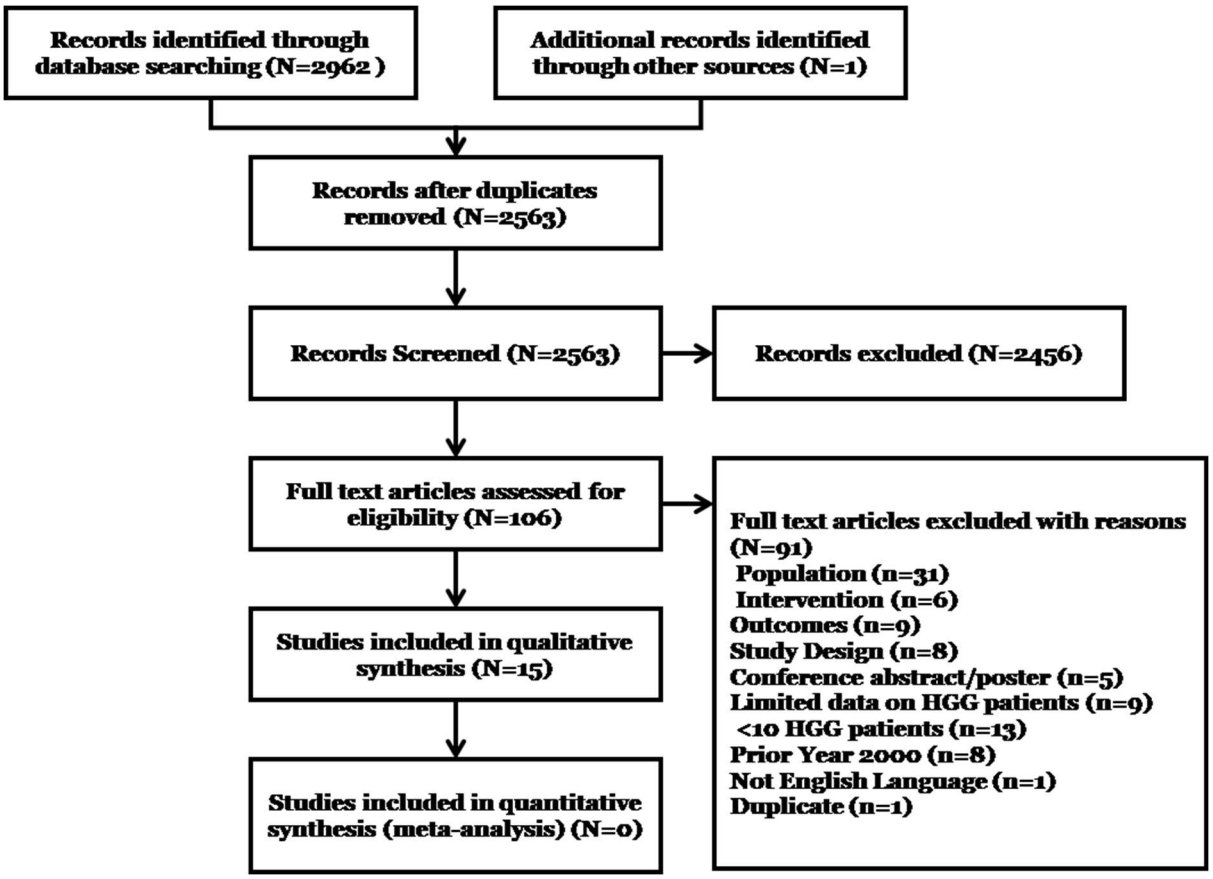

Figure 5 Summary of the process used to identify and select studies for the assessment

A profile of each included study is given in Appendix C. This study profile describes the authors, publication year, study design and quality (level of evidence and risk of bias), setting, length of follow-up of patients, study population characteristics, description of the intervention, description of the comparator (when relevant) and the relevant outcomes assessed. Study characteristics are also summarised in a shorter format in Section B.4.

THE SEARCH OF CLINICAL TRIAL REGISTRIES (

APPENDIX A2 INTERNATIONAL COMPARISONS IG USE

Table 42 International comparisons Ig use recommendations

	Australia[1]	England[3]	Scotland[4]	Atlantic Provinces (Canada)[5]	Alberta, Manitoba, Satskachewan (Canada)[6]	British Columbia (Canada)[7]	Ontario (Canada)
Condition Indication	Secondary HGG unrelated to Haematological malignancy or haematopoietic stem cell transplant (HSCT) Indication for Ig Use: Replacement therapy for recurrent or severe bacterial infections or disseminated enterovirus infection associated with HGG caused by a recognised disease process or B cell depletion therapy and/or immunosuppressant therapy. Specific Conditions: HGG following Solid organ transplantation HGG following B cell depletion therapy Thymoma-associated HGG (Good Syndrome) Other HGG unrelated to haematological malignancies or HSCT	Secondary antibody deficiency – long term use	Secondary antibody deficiency (any cause)	Secondary Immunodeficiency	HGG, secondary: Ig replacement is recommended for preventing recurrent, severe infection due to HGG (excl paraprotein) related to other diseases or medical therapy Separate recommendations for: - Acquired HGG secondary to haematological malignancies (incl. HSCT) - Kidney, active antibody-mediated rejection (ABMR) prevention and management - Solid organ (other than kidney) ABMR (see Table below for further details on solid organ transplantation)	Secondary immune deficiency	Secondary immune deficiency Separate recommendations for solid organ transplantation: - Kidney transplant from living donor to whom the patient is sensitized - Pre-transplant (heart) - Peri-transplant (heart, lung, kidney, pancreas) - Post-transplant (see Table below for further details on solid organ transplantation)
Criteria	A diagnosis must be made by any specialist. Serum IgG to be measured on two separate occasions (at least one hour apart and at least one sample taken when the patient does not have an active infection). Baseline serum levels of IgA and IgM should be provided to allow assessment of immune recovery at review. Significant HGG with serum IgG less than 4g/L (excluding paraprotein) regardless of the frequency and severity of infections; OR Serum IgG (excluding paraprotein) greater than 4g/L but less than the lower limit of the age-related reference range and at least one life-threatening infection in the last 12 months; OR Serum IgG (excluding paraprotein) greater than 4g/L but less the lower limit of the age-related reference range with at least two serious infections in the last six months	Underlying cause of HGG cannot be reversed or reversal is contraindicated; OR HGG associated with drugs, therapeutic monoclonals targeted at B cells and plasma cells (rituximab and other anti-CD20,CD19 agents, daratumumab etc) post-HSCT, NHL, CLL, MM or other relevant B-cell malignancy confirmed by haematologist; AND Recurrent or severe bacterial infection despite continuous oral antibiotic therapy for 6 months IgG < 4g/L (excl paraprotein) Documented failure of serum antibody response to	Underlying cause of HGG cannot be reversed or reversal is contraindicated; OR HGG associated with NHL, CLL, MM or other relevant B-cell malignancy confirmed by haematologist; AND Recurrent or severe bacterial infection despite continuous oral antibiotic therapy for 3 months IgG < 5 g/L (excl paraprotein) Documented failure of serum antibody response to	Adult: Patient has/had recent life threatening or recurrent clinically significant infection(s) related to low levels of polyclonal immunoglobulin Paediatric: Order must be in consultation with an Immunologist	HGG secondary to underlying disease or medical therapy (incl HCST) with all of the following: Serum IgG less than the lower limit of the reference range on two separate occasions; AND At least one of the following: One invasive or life-threatening bacterial infection (e.g., pneumonia, meningitis, sepsis) in the previous year; Recurrent, severe bacterial infections; Clinically active bronchiectasis confirmed by radiology; Assessment by a physician specializing in immunodeficiency indicating a significant antibody defect that would benefit from Ig replacement.	HGG (reduced total IgG or IgG subclasses) with recurrent bacterial infection Monitor IgG trough level as appropriate to achieve desired clinical outcome	Hypogammaglobulinemia (reduced total IgG or IgG subclasses) with recurrent bacterial infection

	Australia[1]	England[3]	Scotland[4]	Atlantic Provinces (Canada)[5]	Alberta, Manitoba, Satskachewan (Canada)[6]	British Columbia (Canada)[7]	Ontario (Canada)
	requiring more than standard courses of antibiotics (e.g. Hospitalisation, intravenous or prolonged antibiotic therapy); OR Evidence of impaired antibody production to vaccination in the context of persistent infections affecting long term function such as persistent purulent suppurative otitis media threatening long term hearing; AND Underlying cause of HGG cannot be reversed; OR Underlying cause of HGG is reversible but reversal is contraindicated A diagnosis of bronchiectasis and/or suppurative lung disease must be consistent with the Thoracic Society of Australia and New Zealand (Chang AB et al. 2014). Initial review is required within six months and ongoing reviews by a specialist at least annually to assess clinical benefit. Documentation of clinical effectiveness is necessary for continuation of Ig therapy. Cessation of Ig therapy should be considered at least after each 12 months of treatment. If serum IgM and IgA levels are trending upwards and near normal, this may suggest recovery of the immune system and a trial might be considered if the patient is well. Once the patient has normal IgA and IgM levels, the IgG is also likely to be normal and a trial off Ig therapy may be undertaken. Ig therapy should be extended as required to enable cessation of therapy in September/October, with repeat clinical and/or immunological evaluation before recommencement of therapy.	unconjugated pneumococcal or other polysaccharide vaccine challenge In these circumstances vaccine challenge may be omitted if it is considered inappropriate clinically. It is acknowledged that not all of the above criteria will need to be fulfilled for an individual patient. In patients developing HGG associated with B-cell aplasia as a consequence of Chimeric Antigen Receptor – T cell therapy (CAR-T cells) targeted against B cell antigens, the prophylactic use of Ig in the absence of a burden of severe infections and vaccine challenge may be appropriate. There is controversy regarding Ig replacement in adult patients with HGG post-HSCT for haematological malignancy. The American Society for Blood and Marrow transplantation and the Canadian Blood and Marrow Transplant group have recently stated as follows: Don't routinely give Ig replacement to adult HSCT recipients in the absence of recurrent infections regardless of the IgG level (Bhella et al. Choosing Wisely BMT. Biol Blood Marrow Transplant 2018;24:909-13)	unconjugated pneumococcal or other polysaccharide vaccine challenge				
Dosing	The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.	0.4-0.6g/kg/month modified to achieve an IgG trough level of at least the lower limit of the	0.4 g/kg/month modified to achieve an IgG trough level of	Adult: 0.4-0.6 g/kg every 4 weeks	Aim to use the dose that achieves a significant reduction in the number of bacterial infections.	Adult: 0.4-0.6 g/kg every 3-4 weeks	Adult: 0.4-0 .6 g/kg every 3-4 weeks

	Australia[1]	England[3]	Scotland[4]	Atlantic Provinces (Canada)[5]	Alberta, Manitoba, Satskachewan (Canada)[6]	British Columbia (Canada)[7]	Ontario (Canada)
	Loading Dose (IVIG) - One loading dose of 0.4 g/kg in the first month of therapy (in addition to the maintenance dose) is permitted if the serum IgG level is <4 g/L. Disseminated Enterovirus Dose (IVIg) - One dose of 2g/kg at any stage is permitted (in addition to the maintenance dose) in the management of disseminated enterovirus infection. Maintenance Dose (IVIg) - 0.4–0.6g/kg every four weeks or more frequently, to achieve IgG trough level of at least the lower limit of the age-specific serum IgG reference range. More frequent dosing to achieve IgG trough level of up to 9 g/L is permitted if chronic suppurative lung disease is not adequately controlled at an IgG trough level at the lower limit of the age-specific serum IgG reference range. A total dose of up to 1 g/kg may be given over any 4-week period. Supplementary Dose (IVIg) - One additional dose of 0.4 g/kg is permitted at any stage (in addition to the maintenance dose) if the serum IgG level is <4 g/L. Loading Dose (SCIg) - One loading dose of 0.4 g/kg in the first month of therapy (in addition to the maintenance dose) is permitted if the serum IgG level is <4 g/L. Disseminated Enterovirus Dose (SCIg) - One dose of 2g/kg at any stage is permitted (in addition to the maintenance dose) in the management of disseminated enterovirus infection. Maintenance Dose (SCIg) - 0.1-0.15g/kg every week or more frequently, to achieve IgG trough level of at least the lower limit of the age-specific serum IgG reference range. More frequent dosing to achieve IgG trough level of up to 9 g/L is permitted if chronic suppurative lung disease is not adequately controlled at an IgG trough level at the lower limit of the age-specific serum IgG reference range. A	age-specific serum IgG reference range	at least the lower limit of the age-specific serum IgG reference range	Paediatric: 0.3-0.6 g/kg every 4 weeks	Maintenance: 0.4 to 0.6 g/kg adjusted body weight IVIg every 4 weeks, or SCIg 0.1 to 0.5 g/kg adjusted body weight weekly, modified to achieve an IgG trough level of at least the lower limit of the age-specific serum IgG reference range, or as needed to achieve clinical effectiveness. Loading: One additional dose of 0.4 g/kg adjusted body weight may be given in the first month of therapy if the serum IgG level is markedly reduced. Chronic suppurative lung disease: 0.4 to 0.8 g/kg adjusted body weight IVIg or equivalent SCIg dose may be given if chronic suppurative lung disease is not adequately controlled at an IgG trough level at the lower limit of the age-specific serum IgG reference range.	Paediatric: 0.3-0.6 g/kg every 4 weeks	Paediatric: 0.3-0 .6 g/kg every 3-4 weeks Doses or frequency to be adjusted by experts according to desired trough level (more than 500 mg/dL and ideally 700 mg/dL) and according to individual patient clinical needs.

	Australia[1]	England[3]	Scotland[4]	Atlantic Provinces (Canada)[5]	Alberta, Manitoba, Satskachewan (Canada)[6]	British Columbia (Canada)[7]	Ontario (Canada)
	total dose of up to 1 g/kg may be given over any 4-week period. Supplementary Dose (SCIg) - One additional dose of 0.4 g/kg is permitted at any stage (in addition to the maintenance dose) if the serum IgG level is <4 g/L.						
Review / Clinical Outcome Measures	Initial review is required within six months and ongoing reviews by a specialist at least annually to assess clinical benefit. Documentation of clinical effectiveness is necessary for continuation of Ig therapy. Cessation of Ig therapy should be considered at least after each 12 months of treatment. If serum IgM and IgA levels are trending upwards and near normal, this may suggest recovery of the immune system and a trial might be considered if the patient is well. Once the patient has normal IgA and IgM levels, the IgG is also likely to be normal and a trial off Ig therapy may be undertaken. Ig therapy should be extended as required to enable cessation of therapy in September/October, with repeat clinical and/or immunological evaluation before recommencement of therapy On review of the initial authorisation period: Monitoring of serum immunoglobulin levels (IgG, IgM and IgA) and infection history; AND There should be regular consideration of a trial period of cessation of Ig for the purposes of immunological evaluation unless medically contraindicated on safety grounds (for example active bronchiectasis and/or suppurative lung disease, neutropenia, or ongoing immunosuppressant medication) or where there is persistence of the underlying condition that would result in severe HGG in the absence of Ig replacement therapy. Trial cessation is best commenced in September or October. When IgA and IgM are trending upwards and close to normal and the patient is well, a trial	Reduction in number of infections and days in hospital (Database parameters will include entry of number of infections and days in hospital pre-treatment and 6 monthly thereafter)	Reduction in number of infections and days in hospital. Database parameters will include entry of number of infections and days in hospital pre-treatment and 6 monthly thereafter.	n/a	Continued use of Ig should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of treatment and at least annually thereafter by a physician specializing in immunodeficiency disorders. If clinical effectiveness has not been achieved, Ig treatment should be discontinued. Cessation of Ig treatment may be possible depending on the status of the underlying disease.	n/a	n/a

	Australia[1]	England[3]	Scotland[4]	Atlantic Provinces (Canada)[5]	Alberta, Manitoba, Satskachewan (Canada)[6]	British Columbia (Canada)[7]	Ontario (Canada)
	off therapy (in September or October) is considered to allow immunological re-evaluation, or is unless medically contraindicated. On review of a continuing authorisation period: Monitoring of trough or serum immunoglobulin levels (IgG, IgA and IgM) and any history of infection; AND There should be regular consideration of a trial period of cessation of Ig for the purposes of immunological evaluation unless medically contraindicated on safety grounds (for example active bronchiectasis and/or suppurative lung disease, neutropenia, or ongoing immunosuppressant medication) or where there is persistence of the underlying condition that would result in severe HGG in the absence of Ig replacement therapy. Trial cessation is best commenced in September or October. When IgA and IgM are trending upwards and close to normal and the patient is well, a trial off therapy (in September or October) is considered to allow immunological re-evaluation, or is medically contraindicated. A diagnosis of bronchiectasis and/or suppurative lung disease must be consistent the guideline of the Thoracic Society of Australia and New Zealand (Chang AB et al. 2014).						
Alternative treatments	Antibiotic therapy may be indicated in addition to Immunoglobulin therapy.	Many patients with secondary antibody deficiency will achieve protection from bacterial infections with prolonged antibiotic prophylaxis. Ig is reserved for those patients in whom antibiotic prophylaxis proves to be ineffective. Since infection susceptibility in patients with haematological malignancies is frequently	n/a	n/a	n/a	n/a	

	Australia[1]	England[3]	Scotland[4]	Atlantic Provinces (Canada)[5]	Alberta, Manitoba, Satskachewan (Canada)[6]	British Columbia (Canada)[7]	Ontario (Canada)
		multifactorial, the reduction in overall burden of infections with long term Ig replacement may be variable. For this reason annual reviews of treatment are recommended. In patients with seasonal preponderance of infections, it may be appropriate to consider temporary cessation of Ig in the summer.					

Abbreviations: CLL= Chronic lymphocytic leukaemia, HGG=hypogammaglobulianemia, HSCT=haematopoietic stem cell transplantation, Ig=immunoglobulin,IVIG=intravenous immunoglobulin, MM=multiple myeloma, NHL=non-Hodgkin lymphoma, SCIG=subcutaneous immunoglobulin
Sources: (Alberta Ministry of Health 2018; European Medicines Agency 2018; New Zealand Blood Service 2016; NHS England 2018; NHS Scotland 2012; British Columbia Provincial Blood Coordinating Office 2019; Nova Scotia Provincial Blood Coordinating Team 2018; NBA 2019a; Ontario Regional Blood Coordinating Network 2018).

Table 43 Separate Ig use recommendations for solid organ transplantation

Country/region	Solid organ transplantation	Recommendations	Dose
Ontario	Kidney transplant from living donor to whom the patient is sensitized	IVIG is recommended to decrease donor-specific sensitization.	2 g/kg/month for 4 months.
	Pre-Transplant (heart)	For desensitization in selected heart transplant recipients who are highly sensitized, medically urgent and unlikely to receive a transplant otherwise – this should be preceded by discussion at the transplant program level.	Suggested dose is up to 1 g/kg/month until transplant.
	Peri-Transplant (heart, lung, kidney, pancreas)	Solid-organ transplant recipient with donor-specific antibodies identified at time of transplant surgery (heart, lung, kidney, pancreas) on virtual crossmatch –first-line agent.	Suggested dose 1 g/kg, can give as divided doses if in association with a course of plasmapheresis.
	Post-Transplant	Acute antibody-mediated rejection in a solid-organ transplant recipient – first-line agent. Chronic antibody-mediated rejection in a solid-organ transplant recipient.	1 g/kg/dose, can give as divided doses if in association with a course of plasmapheresis. 1 g/kg/month.
Alberta, Manitoba, Satskachewan	Kidney, active antibody-mediated rejection (ABMR) prevention and management	Pre-transplant: IVIG is recommended when an antibody or antibodies might preclude transplantation (e.g., donor specific anti-human leukocyte antigen (HLA) antibody or anti-blood group	IVIG with plasma exchange: 0.1 g/kg adjusted body weight after each plasma exchange, to a maximum total dose of 2 g/kg.

Country/region	Solid organ transplantation	Recommendations	Dose
		antibody). IVIG may be continued for up to 3 months post-transplant. Post-transplant: IVIG may be used to treat active ABMR1 when other therapies are ineffective. Patient response to each treatment cycle should be documented according to objective measures of effectiveness established at the outset of treatment.	IVIG alone: 2 g/kg adjusted body weight divided over 2 to 5 days. When IVIG is used alone, further doses may be indicated every 4 weeks for a further 3 cycles, depending on clinical response or biopsy findings. Thereafter, additional treatment cycles (often together with other treatment modalities) may be indicated, but only when biopsy findings and/or clinical response demonstrate ongoing/recurrent active ABMR or chronic active ABMR.1 Demonstration of ongoing/recurrent active ABMR or chronic active ABMR should precede each treatment cycle. Note: Some sucrose-stabilized formulations of IVIG have shown nephrotoxicity and are best avoided in patients with pre-existing kidney impairment.2 Some nephrologists recommend that IVIG infusions be capped at 140 g/day to reduce the risk of nephrotoxicity.
	Solid organ (other than kidney) ABMR	IVIG is recommended in addition to plasma exchange. Where appropriate, biopsy evidence of rejection should be sought. Patient response should be documented according to objective measures of effectiveness established at the outset of treatment.	0.1 g/kg adjusted body weight after each plasma exchange, to a maximum dose of 2 g/kg total.

Source: (Ontario Regional Blood Coordinating Network 2018; Alberta Ministry of Health 2018)

Appendix B Search strategies) identified one ongoing Australian RCT (ACTRN12618001394235)[6] comparing IVIG vs. placebo following lung transplant, currently recruiting participants.

APPRAISAL OF THE EVIDENCE

Appraisal of the evidence was conducted in 4 stages:

- Stage 1: Appraisal of the risk of bias within individual studies included in the review. Some risk of bias items were assessed for the study as a whole, while others were assessed at the outcome level. (Section B.3)
- Stage 2: Extraction of the pre-specified outcomes for this assessment, synthesising (meta-analysing or a narrative synthesis) to determine an estimate of effect per outcome, and determining the assumed baseline risk.
- Stage 3: Rating the overall quality of the evidence per outcome, across studies, based on the study limitations (risk of bias), imprecision, inconsistency of results, indirectness of evidence, and the likelihood of publication bias. This was done to provide an indication of the confidence in the estimate of effect in the context of Australian clinical practice (Evidence profile tables, Appendix D).
- Stage 4: Integration of this evidence for conclusions about the net clinical benefit of the intervention in the context of Australian clinical practice. (Sections B.6-8)

B.3. RISK OF BIAS ASSESSMENT

A structured appraisal was performed to assess the quality of all included studies. Appraisal of the risk of bias within individual studies was done using the Cochrane risk of bias tool for cross-over trials (RoB2) [7] for the RCT (Lederer et al. 2014) included (Table 4) and the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I)[8] for the remaining studies (Table 5).

An overall appraisal of the evidence following GRADE methodology was done for the effectiveness outcomes across the three comparative studies (Appendix D Evidence Profile Tables).

6 Australian Clinical Trials, Immunoglobulin therapy in Lung Transplant, accessed 14 January 2020

7 Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng H-Y, Corbett MS, Eldridge SM, Hernán MA, Hopewell S, Hróbjartsson A, Junqueira DR, Jüni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart LA, Tilling K, White IR, Whiting PF, Higgins JPT. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019; 366: l4898.

8 Current version of ROBINS-I, accessed on 6 January 2020

Table 4 Risk of Bias assessment using RoB2 for cross-over randomised trials

Studies	Randomisation	Deviations from intended interventions	Missing data	Outcome measurement	Reporting	Overall risk of bias
Lederer 2014	Low	Low	Low	Low	Moderate	Moderate

Lederer 2014 (Lederer et al. 2014), the only RCT identified in the systematic review, had a small number of patients (n=11) and overall moderate risk of bias, mainly due to selective presentation of their analyses (i.e. paired analysis conducted but not reported) and a lack of testing for possible carry over effects. The two non-randomised studies (Lichvar et al. 2018; Sarmiento et al. 2016) comparing IVIG with placebo were at serious risk of bias due to selection bias, unbalanced baseline characteristics between the groups and lack of adjustment in their analyses (though given their small sample sizes adjusting for baseline differences would have been difficult). Sarmiento 2016 included a small prospective group of patients with HGG (n=12) and compared their outcomes to HGG transplant patients (n=13) from the same centre who were "not selected" for Ig-RT (reasons not stated) but agreed to be followed up. Lichvar 2018 was a single centre retrospective study that evaluated the effect of on-demand IVIG, defined as "receiving Ig infusion less frequently than 6 weeks apart or less than 6 months of weekly subcutaneous Ig (SCIG)", but treatment patterns were unclear. In addition, a significantly higher proportion of patients treated with Ig-RT had severe HGG at baseline compared to untreated HGG patients (58.8% vs. 30.7%, $p<0.001$), which indicates a very high risk of selection bias (Lichvar et al. 2018). In addition, concomitant antimicrobial treatments were not fully described in any of the studies, and patients at high risk of infection could have received more intensive antibiotic or antiviral treatment.

The risk of bias in the non-randomised cohort studies (Table 5) was serious in most studies, and critical in studies that did not report details about Ig-RT (Boleto et al. 2018; Kawut et al. 2005; Noell, Dawson, and Seethamraju 2013; Rhodes et al. 2014; Yamani et al. 2006; Shankar et al. 2013). It is unclear whether these populations were not treated with Ig-RT or whether this was a limitation in their study reporting. The lack of reported Ig-RT data brings a very high risk of bias to any results in these populations, which prevents confident conclusions with regard to the intervention effect or clinical course in the absence of treatment.

Table 5 Risk of Bias assessment using Robins-I for non-randomised studies

Studies	Confounding	Participant selection	Classification of interventions	Deviations from intended interventions	Missing data	Outcome measurement	Reporting	Overall risk of bias
Boleto 2018	Serious	Serious	Critical	NA	Serious	Critical	Low	Critical
Carbone 2007	Serious	Serious	Serious	NA	Low	Serious	Low	Serious
Carbone 2011	Serious	Serious	Serious	NA	Low	Serious	Low	Serious
Claustre 2015	Moderate	Serious	Serious	NA	Low	Serious	Low	Serious
Farmer 2013	Serious	Serious	Serious	NA	Low	Serious	Low	Serious
Kawut 2015	Serious	Serious	Critical	NA	Low	Critical	Low	Critical
Lichvar 2018	Moderate	Serious	Serious	Moderate	Low	Serious	Low	Serious
Noell 2013	Serious	Serious	Critical	NA	Low	Critical	Low	Critical
Rhodes 2014	Serious	Serious	Critical	NA	Serious	Serious	Low	Critical
Sarmiento 2016	Moderate	Serious	Serious	Moderate	Low	Serious	Low	Serious
Shankar 2013	Serious	Serious	Critical	NA	Low	Critical	Low	Critical
Sun 2015	Serious	Serious	Serious	NA	Low	Serious	Low	Serious
Yamani 2006	Serious	Serious	Critical	NA	Low	Critical	Low	Critical
Zaman 2018	Serious	Serious	Serious	NA	Low	Serious	Low	Serious

NA=not applicable. Studies classified as NA did not compare the interventions

B.4. CHARACTERISTICS OF THE EVIDENCE BASE

See Appendix C Studies included in the Systematic Review for details on the individual studies included in the evidence base. Summaries are provided in Table 6 and Table 7.

Fifteen studies were included in the clinical effectiveness review, including the following patient groups with secondary HGG:

- Lung transplant (Lederer et al. 2014; Lichvar et al. 2018; Claustre et al. 2015; Kawut et al. 2005; Noell, Dawson, and Seethamraju 2013; Shankar et al. 2013)
- Heart transplant (Sarmiento et al. 2016; Carbone et al. 2007; Carbone et al. 2012; Yamani et al. 2006)
- Intestinal transplant (Farmer et al. 2013)
- Infants undergoing cardiopulmonary bypass (CPB) (Rhodes et al. 2014)
- Rheumatoid arthritis (RA) treated with rituximab (Boleto et al. 2018)
- Good syndrome (Sun et al. 2015; Zaman et al. 2019).

Only three of the studies included Ig-RT vs. no Ig-RT comparative evidence in the population of interest (Table 6). These three studies included patients who developed secondary HGG after heart or lung transplantation, which is a small subpopulation within secondary HGG. There were considerable differences in treatment patterns across the studies; i.e. mean time from transplantation to IVIG dose in Sarmiento 2016 was 15.4 days, whereas in Lichvar 2018 the median time from transplant to Ig-RT was 324 days. Lederer 2014 only reports median time from transplant to enrolment (187 days), which is less than the time until start of treatment. The number of Ig-RT doses received also varied: up to seven doses (first two doses every 2 weeks and the remaining doses at days 30, 60, 90, 120 and 150 only if their Ig level was less than 750 mg/dL in the previous visit, with a total of 56 doses given to 12 patients; mean=4.67 doses; median doses not reported) in Sarmiento 2016; three doses (one dose every 4 weeks) in Lederer 2014; and a median of two doses (one dose every 4 weeks) in Lichvar 2018. The follow-up period was also considerably different across the three studies: 6 months, 12 weeks and 5 years, respectively. The amount of IVIG in each of the doses also varied across the three studies: 0.2 to 0.3 g/kg in Sarmiento 2016, 0.4 g/kg in Lederer 2014, and 0.5 g/kg in Lichvar 2018.

Ig-RT use in these trials may be lower than the utilisation recommended in the Australian setting. The criteria for the clinical use of intravenous immunoglobulin in Australia (The Criteria (NBA 2019a)) recommends the following maintenance doses:

- IVIG dose of 0.4–0.6g/kg every four weeks or more frequently to achieve Ig trough level of at least the lower limit of the age-specific serum Ig reference range
- SCIG dose of 0.1-0.15g/kg every week or more frequently to achieve Ig trough level of at least the lower limit of the age-specific serum Ig reference range.

Initial review is recommended within six months and ongoing reviews by a specialist at least annually to assess clinical benefit, which would potentially result in 6 IVIG doses (one dose per month) per patient if treatment duration is 6 months and more than double if treatment continues over one year (NBA 2019a).

Overall, these studies provided insufficient information on Ig-RT given (e.g. mean/median doses, initiation, duration, discontinuation). Further details on the interventions are described in Table 45, Appendix C Studies included in the Systematic Review.

Antibiotic use was not appropriately described in any of the studies (see Table 46 in Appendix C for details). Lichvar 2018 and Lederer 2014 did not include any details on antimicrobial therapy used, although both studies mentioned antibiotic and antiviral treatments (Lederer et al. 2014; Lichvar et al. 2018). Sarmiento 2016 mentioned antimicrobial prophylaxis of all patients with cefazolin on the first day after transplantation, oral trimethoprim-sulfamethoxazole given twice daily on two days per week during the first year, and oral norfloxacin twice daily during the first month. Itraconazole was indicated in patients with risk factors for invasive aspergillosis. Universal prophylaxis with IV ganciclovir or oral valganciclovir was administered to all seropositive recipients. However, the study did not provide information on antimicrobial use by treatment group or change in antibiotic use following IVIG (Sarmiento et al. 2016).

The supportive non-comparative evidence was extracted from prospective and retrospective cohort studies (Table 7). The aim of most of these studies was not to evaluate the effectiveness of Ig-RT in the secondary HGG population, but to compare outcomes in patients with HGG and those without HGG. This provides an indication of whether there may be a capacity to benefit from Ig-RT for those with HGG. The comparison of HGG to no-HGG falls beyond the scope of this review, and therefore only data from the population of interest was extracted. However, a top line summary of key outcome differences between HGG and non-HGG patients found in these studies has been included in Appendix F HGG vs No-HGG comparison for completeness. Three cohort studies did not include a comparison group (Shankar et al. 2013; Sun et al. 2015; Zaman et al. 2019).

No HGG cohort studies were found where it was explicitly stated that patients did not receive Ig-RT. Five studies did not mention whether or not the HGG cohort had received any Ig-RT (Kawut et al. 2005; Noell, Dawson, and Seethamraju 2013; Rhodes et al. 2014; Yamani et al. 2006; Boleto et al. 2018). Given the lack of studies in patients with secondary HGG who were not treated with Ig-RT, these studies were included in the review as a potential untreated population. Their data are presented separately to studies where it was reported that the HGG patients received Ig-RT, as it was unclear if Ig-RT was just unreported or that these patients were truly untreated.

There was a high level of heterogeneity across the studies, with different populations, study designs, analyses, treatments, and follow-up, which prevented us from conducting a meta-analysis.
Included studies are summarised in the following section, with separate subsections for Ig-RT comparative evidence and the supportive cohort studies. Table 45 in Appendix C includes details on Ig-RT doses in all the included studies. Only a few supportive cohort studies reported Ig-RT doses and utilisation (Carbone 2007; Carbone et al. 2012; Claustre et al. 2015; Farmer et al. 2013; Shankar et al. 2013). Doses varied widely across the studies; e.g. IVIG 0.3-0.4 g/kg every 2-3 weeks (Carbone et al. 2012), 0.4 g/kg every 3 months (Claustre et al. 2015), to 0.5 g/kg every 12 days (Farmer et al. 2013). Shankar 2013 was the only study that included patients treated with SCIG, at a dose of 0.1g/kg/week after a loading IVIG dose of 0.4 g/kg (Shankar et al. 2013).

comparing IVIg with no IVIg

/ -up	Risk of bias	Population of interest	Key outcome(s)	Result used in economic model
SC, X-over	Moderate	Secondary HGG (Ig <500 mg/dL) post-lung transplant	Infection Rejection Hospitalisation AE	No
pective Coh, SC	Serious	Secondary HGG (Ig <700 mg/dL) post lung transplant	CLAD Rejection Infection Survival (overall and CLAD-free survival)	No
ctive Coh, SC	Serious	Secondary HGG (Ig<500 mg/dL) post heart transplant	Severe infection Rejection Mortality Hospital stay AE	No

function; Coh=cohort; m=months, HGG=hypogammaglobulinaemia, Ig=immunoglobulin G, PC=placebo-controlled, R=randomised; SC=single centre; TBC=to be

ts without HGG.

cluding secondary HGG patients

/ -up	Risk of bias	Population of interest	Key outcome(s)	Result used in economic model
pective Coh, SC rs (median)	Serious	Secondary HGG (Ig<600 mg/dL) post lung transplant (IVIG-treated)	Infections Rejection Survival (overall and CLAD-free survival)	No
pective Coh, SC	Critical	Secondary HGG (Ig <700 mg/dL) post	Infections	No

Trial/Study	N total (n HGG)	Design/ Follow-up	Risk of bias	Population of interest	Key outcome(s)	Result used in economic model
Shankar 2013	10 (10)	Retrospective Coh, SC 12 months	Critical	Secondary HGG (Ig<750 mg/dL) post lung transplant + recurrent infections (IVIG/SCIG-treated)	Ig levels AEs	No
Heart transplant						No
Carbone 2012	110 (55)	Retrospective Coh, SC 18 months	Serious	Secondary HGG (Ig<600 mg/dL) post heart transplant + severe infections (IVIG treated)	Infections before-after IVIg Rejection Mortality	No
Carbone 2007	123 (29)	Retrospective Coh, SC 51 months	Serious	Secondary HGG (Ig<600 mg/dL) post heart transplant + severe infections (IVIG-treated)	Infections Rejection Mortality ICU length of stay	No
Intestinal transplant						
Farmer 2013	34 (20)	Retrospective Coh, database 8 weeks	Serious	Secondary HGG (Ig< 95% CI of the mean Ig for age, <690 mg/dL in adults) post intestinal transplant (85% IVIG-treated)	Infections Time to infection Rejection Time to rejection	No
Surgery						No
Rhodes 2014	47 (25)	Retrospective Coh, SC NR	Critical	Infants with secondary HGG (Ig<2 SD of mean preoperative levels) post cardiopulmonary bypass (Ig-RT NR)	Length of PICU stay Infection Mortality	No
Yamani 2006	76 (20)	Retrospective Coh, database NR	Critical	Secondary HGG (Ig<700 mg/dL) post VAD implantation and pre-heart transplant (Ig-RT NR)	Infection Rejection Survival	No
Rheumatoid arthritis						
Boleto 2018	134 (23)	Prospective Coh, MC 64 months (mean)	Critical	Secondary HGG (Ig<600 mg/dL) after rituximab treatment for RA (Ig-RT NR)	Severe infection	No
Good syndrome						No
Sun 2015	12 (12)	Retrospective Coh, SC NR	Serious	Good syndrome (HGG<500mg/dL) hospitalised with moderate to severe infections (IVIG-treated n=8)	Remission from infection Mortality	No
Zaman 2019	78 (78)	Retrospective case series, national registry (NR)	Serious	Good syndrome (HGG<600mg/dL) (Ig-RT all patients)	Other clinical outcomes Mortality	No

CLAD=chronic lung allograft dysfunction; Coh=cohort; CS=case series; HGG=hypogammaglobulinaemia, ICU=intensive care unit, Ig=immunoglobulin G, Ig-RT=immunoglobulin G replacement therapy,

IVIG=intravenous immunoglobulin G, MC=multi-centre; PICU=paediatric intensive care unit, SC=single centre; SCIG=subcutaneous immunoglobulin G, SD=standard deviation, TBC=to be considered

B.5. OUTCOME MEASURES AND ANALYSIS

See Appendix C Studies included in the Systematic Review for details on the outcomes measured, along with the statistical methods used to analyse the results. All the included outcomes are generally considered to be objective outcomes. However, HGG definitions, HGG measurement time points, and Ig-RT doses and intervals varied across the studies. In addition, the non-randomised studies were at serious risk of selection bias, and there were important baseline differences between the two treatment groups that were not appropriately accounted for in the statistical analysis. In particular, the primary outcome of number of infections in the non-randomised studies could have been influenced by the lack of blinding, where patients treated with Ig-RT may have received more frequent support and intensified treatment to prevent infections.

Most supportive studies compared patients with HGG to those without HGG and the methods of analysis of the differences between these two populations are not applicable to this review. Therefore, these data are not presented.

Only Carbone 2012 and Shankar 2013 reported before and after IVIG outcomes; infections and Ig levels, respectively. Shankar 2013 did not conduct any statistical analysis and the data from this study were analysed during the preparation of this report using t-test in Microsoft Excel and the mean difference was calculated from the mean and standard deviation using RevMan5.3.

Where relative and absolute differences for the adverse events were not reported RevMan5.3 was also used to calculate them (included in *italics* the safety and effectiveness tables) in section B.6. No meta-analysis was conducted due to the high level of heterogeneity across the studies.

B.6. RESULTS OF THE SYSTEMATIC LITERATURE REVIEW

IS IG-RT SAFE?

Summary – What is the safety of Ig-RT in patients with secondary HGG unrelated to haematological malignancies or HSCT?

Overall, Ig-RT 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)). Given the comparator was "no Ig-RT" and these patients would not have receive infusions, the safety of Ig-RT would be worse than the comparator due to the occurrence of infusion-related AEs.

Only Lederer 2014 reported comparative evidence in patients treated with IVIG vs. placebo. No significant differences in AEs were found 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 only reported low back pain and polypnea during infusion as AEs related to IVIG. This study reported a high number of severe AEs during treatment with IVIG (66%), but AEs in the control group were not reported. Therefore, it is not possible to establish if these AEs were associated with IVIG or the underlying condition.

Shankar 2013 reported that three (30%) patients experienced local infusion site reactions (swelling, erythema, soreness) after SCIG that resolved spontaneously, and one patient (10%) developed transfusion-related acute lung injury (TRALI) after one dose of IVIG.

Three studies reporting on the safety of Ig-RT were identified in the systematic review (Lederer et al. 2014; Sarmiento et al. 2016; Shankar et al. 2013). Of them, only Lederer 2014 compared the occurrence of AEs in Ig-RT-treated and untreated patients (Table 8).

It is important to note that infections, mortality, and graft failure/transplant rejection, are presented in the effectiveness section, rather than as AEs, as indicated in the PICO.

ADVERSE EVENTS

Only Lederer 2014 (Lederer et al. 2014) reported rates of AEs in the IVIG-treated and placebo groups during 12-weeks of follow-up. The absolute and relative differences between these two groups was calculated during the preparation of this assessment based on the data available from the study (Table 8). All patients in the study experienced at least one AE, with no differences between treatment groups. Serious AEs were more common in IVIG-treated patients, but the difference between the two groups was not statistically significant.

Table 8 AEs in post-lung transplant HGG patients treated with IVIG vs placebo (Lederer 2014)

	IVIG N=11	*Placebo N=11*	*Absolute differences (RD 95% CI)*	*Relative difference (RR and 95% CI)*
Any AE	11 (100%)	11 (100%)	0.00 -0.16, 0.16)	1.00 (0.85, 1.18)
Any SAE	3 (27%)	1 (9%)	0.18 (-0.13, 0.50)	3.00 (0.37, 24.58)
Infusion-related AE	1 (9%)	0 (0%)	0.09 (-0.13, 0.31)	3.00 (0.14, 66.53)
Chills	1 (9%)	0 (0%)	0.09 (-0.13, 0.31)	3.00 (0.14, 66.53)
Flushing	1 (9%)	0 (0%)	0.09 (-0.13, 0.31)	3.00 (0.14, 66.53)
Nausea	1 (9%)	0 (0%)	0.09 (-0.13, 0.31)	3.00 (0.14, 66.53)
Infectious				
Fever	2 (18%)	0 (0%)	0.18 (-0.07, 0.44)	5.00 (0.27, 93.55)
Night sweats	0 (0%)	2 (18%)	-0.18 (-0.44, 0.07)	0.20 (0.01, 3.74)
Bronchoscopy	7 (64%)	6 (54%)	0.09 (-0.32, 0.50)	1.17 (0.58, 2.35)
Pulmonary				
Dyspnea	1 (9%)	1 (9%)	0.00 (-0.24, 0.24)	1.00 (0.07, 14.05)
Cough	2 (18%)	1 (9%)	0.09 (-0.19, 0.38)	2.00 (0.21, 18.98)
Sputum production	1 (9%)	1 (9%)	0.00 (-0.24, 0.24)	1.00 (0.07, 14.05)
Cardiac				
Palpitations	1 (9%)	1 (9%)	0.00 (-0.24, 0.24)	1.00 (0.07, 14.05)
Pedal oedema	0 (0%)	3 (27%)	-0.27 (-0.55, 0.01)	0.14 (0.01, 2.48)
Neurological				
Headache	2 (18%)	3 (27%)	-0.09 (-0.44, 0.26)	0.67 (0.14, 3.24)
Stiff neck	2 (18%)	0 (0%)	0.18 (-0.07, 0.44)	5.00 (0.27, 93.55)
Genitourinary				
Urinary frequency	1 (9%)	2 (18%)	-0.09 (-0.38, 0.19)	0.50 (0.05, 4.75)
Pancreatitis	1 (9%)	0 (0%)	0.09 (-0.13, 0.31)	3.00 (0.14, 66.53)
Gastrointestinal				
Diarrhea	0 (0%)	2 (18%)	-0.18 (-0.44, 0.07)	0.20 (0.01, 3.74)
Abdominal discomfort	1 (9%)	2 (18%)	-0.09 (-0.38, 0.19)	0.50 (0.05, 4.75)
Heartburn/GER	1 (9%)	1 (9%)	0.00 (-0.24, 0.24)	1.00 (0.07, 14.05)
Other				
Musculoskeletal pain	2 (18%)	2 (18%)	0.00 (-0.32, 0.32)	1.00 (0.17, 5.89)
Acute kidney injury	1 (9%)	0 (0%)	0.09 [-0.13, 0.31]	3.00 (0.14, 66.53)
Vitreous haemorrhage	1 (9%)	0 (0%)	0.09 [-0.13, 0.31]	3.00 (0.14, 66.53)

Abbreviations: AE=adverse events, GER=gastroesophageal reflux, SAE=serious adverse events,
Italics: calculated during the preparation of this report using RevMan5.3
Source: Lederer 2014

Sarmiento 2016 only reported low back pain and polypnea during infusion as AEs related to IVIG. The authors reported AE and severe AEs (SAEs) in patients treated with IVIG during IVIG treatment (4 months) (Table 9), but due to the lack of AE reporting in non-IVIG HGG patients it is unclear if these AEs are associated with IVIG or the underlying condition. The quality of AEs reporting in this study is quite poor; SAEs were reported within the text but it is not clear if this list was exhaustive or if the listed SAEs were just more detailed adverse events already noted in a separate table in the study (e.g. diarrhoea and severe diarrhoea). Also, renal failure was considered an AE rather than a SAE.

Table 9 AE in post heart transplant HGG patients treated with IVIG (Sarmiento 2016, n=12)

AE IVIG	*n (%)*	*Severe AE IVIG**	*n (%)*
Anemia	2 (16.6)	Lower limb neuropathy	1 (8.3)
Leukocytosis	1 (8.3)	Sensory and motor polyneuropathy	1 (8.3)
Lymphopenia	1 (8.3)	Rectorrhagia	1 (8.3)
Auricular fibrillation	1 (8.3)	Septic shock	2 (16.6)
Pericardial effusion	1 (8.3)	Severe diarrhoea	1 (8.3)
Diarrhoea	1 (8.3)	Pancytopenia	1 (8.3)
Renal failure	2 (16.6)	Primary graft failure	1 (8.3)
Muscular neuropathy	1 (8.3)		
Post-bleeding hypotension	1 (8.3)		

AE=adverse events; * It is not clear whether this list is exhaustive or whether it is a subset of the AE listed in the first column

Shankar 2013 reported that three (30%) patients experienced local infusion site reactions (swelling, erythema, soreness) after SCIG that resolved spontaneously. One patient (10%) developed transfusion-related acute lung injury (TRALI) after one dose of IVIG, but no other AEs were reported during the 1-year study period.

IS IG-RT EFFECTIVE?

Summary – Is Ig-RT effective in the treatment of secondary HGG unrelated to haematological malignancies or HSCT?

Only three studies presented comparative evidence of Ig-RT vs. no Ig-RT in the population of interest, and the quality of the available evidence was very low for all the effectiveness outcomes. Therefore, there is a very high level of uncertainty around the effectiveness of Ig-RT in this population.

Sarmiento 2016 indicated a significant reduction in the risk of infections for IVIG-treated HGG patients after heart transplant, but it is unclear whether this effect is generalisable to other patients with HGG. Effectiveness of Ig-RT in lung transplant patients was contradictory, with each study indicating a different direction of the Ig-RT effect for the key outcome of infections. No comparative evidence from other HGG populations was found.

The effect of Ig-RT on survival is very uncertain.

EFFECTIVENESS OUTCOMES IG-RT VS NO IG-RT

Three studies reporting on the effectiveness of Ig-RT compared to no Ig-RT in the population of interest were identified in the systematic review (Lederer et al. 2014; Sarmiento et al. 2016; Lichvar et al. 2018). Detailed information on Ig-RT treatment duration and follow up was limited (Appendix C Studies included in the Systematic Review).

Results from these studies are presented by outcome below, and summarised in the evidence profile tables in Appendix D. A meta-analysis was not possible due to the heterogeneity across the included studies, and the evidence profile tables were adapted accordingly.

INFECTIONS AND SEVERE INFECTIONS

Table 10 presents the comparative evidence assessing IVIG vs. no IVIG for the outcomes of infections and severe infections.

In the two studies of lung transplant patients with HGG, there were no significant between-group differences for the outcome of "any infections" (Lichvar et al. 2018; Lederer et al. 2014). These two studies had very different study designs:

- Lederer 2014 was a crossover RCT with only 11 patients with 12-week treatment/placebo intervals and 12-week washout period, with the primary outcome being the number of bacterial infections.
- Lichvar 2018 was a large retrospective study with a 5-year follow-up, and the primary outcome was the development of chronic lung allograft dysfunction (CLAD).

The heterogeneity between these studies was too high to conduct a meaningful meta-analysis.

In heart transplant patients with HGG, Sarmiento 2016 reported a significantly reduced risk of severe infections following IVIG treatment compared to no IVIG treatment. In addition, results indicated that HGG patients given IVIG were significantly more likely than no IVIG patients to spend longer free from severe infections during the 6-month follow-up period (Cox regression model HR=4.58, 95% CI 1.16-16.83, p=0.021)(Sarmiento et al. 2016).

Table 10 Infections and severe infections: Ig-RT vs. No Ig-RT

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
Any infections							
Lederer 2014[a]	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[b]	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[d]	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[e]	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[a]	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[a]	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[f, g]	Heart transplant	Serious	3/12 (25)	9/13 (69.2)	***-0.44 (-0.79, -0.09)***	*RR 0.36 (0.13, 1.03)*	6m

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

Italics=unadjusted analysis calculated during the preparation of this report using RevMan5.3. **Bold**=significant difference

[a] Only OR reported in the study, analysis done using generalised estimating equations and logit, adjusted for drug and period

[b] Only % infections reported, no statistical analysis comparing IVIG vs. no-IVIG conducted in the study

[c] 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)

[d] Only p value reported (p=0.009) in the study, analysis done using Chi-square

[e] Only p value reported (p=0.016) in the study, analysis done using Chi-square

[f] Bacterial infection requiring IV therapy

[e] Only p value reported (p=0.027) in the study, analysis done using Chi-square

Data on antibiotic prophylaxis or treatment for bacterial infections was poorly described across the trials (see Table 46 in Appendix C). Lichvar 2018 defined infections as requiring oral or parenteral antibiotic or antiviral treatment, but no details on concomitant treatment were included (Lichvar et al. 2018). Sarmiento 2016 only mentioned that antibiotic prophylaxis with cefazolin was conducted on the first day after transplantation, oral trimethoprim-sulfamethoxazole given two days (twice each day) a week during the first year, and oral norfloxacin twice daily during the first month.

Universal prophylaxis with IV ganciclovir or oral valganciclovir was administered to all patients positive for viral infections. However, there was no data on doses given and differential treatment/duration between the groups (Sarmiento et al. 2016).

Lederer 2014 was the only study reporting antibiotic initiation data in the IVIG-group vs. placebo (OR 1.4, 95% CI 0.3 to 6.0, p = 0.61), but the specific antibiotics used or treatment duration were not mentioned (Lederer et al. 2014).

TRANSPLANT REJECTION

There were no significant differences between treatment groups for the outcome of acute rejection (Table 11). In Lichvar 2018, median A-grade rejection scores (sum A grades/total number of biopsies) were significantly higher in IVIG-treated patients 5 years after transplantation, but no significant differences were seen at Year 1 and 2. By year 5, patients given IVIG were less likely to experience grade 2 CLAD than IVIG-untreated patients, but there were no significant differences in grade 3 CLAD rates. CLAD encompasses a range of pathologies that cause a transplanted lung to not achieve or maintain normal function, and is predominantly a result of chronic rejection[9].

[9] Gauthier JM, Hachem RR, Kreisel D. Update on Chronic Lung Allograft Dysfunction. Curr Transplant Rep. 2016;3(3):185–191.

Table 11 Acute rejection and Chronic lung allograft dysfunction: Ig-RT vs. No Ig-RT

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
Acute rejection							
Lederer 2014	Lung transplant	Moderate	0/11 (0)	0/11 (0)	NA	NA	12w (2.7 months)
Sarmiento 2016[a]	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
Severe CLAD (Grades2&3)							
Lichvar 2018[b]	Lung transplant	Serious	Grade2: 13/145 (8.9) Grade3: 20/145 (13.8)	Grade2: 31/177 (17.5) Grade3: 17/177 (9.6)	***Grade2: -0.09 (-0.16, -0.01)*** *Grade3: 0.04 (-0.03, 0.11)*	***Grade2: RR 0.51 (0.28, 0.94)*** *Grade3: RR 1.44 (0.78, 2.64)*	5y
A-grade rejection score[c]			**Median (IQR)**	**Median (IQR)**			
Lichvar 2018	Lung transplant	Serious	Y1: 0.50 (0.33-1.00) Y2: 0.50 (0.29-0.83) Y5: 0.50 (0.30-0.83)	Y1: 0.50 (0.33-0.75) Y2: 0.50 (0.33-0.75) Y5: 0.38 (0.25-0.60)	NR	NR	5y

CLAD: chronic lung allograft dysfunction, HGG=hypogammaglobulinaemia, Ig-RT=immunoglobulin G replacement therapy, IQR=interquartile range, m=months, OR=odds ratio, RD=risk difference, RR=relative risk, w=weeks, y=years
Italics=unadjusted analysis calculated during the preparation of this report using RevMan5.3. Bold=significant difference
[a] Defined as rejection requiring intensified immunosuppression
[b] Only p values reported (p=0.03 for Grade2, p=0.04 for Grade3 for the difference between the HGG- treated, HGG-untreated and non-HGG groups in the study, analysis done using Chi-square
[c] Only p values reported: Y1 p=0.43, Y2 p=0.09, Y3 p=0.02 for the difference between the HGG- treated, HGG-untreated and non-HGG groups in the study, analysis done using analysis of variance, Wilcoxon rank sum test, Mann-Whitney U test or Kruskal-Wallis test.

SURVIVAL OUTCOMES

Overall survival and CLAD-free survival results are presented in Table 12 and Table 13, respectively.

Overall survival

Survival analysis in Lichvar 2018 was conducted using the Kaplan-Meier method with logrank comparisons, with results showing significantly better survival at 1, 2 and 5 years for HGG patients without Ig-RT compared to those treated with Ig-RT. These results need to be taken with caution, given the higher proportion of patients with severe HGG in the Ig-RT group and lack of adjustment for HGG severity.

Sarmiento et al. 2016 reported no significant differences in overall mortality rates. The cause of death in the IVIG-treated group was primary graft failure after retransplantation in one patient and postoperative complications and septic shock in two other patients; in the IVIG-untreated group two patients died of septic shock and one of postoperative complications and bacteraemia. Kaplan Meier analysis with logrank comparisons during the 6-month study period indicated that severe infection-free survival was significantly lower in HGG IVIG-untreated patients compared to IVIG-treated patients (logrank 15.31, p=0005). Given the similar overall mortality rates, these results suggest the difference in infection-free survival is likely due to the higher rate of severe infections in patients who did not receive IVIG.

Table 12 Overall survival: Ig-RT vs. No Ig-RT

Study ID	Cause of secondary HGG	Risk of bias	Ig-RT % survival	No Ig-RT % survival	Absolute difference (% survival)	Relative difference OR/RR (95%CI)
1-year overall survival						
Lichvar 2018 [a]	Lung transplant	Serious	75.0	88.0	*13*	P=0.006
2-year overall survival						
Lichvar 2018[a]	Lung transplant	Serious	64.8	81.3	16.5	p<0.001
5-year overall survival						
Lichvar 2018[a]	Lung transplant	Serious	56.0	67.2	11.2	P=0.006
Mortality rate (6 months)			**n with event/N (%)**	**n with event/N (%)**	**Absolute difference (RD 95% CI)**	**Relative difference OR/RR/HR (95%CI)**
Sarmiento 2016[b]	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

CLAD: chronic lung allograft dysfunction, HGG=hypogammaglobulinaemia, Ig-RT=immunoglobulin G replacement therapy, NR=not reported, OR=odds ratio, RR=relative risk

Italics=unadjusted analysis calculated during the preparation of this report using RevMan5.3.

[a] Only %survival and p numbers reported. Kaplan Meier curve not presented, number of people at risk not reported, so it was not possible to calculate the effect estimate. Logrank comparisons used in the study to calculate the p values

[b] Only p values reported, analysis done using Chi-square

CLAD-free survival

In Lichvar 2018, CLAD-free survival appeared to be similar between the two groups, but no statistical analysis was conducted in the study and data were unavailable to evaluate the difference during this assessment.

Table 13 CLAD-free survival: Ig-RT vs. No Ig-RT

Study ID	Cause of secondary HGG	Risk of bias	Ig-RT % survival	No Ig-RT % survival	Absolute difference (% survival)	Relative difference OR/RR/HR (95%CI)
1-year CLAD-free survival[a]						
Lichvar 2018[b]	Lung transplant	Serious	74.6	78.2	3.6	NR
2-year CLAD-free survival[a]						
Lichvar 2018[b]	Lung transplant	Serious	52.53	56.32	3.8	NR

CLAD: chronic lung allograft dysfunction, HGG=hypogammaglobulinaemia, Ig-RT=immunoglobulin G replacement therapy, NR=not reported, OR=odds ratio, RR=relative risk

[a] Only % survival reported, Kaplan Meier curve not presented, logrank comparisons not reported

HOSPITALISATIONS

Two studies included number of hospitalisations (Table 14), but the definitions were different. Lederer 2014 reported hospitalisations during the treatment period (Ig-RT or placebo), whereas Sarmiento 2016 reported hospital readmissions after discharge in patients who completed the 6-month follow-up period.

Lederer 2014 did not find any significant differences between the two groups. In Sarmiento 2016, unplanned readmission after discharge was only seen in IVIG-untreated patients and they reported a significant difference (p=0.013), but the RR calculated during this assessment did not confirm this. The number of events for this outcome was very low and both studies included a very small number of patients, so these results need to be interpreted with caution.

Table 14 Hospitalisations/Readmissions and length of hospital stay

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 risk OR/RR (95%CI)	Follow-up
Hospitalisations/Readmissions							
Lederer 2014[a,c]	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)
Sarmiento 2016 [b,d]	Heart transplant	Serious	0/9 (0)	5/11 (45.4)	***-0.45 (-0.77, -0.14)***	*RR 0.11 (0.01, 1.74)* P=0.013	6m
Length of hospital stay, days (range)							
Sarmiento 2016 [b]	Heart transplant	Serious	32 (16-200)	48 (12-191)	*16*	p=0.57	6m

HGG=hypogammaglobulinaemia, Ig-RT=immunoglobulin G replacement therapy, IVIG=intravenous immunoglobulin G, m=months, OR=odds ratio, RD=risk difference, RR=relative risk, w=weeks

Italics=unadjusted analysis calculated during the preparation of this report using RevMan5.3. Bold=significant difference

[a] Hospitalisation during the treatment period

[b] Hospital readmission after discharge due to infection in patients who completed follow-up

[c] Only OR reported in the study, analysis done using generalised estimating equations and logit, adjusted for drug and period

[d] Only p value reported in the study based on the Mann-Whitney test. The RR and RD and confidence intervals were calculated during the evaluation and are not associated with the p value.

IG LEVELS

Lederer 2014 reported a significant difference in Ig levels between the IVIG and placebo groups after treatment; mean 765.3 mg/dL (95% CI 720.1- 810.6) vs. 486.3 mg/dL (441.0 – 531.5), p<0.001.

SUPPORTIVE EVIDENCE: PATIENT COHORTS WITH SECONDARY HGG (UNRELATED TO HAEMATOLOGICAL MALIGNANCIES OR HSCT)?

Twelve studies including patient cohorts with secondary HGG were considered as supportive evidence. Three studies (Shankar et al. 2013; Sun et al. 2015; Zaman et al. 2019) did not have any comparator group, and the rest compared HGG patients to those without HGG (Claustre et al. 2015; Kawut et al. 2005; Noell, Dawson, and Seethamraju 2013; Carbone et al. 2007; Carbone et al. 2012; Farmer et al. 2013; Rhodes et al. 2014; Yamani et al. 2006; Boleto et al. 2018). Only data from the HGG group was extracted, as the comparison to patients without HGG is beyond the scope of this review. No supportive cohort studies were found that explicitly reported that the HGG population was not given Ig-RT. Five studies (Kawut et al. 2005; Noell, Dawson, and Seethamraju 2013; Rhodes et al. 2014; Yamani et al. 2006; Boleto et al. 2018) did not mention Ig-RT use in the HGG population and these data are presented separately to studies where it was reported that the HGG patients received Ig-RT, as it is unclear if Ig-RT was just unreported or those patients were truly untreated. Two studies included before and after Ig-RT data on Ig levels (Carbone et al. 2012; Shankar et al. 2013), but only Carbone 2012 reported number of infections before and after Ig-RT (Carbone et al. 2012).

There was a high level of heterogeneity across the studies (e.g. wide variations in population, design, follow up). The tables were adapted to present key information on the studies, and only a narrative review of the included data was possible.

INFECTIONS AND SEVERE INFECTIONS

Carbone 2012 evaluated the number of infections before and after IVIG infusions (every 2 to 3 weeks) in patients who received a heart transplant and had severe infections (Table 15).

There was a significant improvement in the number of infections after IVIG treatment across all infection outcomes. This study did not include a control group of HGG IVIG-untreated patients and all HGG IVIG-treated patients were required to have a diagnosis of severe infections before starting IVIG infusions. Therefore, the extent of the effect of IVIG on infections is uncertain as the decrease in the number of infections may be the result of the clinical course and concomitant antimicrobial medication (i.e. infections were treated with intravenous antimicrobial therapy).

Table 15 Number of infections before/after IVIG in Carbone 2012

Outcome	N patients	N infusions	Before IVIG mean (SD)	After IVIG mean (SD)	Mean difference (95% CI)[a]	Follow-up
N severe infections	55	NR	1.95 (1.2)	0.33 (0.8)	<0.001	18m
N other infections*	55	NR	0.94 (0.9)	0.33 (0.1)	<0.001	
N infections (all) stratified by n infusions	39	3	1.59 (1.0)	0.16 (0.4)	<0.001	
	9	6	2.14 (0.9)	0.14 (0.4)	0.001	
	7	>6	3.43 (1.1)	1.28 (1.4)	0.015	

Source: (Carbone et al. 2012)
CI=confidence interval, IVIG=intravenous immunoglobulin G, m=months, SD=standard deviation
*Reported as "other" infections (i.e. not severe)
[a]Only p values reported, Mann-Whitney test

Infection rates from other cohort studies are presented in Table 16 (Claustre et al. 2015; Kawut et al. 2005; Noell, Dawson, and Seethamraju 2013; Carbone et al. 2007; Farmer et al. 2013; Rhodes et al. 2014; Yamani et al. 2006; Boleto et al. 2018). The proportion of patients with HGG who developed infections varied widely across the studies, from 8.5% after lung transplantation (Claustre et al. 2015) to 95% after ventricular assist device (VAD) implantation (Yamani et al. 2006). All HGG patients in Claustre 2015 were treated with IVIG, whereas Ig-RT-status is unclear in Yamani 2006 and Rhodes 2014. Yamani 2006 explained the number of infections is usually high after VAD implantation. Rhodes 2014 stated that high (40%) infection rates were likely due to the high proportion of complex neonatal repairs (>80%) in the study population (median age was 7 days).

Mean number of infections per patient ranged from 1.4 after heart transplant (Carbone et al. 2007) to 1.89 after intestinal transplant (Farmer et al. 2013), over a follow-up period of 4.25 years and 8 weeks, respectively (see Table 16).The occurrence of bacteraemia in the HGG population was high after VAD implantation (70%), but rates were lower following VAD implantation with heart transplant (15%) (Yamani et al. 2006). More than half (62.5%) of patients with HGG who underwent lung transplantation developed pneumonia (Kawut et al. 2005), and CMV infection rates were 45% after heart transplant (Yamani et al. 2006).

Claustre 2015 reported CMV prophylaxis with ganciclovir was given to post-transplant CMV+ patients for 100 days, and to patients receiving transplants from CMV+ donors for at least 180 days, but the exact number of patients receiving CMV prophylaxis is not indicated (Claustre et al. 2015). Similarly, Kawut 2005 mentioned ganciclovir was given for the first 6-12 months depending on the donor/recipient CMV serology, but no further details were included (Kawut et al. 2005). Yamani 2006 did not mention any CMV prophylaxis protocols (Yamani et al. 2006).

Time to infection (0.9 days) was only reported in one study of patients who underwent intestinal transplant and received Ig-RT (Farmer et al. 2013).

Table 16 Infections and severe infections in patients with secondary HGG

Study ID	Cause of secondary HGG	HGG + Ig-RT	HGG - Ig-RT NR	Follow-up
Any Infections		**n with event/N (%)**	**n with event/N (%)**	
Claustre 2015	Lung transplant	5/59 (8.5)	-	3.2 years (median)
Rhodes 2014	Cardiopulmonary bypass (infants)	-	10/25 (40)	NR (postoperative period)
Yamani 2006	VAD implant		19/20 (95.0)	4 months (median duration of VAD support)
		Mean (SD)		
Carbone 2007	Heart transplant	1.89 (NR)	-	4.25y (mean)
Farmer 2013[b]	Intestinal transplant	1.4 (1.0)	-	8w
Severe infections		**n with event/N (%)**	**n with event/N (%)**	
Boleto 2018	Rituximab therapy	-	6/23 (26.1)	5.3y (mean)
Bacteraemia		**n with event/N (%)**	**n with event/N (%)**	
Yamani 2006	VAD implant		14/20 (70)	4m (median duration of VAD)
Yamani 2006	VAD implant+heart transplant	-	3/20 (15.0)	NR (post-transplant)
CMV			**n with event/N (%)**	
Yamani 2006	VAD implant+heart transplant	-	9/20 (45.0)	NR (post-transplant)
Kawut 2005[a]	Lung transplant		1/8 (12.5)	2y
Claustre 2015	Lung transplant		0	3.2y (median)
Pneumonia			**n with event/N (%)**	
Kawut 2005[a]	Lung transplant	-	5/8 (62.5)	2y
Community-acquired respiratory viruses			**n with event/N (%)**	
Noell 2013	Lung transplant Heart+lung transplant	-	45/192 (23.4)	1.67y (mean)
Time to infection		**Mean days (SD)**		
Farmer 2013[b]	Intestinal transplant	20.4 (17.1)		8w

CMV=cytomegalovirus, m=months, NR=not reported, VAD=ventricular assist device, SD=standard deviation, w=weeks, y=years
[a] Patients with severe HGG (<400mg/dL) only
[b] IVIg was given to 85% of patients with HGG.

TRANSPLANT REJECTION

The number of patients with HGG experiencing transplant rejection is presented in Table 17. The rates of rejections in HGG patients undergoing lung transplant ranged from 0% in Claustre 2015 to 35% in Noell 2013. All HGG patients in Claustre 2015 were IVIG-treated whereas Ig-RT was not mentioned in Noell 2013. In addition, patients in Claustre 2015 were younger than in Noell 2013 (mean 44.7 vs. 60 years).

The proportions of transplant rejections ranged from 32% after heart transplant to 90% after intestinal transplant.

Table 17 Transplant rejection in patients with secondary HGG

Study ID	Cause of secondary HGG	HGG + Ig-RT	HGG - Ig-RT NR	Follow-up time
Rejection		**n with event/N (%)**	**n with event/N (%)**	
Noell 2013[b,d]	Lung transplant	-	69/192 (35.9)	1.67y (mean)
Claustre 2015[a,e]	Lung transplant	0	-	2.8y (median)
		Mean (SD)	**Mean (SD)**	
Farmer 2013[a]	Intestinal transplant	0.9 (1.3)	-	8w (median)
Yamani 2006[c]	VAD implant+heart transplant	-	0.5 (0.4)	NR
Carbone 2012	Heart transplant	0.32 (0.60)	-	1.5y
Carbone 2007	Heart transplant	0.86 (NR)	-	4.25y (mean)
Time to rejection		**Mean days (SD)**		
Farmer 2013 [a]	Intestinal transplant	17.5 (6.3)	-	8w (median)

NR=not reported, y=year, w=weeks
[a] Acute cellular rejection
[b] biopsy-proven acute rejection
[c] mean episodes of acute rejection per patient
[d] 6 patients (3%) had a double lung+heart transplantation
[e] 2 patients (4%) had a double lung+heart transplantation

SURVIVAL OUTCOMES

Table 18 presents survival outcomes in the HGG group in the cohort studies.

Overall survival

Three studies conducted Kaplan Meier survival analysis (Kawut et al. 2005; Claustre et al. 2015; Yamani et al. 2006). The 5-year percent survival was 65% in IVIG-treated HGG patients who underwent lung transplantation (Claustre et al. 2015) to 80% in heart transplant patients with HGG (Ig-RT-status unknown) (Yamani et al. 2006). In lung transplant patients with severe HGG (Ig-RT-status unknown), the 2-year survival was 50%(Kawut et al. 2005).

Four studies (Noell, Dawson, and Seethamraju 2013; Carbone et al. 2012; Carbone et al. 2007; Rhodes et al. 2014) reported mortality rates during follow-up periods that varied from 1.5 to a mean of 4.25 years. Rhodes 2014 included deaths in infants with HGG after cardiopulmonary bypass, but their follow-up length was not reported.

Table 18 Survival outcomes in patients with HGG

Study ID	*Cause of secondary HGG*	*HGG + Ig-RT*	*HGG - Ig-RT NR*	*Follow-up*
Overall Survival		**(%)**	**(%)**	
Kawut 2005[a]	Lung transplant	-	50	2y
Claustre 2015	Lung transplant	65	-	5y
Yamani 2006	VAD implant+heart transplant	-	80	5y
Mortality rate		**n/N (%)**	**n/N (%)**	
Noell 2013	Lung transplant Heart+lung transplant	-	31/192 (16.7)	3y
Carbone 2012	Heart transplant	0	-	1.5y
Carbone 2007	Heart transplant	2/29 (6.9)	-	4.25y (mean)
Rhodes 2014	CPB (infants)	-	3 /25 (12)	NR (postoperative)

[a]Death-censored
VAD=ventricular assisted device
[a] patients with severe HGG (<400mg/dL)

CLAD-free survival

Claustre 2015 reported a median CLAD-free survival after lung transplant in IVIG-treated patients of 2.42 years (95% CI 1.2-4.7) (Claustre et al. 2015).

HOSPITALISATIONS

Table 19 presents data on length of ICU stay from two studies (Carbone et al. 2007; Rhodes et al. 2014). The populations in these two studies are not comparable; neonates undergoing cardiac surgery with a high proportion of complex repairs (>80%) in Rhodes 2014, and adults (mean age 54 years) who had a heart transplant in Carbone 2007.

Table 19 Length of ICU/PICU stay in patients with HGG

Study ID	Cause of secondary HGG	HGG + Ig-RT	HGG – Ig-RT NR	Follow up
Length of ICU stay		**Mean days (SD)**	**Mean days (SD)**	
Carbone 2007	Heart transplant	6.2 (3.6)		4.25y (mean)
Rhodes 2014	CPB in infants	-	16 (11)	NR (postoperative)

CPB= Cardiopulmonary bypass, HGG=hypogammaglobulinaemia, ICU=intensive care unit, Ig-RT=immunoglobulin G replacement therapy, NR=not reported, PICU=paediatric intensive care unit,

IG LEVELS (BEFORE/AFTER)

Table 20 presents data from the two studies that reported Ig levels (mg/dL) before and after IVIG treatment in patients with HGG (Carbone et al. 2012; Shankar et al. 2013), with significant increases reported after IVIG in both studies.

Table 20 Ig levels before and after IVIG

Study	N patients	N infusions	Before IVIG mean (SD)	After IVIG mean (SD)	Mean difference* (95% CI)	Time after infusion
Shankar 2013[a]	10	NR	*490.7 (134.7)*	*1036.6 (368.1)*	***546.60 (303.66, 789.54)***	3m
	10	NR	*490.7 (134.7)*	*972.2 (253.5)*	***481.50 (303.58, 659.42)***	6m
Carbone 2012	39	6	501 (28)	766 (254)	***265.00 (184.80, 345.20)***	NR[b]
	7	>6	352 (78)	1141 (203)	***789.00 (627.90, 950.10)***	

CI=confidence interval, IVIG=intravenous immunoglobulin G, m=months, NR=not reported, SD=standard deviation
*Mean differences were calculated during the preparation of this report using RevMan5.3, p value <0.01
[a] Shankar 2013 only reported individual levels of Ig for each of the 10 patients, the analysis was conducted during the preparation of this report.
[b] Study only mentioned Ig levels were measured 12 months after transplantation, but did not report the time after infusion
Ig levels in mg/dL

GOOD SYNDROME

Two studies that included patients with Good syndrome (thymoma and HGG) were identified (Sun et al. 2015; Zaman et al. 2019), both of which mainly investigated the clinical characteristics and disease course. Only a narrative review of these two studies was possible and it is presented below.

Sun 2015 presented a case series of 12 patients with Good syndrome hospitalised for moderate to severe infections. The sites of infection were respiratory (n=7), intestinal tract (n=4), and unidentified (n=1). CMV was present in 5 patients, and pure red cell aplasia (n=3) and leukopenia (n=4) were common comorbidities. Ten (83%) patients were treated with IVIG in addition to antibiotics, of whom eight (80%) achieved remission from infection, one had no response and one died (older woman who developed pure red cell aplasia). One patient received supportive care and remained stable, and one patient was given only antibiotics and achieved remission. Thymectomy was performed in ten (83%) patients.

Zaman 2018 conducted a case series of 78 patients with Good syndrome. HGG was diagnosed concurrently with thymoma in 74% of patients, whereas 12% had the HGG diagnosis 1 to 8 years before finding the thymoma, and 14% were diagnosed with HGG 1 to 6 years after the thymoma diagnosis. Initial symptoms were recurrent sinopulmonary infections in almost all patients (94%), and almost half (48%) had radiological evidence of bronchiectasis. Autoimmune disorders were present in 26% of patients (n=20), with red cell aplasia being the most common autoimmune comorbidity (n=8), followed by hypothyroidism (n=6), inflammatory arthritis (n=4), myasthenia gravis (n=3), systemic lupus erythematosus (n=3), and Sjögren's syndrome (n=2). All patients received Ig-RT and had a thymectomy; six of them had also been treated with radiotherapy, four with chemotherapy, and three with both. The authors mentioned that HGG was not improved after thymectomy in their study. Seven (9%) patients died in the 9-year period; two of metastatic thymoma, two of bacterial sepsis, one of progressive multi-focal encephalopathy and the causes of death in the other two (one of whom was aged 90 years old) were unclear.

B.7. EXTENDED ASSESSMENT OF HARMS

No post-market surveillance or unpublished data on harms were identified for this population. See section B.6 for included safety evidence.

B.8. INTERPRETATION OF THE CLINICAL EVIDENCE

On the basis of the evidence profile (summarised in Appendix D), it is suggested that, relative to no Ig-RT in patients with secondary HGG unrelated to haematological malignancies or HSCT, Ig-RT has inferior safety (though generally well tolerated with transient infusion-related AE and rare SAE) and uncertain effectiveness.

There was a high level of heterogeneity across the studies in terms of populations, treatments and study designs. The risk of bias was serious in most studies and the overall quality of the available evidence was very low, which means that we are very uncertain about the effect estimate for all of the outcomes (Appendix D Evidence Profile Tables). Many of the studies were small and were not statistically powered to detect even moderate differences in many of the outcomes considered Patients in these studies received antibiotic and antiviral prophylaxis and/or treatment of infections, but the specific treatment protocols and utilisation for each patient group were not reported.

Only one study (Sarmiento 2016), conducted in heart transplant patients, found significantly lower rates of severe infections in patients with secondary HGG treated with IVIG compared to those who did not receive IVIG (25.0% vs. 76.9%), but this study only included 25 patients (12 in the treatment group) and selection bias is a concern. There were no significant differences in any of the studies comparing Ig-RT to no Ig-RT for the other infection outcomes reported. Of interest, IVIG doses used in Sarmiento 2016 were lower than those recommended under The Criteria (0.4-0.6g/kg every 4 weeks); initially patients were administered two infusions of 0.2g/kg given two weeks apart, followed by up to 5 infusions of 0.3g/kg each, given every 4 weeks. In the Australian setting, the average dose per episode given to this population of patients with secondary HGG was 0.38g/kg (NBA 2020a) [10]

In the included supportive evidence, Carbone 2012 found a significant decrease in infections after IVIG treatment, but all HGG patients who received IVIG had severe infections at baseline and they were also treated with antimicrobial therapy, so it is not possible to attribute the decrease in infection rates to IVIG treatment without having a comparator group who did not receive IVIG.

There were no available comparative data (Ig-RT vs. no Ig-RT) for patients with HGG following B-cell depletion. However, in the cohort of patients with rheumatoid arthritis who developed HGG after

[10] NBA analysis of data indicated that the average dose when annual figures are used equates to 0.28g/kg every 4 weeks

rituximab treatment (Boleto et al. 2018), 26.1% experienced severe infection(s) over a follow-up of 5.3 years (mean), but it is unclear if these patients were treated with Ig-RT (not reported).

There were no significant between-group differences for transplant rejection, except for a significantly lower grade 2 CLAD at 5 years in patients treated with on-demand IVIG compared to no IVIG (Lichvar et al. 2018). In the same study, 1-year, 2-year and 5-year survival was significantly worse in HGG patients treated with Ig-RT than in HGG patients who did not receive Ig-RT. However, HGG patients treated with Ig-RT had more severe HGG at baseline and underwent more bilateral lung transplants than those who did not receive Ig-RT, which could have biased survival outcomes against the Ig-RT group. In the supportive studies, 5-year survival in another study of lung transplant recipients (Claustre et al. 2015) was higher than that reported by Lichvar 2018 (65% vs. 56.0%). Lichvar 2018 reported a longer time from transplant to Ig-RT initiation and shorter duration of Ig-RT than in Claustre 2015, which could have also had an impact on poorer outcomes. Another cohort of lung transplant patients with HGG had a lower survival at 2 years (50%), but the study did not report any details on Ig-RT (Kawut et al. 2005).

For the outcome of 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-RT versus no Ig-RT. However, both studies included a very small number of patients and hospitalisations, limiting our confidence in any conclusions.

The authors in Lichvar 2018 stated that on-demand Ig-RT remains “problematic” in lung transplant patients and further studies are needed to identify optimal therapeutic strategies. Similar conclusions were reached by Lederer 2014, the only RCT of IVIG vs. placebo, in lung transplant patients. Sarmiento et al. were more positive, suggesting “preliminarily” that IVIG could reduce the frequency of severe infections in patients undergoing heart transplantation.

SECTION C TRANSLATION ISSUES

C.1. APPLICABILITY TRANSLATION ISSUES

POPULATION

Our population of interest includes patients with secondary HGG excluding haematological malignancies and HSCT:

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

These patient subgroups are very heterogeneous, with different underlying conditions, concomitant treatments, and HGG course. For example, contributing factors to development of HGG include underlying patient (including inherited/genetic) factors, along with autoimmune (such as in Good syndrome) and other diseases, or receiving one or more therapies (including immunosuppression and transplantation) for a range of other primary diseases, any or all of which may introduce qualitative and quantitative deficiencies in a patient's own ability to both produce antibodies, and other aspects of mounting an immune response. For example, patients undergoing solid organ transplantation receive different immunosuppressive therapies depending on their underlying disease necessitating the transplantation, the organ(s) being transplanted, and individual comorbidities. They are at high risk of a range of viral, bacterial and other infections as well as transplant rejection; and their IGRT requirements may differ from the other subgroups. Furthermore, the cause of HGG in the "Other" subgroup is unknown, which makes it difficult or even impossible to evaluate the outcomes of Ig treatment.

Only three studies of patients with HGG following solid organ transplantation, two lung transplants studies (Lederer et al. 2014; Lichvar et al. 2018) and one heart transplant study (Sarmiento et al. 2016) included comparative data of patients treated with Ig-RT vs. no Ig-RT such that an economic evaluation could be considered. Even in these comparative studies there is only limited information available thus making a full economic evaluation difficult. These solid organ transplantation patients are a very specific subpopulation of patients with secondary HGG, and clinical outcomes from these studies are not generalisable to the wider population of patients with secondary HGG excluding haematological malignancies or HSCT, in particular given their high risk of infection, transplant rejection and mortality. There is not enough available evidence that could be used to inform an economic evaluation for patients with HGG following B-cell depletion or Good Syndrome. In

addition, patients in the group of "Other HGG unrelated to haematological malignancies or HSCT) accounted to 51.9% of Ig use for this condition in the calendar year 2019 where underlying condition was recorded in V3 (NBA 2020a)[11] and given the lack of an indication it is not possible to know the effectiveness and thus cost-effectiveness of Ig-RT in this case.

The patients' ages in these comparative solid organ transplantation studies are similar to BloodSTAR data[1] for the year 2017-18. The average age of patients treated with Ig-RT in the patients with secondary HGG excluding haematological malignancies or HSCT was 56 years, the same as heart transplant patients treated with IVIG in Sarmiento 2016. Patients treated with IVIG in the two lung transplant studies were slightly older on average (60 years old).

UTILISATION DATA

The data from the three studies that compared Ig-RT to no-Ig-RT in solid organ transplant patients (Sarmiento et al. 2016; Lederer et al. 2014; Lichvar et al. 2018) could be potentially used in the model, but Ig-RT use in these trials may be lower than the utilisation recommended in the Australian setting. The total number of doses in Lederer 2014 and Sarmiento 2016 were three and up to seven, respectively, while Lichvar 2018 reported a median of only two doses. No other utilisation data was found in the studies for patients with HGG following B-cell depletion or Good Syndrome.

The criteria for the clinical use of intravenous immunoglobulin in Australia (NBA 2019a) recommends the following maintenance doses:

- IVIG dose of 0.4–0.6g/kg every four weeks or more frequently to achieve Ig trough level of at least the lower limit of the age-specific serum Ig reference range
- SCIG dose of 0.1-0.15g/kg every week or more frequently to achieve Ig trough level of at least the lower limit of the age-specific serum Ig reference range.

Initial review is recommended within six months and ongoing reviews by a specialist at least annually to assess clinical benefit, which would potentially result in 6 IVIG doses (one dose per month) per patient if treatment duration is 6 months and more than double if treatment continues over one year. Doses may be given more frequently than every 4 weeks if deemed necessary. It is recommended that any cessation of the therapy occurs in September/October, with repeat clinical and/or immunological evaluation to consider the need for recommencement of therapy (NBA 2019a).

[11] Unpublished Australian data provided by the NBA on Ig use and cost

The amount of IVIG in each of the doses also varied across the three studies: 0.2 to 0.3 g/kg in Sarmiento 2016, 0.4 g/kg in Lederer 2014, and 0.5 g/kg in Lichvar 2018. The average dose in the Australian setting was 0.38g/kg/episode (NBA 2020a)[12]. For 2017/18 and 2018/19 using annual figures, average dose/month = 0.28g/kg. It should also be noted that initiation doses are normally larger and these averages do not distinguish between initiation doses and doses associated with longer term use. There are some caveats relating to these data that need to be considered:

- Data is incomplete for some records in both patient and authorisation data. For example, data from STARS and BloodSTAR may not include weight. Legacy data entered into BloodSTAR did not include weight.
- Patient Counts are distinct counts and will not sum for National or Total rows and columns, as patients may have more than one specific condition, have product dispensed in more than one state, have dispense episodes recorded at a private facility and at a public facility, have received IVIG and SCIG or received both domestic and imported product.
- Previous reporting for Ig named conditions as Primary Diagnosis or grouped conditions as Disease Category. In BloodSTAR these are known as Specific Conditions or Medical Conditions respectively.
- For 2017-18 Specific and Medical Conditions are based on the Criteria for the clinical use of intravenous immunoglobulin in Australia (the Criteria) version 2 (V2). For 2018-19 where there is a one to one map Specific and Medical Conditions are based on Criteria version 2 and for all others it is Criteria version 3 (V3).
- Age data is based on the patient's age at 1 January each year.

Table 21 presents mean Ig doses used by a sample of patients with secondary HGG during the first 180 days of Ig treatment (unpublished NBA patient-level analysis). A total of 161 Australian patients started Ig treatment for secondary HGG from November 2018 to April 2019, however a number of these patients (67), although commenced on V3 still had data mapped to V2 when they started Ig treatment which did not provide a breakdown of the Criteria V3 sub-groups they would be allocated to and were therefore excluded from the analysis. Where the underlying condition was recorded when starting treatment, the mean Ig doses used during this treatment period were similar across the three patient subgroups, ranging from 184.0 g in patients treated for HGG due to "other" underlying causes to 189.4 g in those treated for HGG following B-cell depletion therapy. There were no patients with Good syndrome in this sample. There was insufficient data available to understand the long-term use and length of treatment in each subpopulation of interest.

[12] Based on a combination of STARS and BloodSTAR data. Not all transactions have age and weight so the Ig g/kg and age calculations may be incomplete. Treatment episodes have not been completed or are not correct for some STARS data, so the calculations may be overstated. Some patients may have doses split over consecutive days and these may be recorded as either one or two episodes of treatment, which may lead to an underestimation of the dosage used.

Table 21 Mean Ig dose (grams) in the first 180 days of treatment, by underlying HGG underlying cause

Secondary HGG by underlying cause	N (%)	Mean dose (g)	Max dose (g)	Min dose (g)
B cell depletion therapy	36 (22.4)	189.4	302.5	55
Solid organ transplantation	21 (13)	185.8	262.5	75
Other underlying causes	37 (23)	184.0	280	60
Good syndrome*	-	-	-	-

*There were no patients with secondary HGG following Good syndrome in the sample Not that a number of patients started treatment still under V2.
Source: Individual patient-data analysis provided by the NBA and analysed by the Department of Health.

CLINICAL DATA

Clinical data from patients with HGG following heart transplant (Sarmiento et al. 2016) and lung transplant (Lichvar et al. 2018; Lederer et al. 2014) is presented in Table 22. As mentioned in Section B, these studies are at very high risk of bias and our confidence in the effect estimates is very low.

Table 22 Clinical data from Section B to consider for the economic model

Outcomes	Ig-RT n/N (%)	No Ig-RT n/N (%)	Follow up	Study
HGG after lung transplant				
Any infections	7/11 (63.6)	3/11 (27.3)	12 weeks (2.7months)	Lederer 2014
	139/216 (64.3)	139/192 (72.4)	5 years	Lichvar 2018
Transplant rejection	0/11 (0)	0/11 (0)	12 weeks (2.7months)	Lederer 2014
5-year Survival	56.0%	67.2%	5 years	Lichvar 2018
Hospitalisations[a]	3/11 (27.3)	1/11 (9.1)	12 weeks (2.7months)	Lederer 2014
Length of Hospital stay	NR	NR	NR	NR
HGG after heart transplant				
Severe infections	3/12 (25.0)	10/13 (76.9)	6 months	Sarmiento 2016
Transplant rejection	1/12 (8.3)	1/13 (7.7)	6 months	Sarmiento 2016
Mortality rate	3/11 (27.3)	3/12 (25)	6 months	Sarmiento 2016
Hospital Readmission[b]	0/9 (0)	5/11 (45.4)	6 months	Sarmiento 2016
Length of Hospital stay (days)	32 (16-200)	48 (12-191)	6 months	Sarmiento 2016

[a] Hospitalisation during the treatment period
[b] Hospital readmission after discharge due to infection in patients who completed follow-up

QOL DATA

None of the studies included in Section B reported QoL data. The economic literature review conducted in Section D identified a recent Australian cost-utility analysis (CUA) that included utilities for the population of secondary HGG following malignancies (Windegger et al. 2019), but only treated patients with IVIG or SCIG were included and their patient population was different from the population of interest in this assessment (see Section D). The applicability of QoL data to our population may be limited.

HEALTHCARE UTILISATION AND COST DATA

None of these studies (Sarmiento et al. 2016; Lederer et al. 2014; Lichvar et al. 2018) reported cost data. There was limited data on hospitalisations and length of hospital stay, and no data on the impact of infections on healthcare utilisation. BloodSTAR Ig utilisation data from 2017-18 and 2018-19 was provided by the NBA (NBA 2020a) along with Ig use in the 2019 calendar year and is presented in Section D and Section E.

EVIDENCE GAPS

There is a lack of evidence to estimate the cost and health implications of funding Ig in patients with secondary HGG unrelated to haematological malignancies or HSCT.

The population of interest includes very heterogeneous subpopulations, and there was only very low-quality evidence in the subpopulation of HGG following heart and lung transplant. This is a very specific subpopulation of patients with secondary HGG, and clinical outcomes from these studies are not generalisable to the wider population of patients with secondary HGG excluding haematological malignancies or HSCT, in particular given their high risk of infection, transplant rejection and mortality.

There were not enough data to inform an economic evaluation for patients with HGG following B-cell depletion or Good Syndrome. In addition, patients in the group of "Other HGG unrelated to haematological malignancies or HSCT accounted to 51.9% of Ig use in Australia in the 2019 calendar year according to NBA data (NBA 2020a) and given the lack of details on the underlying conditions it is not possible to know the effectiveness and cost-effectiveness of Ig-RT in this HGG subpopulation.

None of the studies included in Section B reported QoL data.

Ig-RT use: Data on Ig-RT use from the three studies that compared Ig-RT to no-Ig-RT in solid organ transplant patients (Sarmiento et al. 2016; Lederer et al. 2014; Lichvar et al. 2018) could be potentially used in the model, but Ig-RT use in these trials may be lower than the utilisation recommended in the Australian setting. The total number of doses in Lederer 2014 and Sarmiento 2016 were three and up to seven, respectively, while Lichvar 2018 reported a median of only two doses. No other data on Ig-RT use was found in the studies for patients with HGG following B-cell depletion or Good Syndrome.

Healthcare utilisation and cost data: None of these studies (Sarmiento et al. 2016; Lederer et al. 2014; Lichvar et al. 2018) reported cost data. There was limited data on hospitalisations and length of hospital stay, and no data on the impact of infections on healthcare utilisation. BloodSTAR Ig utilisation data from 2017-18 and 2018-19 was provided by the NBA (NBA 2020a), along with use in the calendar year 2019, and is presented in Section D and Section E.

Further research to address the gaps: Given the heterogeneous population and small numbers of patients in each treatment group it is unlikely that sufficiently large randomised controlled trials will be conducted in the immediate future to inform an economic evaluation. Further research that links patient-level Ig-RT use to hospitalisation, Medicare and mortality data may be warranted to allow a better understanding of the healthcare use and outcomes for this population.

SECTION D ECONOMIC EVALUATION

D.1. OVERVIEW

The clinical evaluation suggested that, relative to no Ig-RT, Ig-RT has inferior safety and uncertain effectiveness based on the evidence profile given in Section B. Table 23 sets out the framework that was used to classify the clinical evidence in Section B so that a decision could be made about the type of economic analysis to undertake (if any) in this Section.

Table 23 Classification of the comparative effectiveness and safety of the proposed therapeutic medical service compared with its main comparator and guide to the suitable type of economic evaluation

Comparative safety	Comparative effectiveness			
	Inferior	Uncertain[a]	Non-inferior[b]	Superior
Inferior	Health forgone: need other supportive factors	Health forgone possible: need other supportive factors	Health forgone: need other supportive factors	? Likely CUA
Uncertain[a]	Health forgone possible: need other supportive factors	?	?	? Likely CEA/CUA
Non-inferior[b]	Health forgone: need other supportive factors	?	CMA	CEA/CUA
Superior	? Likely CUA	? Likely CEA/CUA	CEA/CUA	CEA/CUA

CEA=cost-effectiveness analysis; CMA=cost-minimisation analysis; CUA=cost-utility analysis
? = reflect uncertainties and any identified health trade-offs in the economic evaluation, as a minimum in a cost-consequences analysis
[a] 'Uncertainty' covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or the comparative safety considerations
[b] An adequate assessment of 'non-inferiority' is the preferred basis for demonstrating equivalence

D.2. POPULATION AND SETTINGS

Our population of interest includes patients with secondary HGG excluding haematological malignancies and HSCT, including:

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

Ig-RT can be delivered by IV infusion (IVIG) or subcutaneously (SCIG). Patients receiving IVIG will generally attend hospital for a day procedure to be infused by a nurse or doctor, and patients or carers administering SCIG will require training and sufficient capability to administer the product at home. SCIG delivery also requires the appropriate infusion equipment for the particular product. SCIG programs are not available at all hospitals. This varies depending on the local jurisdiction's policy, and the local hospital's capacity.

D.3. STRUCTURE OF A POTENTIAL ECONOMIC EVALUATION

LITERATURE REVIEW

In order to appraise the published economic evidence around treatment of secondary HGG, a systematic literature review was undertaken. The economic literature was searched on 28th January 2019 with no date limits. The search strategy used CADTH's Economic Search Filters[13] and the databases OVID MEDLINE, Embase, NHS EED and Cochrane. An overview of the method is provided in Table 24.

Table 24: Method for reviewing economic literature pertaining to secondary HGG

Inclusion Criteria	Exclusion criteria	Outcomes of interest
• Studies comparing Ig-RT versus no Ig-RT in patients with secondary HGG excluding haematological malignancies • English language full-text publications • Cost-utility analyses, cost-effectiveness analysis, cost-benefit analyses, or cost minimisation analyses	• Abstracts, posters, letters and editorials • Unpublished studies • Publication year <2000.	• Costs • Health-related quality of life, health state utility values or QALYs • Incremental cost effectiveness including ICER

HGG=hypogammaglobulinaemia, ICER=incremental cost effectiveness ratio, Ig-RT=immunoglobulin G replacement therapy, QALY=quality adjusted life year

The search strategy identified 325 citations, with 37 duplicates. There were no studies relevant to our population and the majority of the studies contained information on HRQOL and costs for patients with secondary HGG following haematological malignancies or primary immunodeficiency.

There were no studies relevant to our population of interest. An Australian study in patients with secondary HGG following malignancies or associated treatment, including haematological malignancies was identified (Windegger et al. 2019). This study conducted a cost-utility analysis, using a healthcare payer perspective, of IVIG versus SCIG for patients, and contains some HRQOL and costing information, but the applicability to our population is limited due to the substantial differences in underlying diagnosis and management of these conditions, (see Section C1 Applicability translation issues for a description of these differences and Appendix F for further details on this cost utility study).

While some of these cost and outcomes may be adapted to our population to model high-level estimates of cost-effectiveness, the required assumptions needed are unlikely to hold in practice, and thus is likely to result in an extremely high level of uncertainty to the evaluation.

[13] https://www.cadth.ca/resources/finding-evidence/strings-attached-cadths-database-search-filters

POSSIBLE MODEL STRUCTURE

The key outcomes included in the PICO required to develop the economic model are presented in Table 25.

Table 25: Model Outcomes from PICO

Clinical effectiveness outcomes	Healthcare system resource utilisation
• Infections • Quality of life • Mortality • Transplant rejection rates • Ig trough levels	• Ig products • 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

ICU=intensive care unit, Ig=immunoglobulin G, IVIG=intravenous immunoglobulin G, SCIG=subcutaneous immunoglobulin G
Source: MSAC PICO 1591 ratified.

Current available data from Windegger 2019 (Windegger et al. 2019) includes patients with secondary HGG following haematological malignancies, and there is little information available from studies of patients with secondary HGG excluding haematological malignancies and HSCT. There is also minimal clinical data and a near complete lack of cost information for the control arm, that is, for patients with secondary HGG excluding haematological malignancies and HSCT who do not receive Ig-RT. This makes it difficult to build even a simple model, such as the one proposed below (Figure 6), as any cost-effectiveness estimates obtained from such a model using data from Windegger 2019 will not be applicable to our population of interest.

This model would only consider heart and lung transplant patients for whom some information is available. However, this information is incomplete and some inputs would need to be obtained from studies of heart and lung transplant patients without HGG, which is not the specified population in the control arm of the model. In addition, outside of the solid organ transplant group, information is lacking on the other three subpopulations of patients with secondary HGG (i.e. Good syndrome, HGG following B cell depletion therapy, and Other secondary HGG unrelated to haematological malignancies or HSCT).

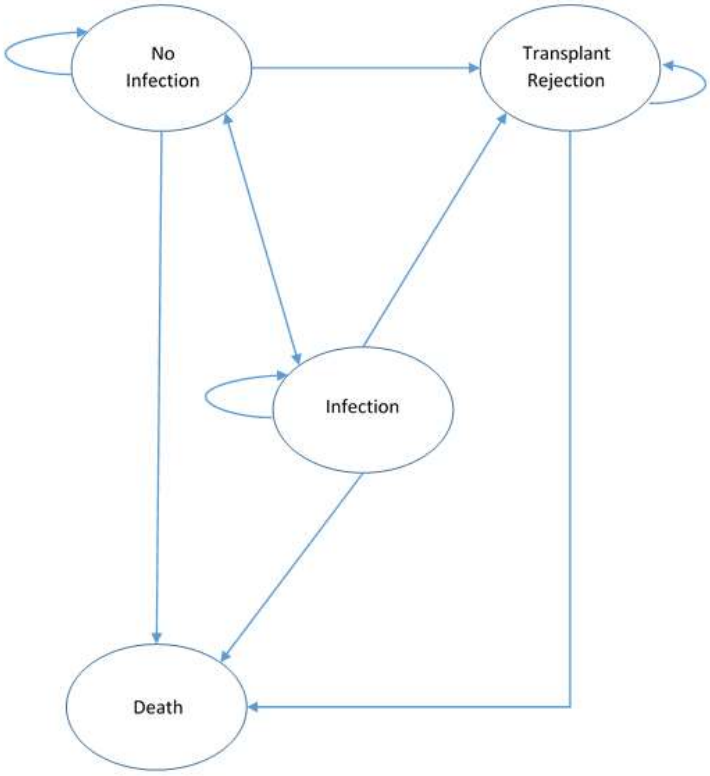

Figure 6 Proposed Simplified Economic Evaluation Model for solid organ transplant patients Only

Transplant patients would enter the model without an infection. They would either remain in this no infection state or develop an infection, reject their transplant or die. Those who developed an infection could either transition back to the no infection stage, remain in the infection state, reject their transplant or die. If a patient rejected their transplant, they would remain in that state or die. This model could be run over a 10-year time horizon, with 1-week cycles. However, given the lack of information on many of the clinical outcomes and costs of Ig-RT vs. no Ig-RT, it is not possible to populate this model and strong assumptions would need to be made. Hence, any results obtained from this model would not be generalizable to the much larger target population and would not fully capture all health and healthcare utilisation impacts.

D.4 INPUTS TO THE ECONOMIC EVALUATION

The sections below highlight the gaps and data limitations in the inputs required to populate an economic model.

TRANSITION PROBABILITIES

Data on transition probabilities could be obtained from Windegger 2019 (Windegger et al. 2019), which is the only study found in the Australian setting (Table 26). It should be noted that this study includes secondary HGG due to haematological malignancies and is not directly applicable to patients with HGG following solid transplant. The applicability of this study to our population of interest is limited, but is the only available source for probabilities in patients with secondary HGG.

Table 26: Transition Probabilities (1 year) – Secondary HGG (incl haematological malignancies), Ig-RT

	No Infection	Infection	Transplant Rejection	Death	Source	Applicability
IVIG						
No Infection	0.947	0.053	Not Available	0.00034	Windegger 2019	Different population of secondary HGG
Infection	0.592	0.313	Not Available	0.00142	Windegger2019	Different population of secondary HGG
Transplant Rejection	Not Applicable	Not Applicable	Not Applicable	Not Available	Not Available	
SCIG						
No Infection	0.956	0.044	Not Available	0.00034	Windegger 2019	Different population of secondary HGG
Infection	0.463	0.486	Not Available	0.00142	Windegger 2019	Different population of secondary HGG
Transplant Rejection	Not Applicable	Not Applicable	Not Applicable	Not Available	Not Available	

Source: (Windegger et al. 2019)

Transition probabilities in the population of lung and heart transplant patients could be derived from data for IVIG in the treated and untreated populations (Table 27). However, there are serious limitations regarding these data. As earlier mentioned, these studies are at very high risk of bias and our confidence in the effect estimates is very low. Even though we know the overall rate of transplant rejection in both arms for these studies we do not know if these were preceded by an infection and, therefore, the transition probabilities from infection to transplant rejection could not be calculated.

Table 27: Transition Probabilities availability – Secondary HGG (incl haematological malignancies), Transplant Patients (Ig-RT vs No Ig-RT)

	No Infection	Infection	Transplant Rejection	Death	Source	Applicability
IVIG						
No Infection	Possible	Possible	Not available	Possible	Sarmiento 2016, Lederer 2014, and Lichvar 2018	Only heart and lung transplant patients. Low quality evidence.
Infection	Not available	Not available	Not available	Not available	Not available	-
Transplant Rejection	Not available	Not available	Not available	Not available	Not available	-

	No Infection	Infection	Transplant Rejection	Death	Source	Applicability
SCIG						
No Infection	Not available	Not available	Not available	Not available	Not available	-
Infection	Not available	Not available	Not available	Not available	Not available	-
Transplant Rejection	Not available	Not available	Not available	Not available	Not available	-

Source: (Lederer et al. 2014) (Lichvar et al. 2018; Sarmiento et al. 2016)

Data from a US study in lung transplant patients (Alrawashdeh et al. 2017) could be used to derive the probabilities in the no-Ig-RT group (Table 28). However, this study did not evaluate HGG or Ig-RT. These are the probabilities of a wider population of lung transplant patients, including those without HGG, and, hence, are unlikely to accurately respresent our control group. In addition, infection and/or transplant rejection were only reported as the cause for readmission, so this may be an underestimate as infections that occurred before hospital discharge were not included.

Table 28: Probabilities (1 year) – Lung Transplant, no Ig-RT, no HGG

Probabilities	Data	Source	Applicability
Infection	0.254	Alrawashdeh 2017	Cause or readmission during first year after transplant (USA)
Transplant Rejection	0.099	Alrawashdeh 2017	
Infection and Transplant Rejection	0.07	Alrawashdeh 2017	
Readmission	0.836	Alrawashdeh 2017	
Death	Not available	Not available	-

Source: (Alrawashdeh et al. 2017)
Includes all heart transplant patients and not just those eligible for Ig-RT.

A UK HTA in heart patients (Sutcliffe et al. 2013) reported monthly transition probability from support on heart transplant to death, presented in Table 29 below. No other transition probabilities were found for heart transplant patients who did not receive Ig. This represents probabilities for all heart transplant pateints, including patients who are not eligible for Ig-RT and hence are unlikely to accurately represent the experience of our control group.

Table 29: Probabilities (1 month) – Heart Transplant, no Ig-RT, no HGG

Probabilities	Data	Source	Applicability
Infection	Not available	Not available	-
Transplant Rejection	Not available	Not available	-
Death Month 1 – 3	0.070	Sutcliffe 2013	UK
Death Month 4 – 284	0.003	Sutcliffe 2013	

Source: (Sutcliffe et al. 2013)
Includes all heart transplant patients and not just those eligible for Ig-RT.

UTILITIES

For utilities, the only information available for Ig-RT- treated patients is from Windegger 2019 (Windegger et al. 2019), who report values for patients with secondary HGG, including haematological malignancies, treated with Ig-RT. In no-Ig-RT patients, utilities may be obtained from the UK HTA on heart transplant patients (Sutcliffe et al. 2013) and a Portuguese cost-effectiveness study in lung transplant patients (Mendonca et al. 2014). These are presented in Table 30.

Table 30: Utilities

Health States	Utility Score	Source	Applicability
No Infection	0.71 [0.67;0.75]	Windegger 2019	Includes HGG due to haematological malignancies
Infection	0.70 [0.63;0.76]	Windegger 2019	
Single lung transplant			
First 6 months	0.69	Mendonça 2014	Portuguese
7 – 18 months	0.66	Mendonça 2014	
19 – 36 months	0.65	Mendonça 2014	
37 Months+	0.61	Mendonça 2014	
Double lung transplant			
First 6 months	0.75	Mendonça 2014	Portuguese
7 – 18 months	0.83	Mendonça 2014	
19 – 36 months	0.81	Mendonça 2014	
37 Months+	0.82	Mendonça 2014	
Heart Transplant	0.76 [0.73;0.79]	Sutcliffe 2013	UK

Source: (Sutcliffe et al. 2013; Mendonca et al. 2014; Windegger et al. 2019)

COSTS

Cost data could only be obtained from Windegger 2019, but as previously mentioned, the applicability to our population of interest is limited (Table 31 and Table 33). The estimated (base case) cost for Ig was $60.41 per gram (with a lower and upper estimate ranging from $44.94 to $140.18). The estimated base case cost is calculated based on the average cost of 2017/2018 domestic IVIG (Total Domestic IVIG Cost: $191 million, Total Domestic IVIG Grams: 3.2 million, Domestic IVIG Cost per Gram: $60.41) (NBA 2020c). The estimated lower bound cost is obtained using the average costs of 2017/18 imported IVIG (Total Imported Cost: $124 million, Total Imported IVIG Grams: 2.8 million, Imported IVIG Cost per Gram: $44.94). The estimated upper bound cost is obtained by adding the cost of plasma for fractionation (excluding hyperimmune plasma for fractionation) of $252.2 million to the domestic IVIG costs (Total Domestic IVIG + Plasma Cost: $443.2 million, Total Domestic IVIG Grams: 3.2 million, Domestic IVIG + Plasma Cost per Gram: $140.18). In addition, a weighted average Ig costs of $94.51 (Total Domestic + Imported IVIG & SCIG + Plasma Cost: $579.2 million, Total Domestic + Imported IVIG & SCIG Grams: 6.1 million, Domestic + Imported IVIG & SCIG + Plasma per Gram: $94.51) (NBA 2020c).

Table 31: Mean Cost per patient and other Model Data – Secondary HGG (incl. haematological malignancies)

All costs in AUD (2018)	IVIG	SCIG	Source	Applicability
Mean Weekly Costs per patient				
Ig product	357.29	417.10	Windegger 2019	Different population of secondary HGG
Consumables	4.94	20.88	Windegger 2019	
Springfusor® pumps for SCIg only	0	1.0	Windegger 2019	
Direct and Indirect ward cost for treatment	53.54	24.08	Windegger 2019	
Initial training cost for SCIg	0	600.00	Windegger 2019	
Haematologist consult fee (2 visits/year)	6.84	6.84	Windegger 2019	
Pathology test	6	4	Windegger 2019	
Mean costs per infection				
Infection with no hospitalisation	160.05	123.38	Windegger 2019	Different population of secondary HGG
Infection with hospitalisation	6927	5884	Windegger 2019	

Source: (Windegger et al. 2019)

National data on cost of Ig, total usage, usage per patient, and the number of new patients was obtained from a for-purpose HTA conditions data workbook (NBA 2020a) provided by the NBA (Table 32). NBA provided data on Ig utilisation for the year 2018-2019. The dataset included some utilisation data for the different HGG subgroups (collected under Criteria V3) but some 2018-2019 use was also collected under Criteria V2 where the subpopulation split was not available.

We estimated the HGG following solid organ transplant utilisation and costs using data from the HGG subgroup split (Criteria V3 classification) and scaled this up based on the overall use in the full population of HGG (excluding haematological malignancies) collected using both V2 & V3 in 2018-2019. Also, it should be noted that the per patient average use is for use in that calendar year only and some patient's treatment may have crossed over years (they may have been receiving treatment in the prior calendar year or they may continue to receive treatment into the next calendar year). Thus, the average per patient figures are an underestimate of the use and total cost for each patient over the full course of their treatment. In addition, some patients may receive both IVIG and SCIG in the same year and to obtain numbers below we have assumed they are different patients. It was also difficult to estimate administration costs because the recorded treatment episodes may have included multiple doses. Doses may have been given more frequently than every 4 weeks, with dose divisions permitted for disseminated enterovirus and maintenance therapy.

Table 32: Ig cost and utilisation Data – HGG following Solid organ transplantation

HGG following solid organ Transplantation (2019)	IVIG	SCIG	Source	Applicability
	Predicted**	Predicted**	HTA conditions data workbook (NBA 2020)	Only available for 2019 where underlying indication
Total Usage (grams)	63,163	2,870		
Total Patient Count (number of)	294	9		
Total Cost ($)***	3,815,662	173,377		
Average Usage per Patient for a calendar year (grams)****	215	336		

Calendar Year Average Cost per Patient ($)****	12,972	20,327		was recorded*

Source:(NBA 2020a)
* Available for 2019, but only where Criteria V3 was used (some use for this period was also collected using Criteria 2 which did not provide a breakdown by underlying condition). V3 was also used for a small proportion of the data collected in 2018.
**Uses available criteria V3 distributions applied to V2 and V3 data on overall use across all Secondary HGG (excluding haematological malignancies) for 2018-2019
***Note that this assumes a $60.40 cost per gram which is our base case cost estimate and does not include additional costs related to treatment
**** It is unknown the extent to which patient use crosses over years and thus the average use for each patient across their full course of Ig treatment. Therefore, we only present the average patient cost in a particular calendar year. It should also be noted that some patients may be counted twice because they use IVIG and SCIG.

Currently no reliable healthcare use or cost information is available for the no-Ig-RT group for our population of interest, requiring some underlying assumptions (see section below Gaps in Data and assumptions).

OTHER DATA

In addition to the transition probabilities, utilities and costs data, we are able to obtain other model data from Windegger 2019, presented in Table 33. However, these data are not directly applicable to our population, as previously mentioned and therefore is likely to create bias.

Table 33: Other Model Data

	IVIG	SCIG	Source	Applicability
Mean cohort product usage	29.46 g/month	31.15g/month	Windegger 2019	Different population of secondary HGG
Mean annual number of infections	1.85	2.31		
Hospitalisation rate due to infection	1/24 (0.13)	1/30 (0.03)		
Treatment sought for infection at ED/GP	9/15 (0.6)	8/22 (0.36)		
Mean length of hospital stay per infection – days (without Bronchiectasis)	3.75	2.67		

Source: (Windegger et al. 2019)

D.5. GAPS IN DATA AND ASSUMPTIONS

Given the lack of information on the non-Ig-RT HGG arm for our population of interest, significant assumptions on transition probabilities, utilities and costs would have to be made for any economic evaluation model. This information would need to be available not just for solid organ transplant patients but also other patients with secondary HGG excluding haematological malignancies and HSCT.

Identified data gaps for a simplified economic model include;

- Transition probabilities from:
    - No Infection to Infection (for all treated groups and untreated group)

- Even though we know the overall rate of transplant rejection in both arms for these studies (Lederer et al. 2014; Lichvar et al. 2018; Sarmiento et al. 2016) we do not know if these were preceded by an infection. Also, the quality of this evidence is very low.
- Infection to transplant rejection (for solid organ transplant group both treated and untreated group)
- Transition from all other health states to death (for all groups both treated and untreated). Windegger 2019 (Windegger et al. 2019) provides transition probabilities for secondary HGG following malignancies while the identified clinical studies (Lederer et al. 2014; Lichvar et al. 2018; Sarmiento et al. 2016) provide limited information on transition probabilities from all health states to death.

- Utilities for all health states for both the treated and untreated groups. We only have limited information all heart and lung transplant patients, including patients without HGG who are not eligible for Ig-RT. This control group is not directly applicable to our population.
- Healthcare utilisation and Costs.
  - The costs of Ig itself for our patient groups of interest is limited given the data available on the duration of treatment and breakdown of use by indication
  - We currently only have Ig-related costs for the Ig-RT-treated group of patients with secondary HGG following malignancies (Windegger et al. 2019), but not for the population of interest
  - We have no cost data for patients with secondary HGG who did not receive treatment with Ig-RT
  - We have very poor information on healthcare utilisation from the comparative clinical trials included in Section B (Lederer et al. 2014; Lichvar et al. 2018; Sarmiento et al. 2016)
  - We do not have any information on treatment duration for each subpopulation of interest, which affects calculations for both clinical effectiveness and costs.

In addition, there are other gaps in the available data that an economic model would need to consider (see Table 34).

Table 34: 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

Other Inputs	Healthcare utilisation
	Training of patient or carer to provide infusions (SCIG only), Product dispensing and disposal of any unused product Follow-up and/or monitoring visits

CONCLUSION

There were insufficient data to develop an economic model. For most subpopulations there was no usable data, and only very low quality evidence were available for patients with HGG following heart and lung transplantation, leading to a conclusion of uncertain effectiveness of Ig-RT. No studies reported quality of life outcomes or cost data, and no further cost information or utilities were identified in the economic search for this population.

The Ig Reference Group agreed that the results of any economic modelling would have limited applicability to the population for this indication, would be highly uncertain and may be misleading. Further research is needed to inform an economic model to allow the value of Ig-RT in this population.

SECTION E FINANCIAL IMPLICATIONS

E.1. JUSTIFICATION OF THE SELECTION OF SOURCES OF DATA

The data provided by the NBA (from STARS and BloodSTAR systems) is the only Australian data source for the population of patients with secondary HGG (excluding haematological malignancies and HSCT) who are treated with Ig. This dataset was provided for this review and is referred to as the HTA conditions data (NBA 2020a) workbook. These workbooks contained available data from July 2014 until March 2020. There are however significant issues with this data worth noting. Patient data collected to October 2018 followed the Criteria V2 classification where all patients with secondary HGG unrelated to haematological malignancies or HSCT were grouped together. However, due to transition to V3 of the Criteria from October 2018 some patient data was collected under Criteria V2 (NBA 2016), where the population was classified as patients with secondary HGG unrelated to haematological malignancies; and some patient data was collected under Criteria V3, which included patients with secondary HGG unrelated to haematological malignancy or HSCT (NBA 2019a) and were stratified into the following four subpopulations:

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

By July 2019 approximately 1% of the total Ig use for secondary HGG unrelated to haematological malignancies or HSCT was still collected under Criteria V2. By October 2019 all Ig use for secondary HGG unrelated to haematological malignancies or HSCT was being collected under Criteria V3, with Ig use being fully split into the subpopulations mentioned above.

These subpopulations have very different underlying conditions, with different disease progression, treatment requirements, infection rates and other clinical variables. Even within these subpopulations there is likely to be considerable variability in these factors (for example, clinical variability across different types of solid organ transplantation and across different indications for the use of B cell depletion therapies). It is also problematic that there is no clinical information on the subgroup of patients in the "Other HGG" subgroup. This aggregate information makes it nearly impossible to predict treatment needs over any time period. Where subpopulation data was collected in the calendar year 2019, more than half of the patients (52%) were grouped under "Other HGG unrelated to haematological malignancies or HSCT". This very large subgroup likely includes patients with various underlying conditions that caused HGG, and thus have unknown disease progression, infection rates, incidence, treatment duration and other clinical variables.

Given the limited data to extrapolate trends for each subpopulation, we instead extrapolated the likely HGG subgroup utilisation and costs for the overall group based on the trends in Ig use both before the change in Criteria from V2 to V3 (April 2015- March 2018) and in the nine months after the majority of the transition had taken place (July 2019 until March 2020). These growth rates were similar.

We do not separately consider the costs related to IVIG versus SCIG, although we do report trends in the proportion of Ig Use that is administered as SCIG. We also report the recent monthly trends in Ig use for each subpopulation. For Ig use during this period, which was collected under the Criteria V3 classification, we reassigned this Ig use to subpopulations based on the distribution of use across subpopulations where the Criteria V3 classification was used in that month. In a sensitivity analysis we also explore the use of Ig overall and by subpopulation if these recent trends in Ig use by subpopulations continued into the future. Using recent trends in the subpopulations over the last nine months to extrapolate use for the next 5 years may be problematic, especially where these recent trends may be driven by recent changes in treatments that may be unlikely to continue at the same rate. For example, the Ig Reference Group noted the recent increase in use of B-cell depleting therapies and small molecule inhibitors, which may be driving recent trends in Ig use. However, this may be unlikely to continue at the same rate unabated for the next 5 years. Instead one may expect the growth in Ig use related to B-cell depleting therapies to slow at some point in the future.

Data on Ig use in Australia (NBA 2020a) are presented in Table 35 to

Table 37. We present information on total Ig usage in grams, total number of patients and usage per patient all specific to Secondary HGG (excluding haematological malignancies or HSCT). For the financial year 2017-18, we have no information for the subgroups. In addition, sub-group information for the year 2018 to 2019 was only available for a small proportion of the Ig use (less than 40%) where Criteria V3 data collection was used. Thus, we applied the distribution of Ig use where V3 was used in 2019 and applied it to the overall Ig use in 2018-19. To scale up the subgroup use to be equivalent to a full year we assume that the full year data will have the same distribution at the sub-group level where this information was collected in V3 in 2019. Given that we only have information for two years for the population of interest, it may be misleading to do a trend analysis for patient count number and cost per gram especially given that during these two years the Criteria for use also changed. This leads to a few assumptions in Section E2 to model out the long-term projections of use and cost.

Table 35: Ig Usage (grams) for Secondary HGG (excluding haematological malignancies or HSCT)

	2017 – 2018	2018 – 2019	2017 - 2018	2018 – 2019	
	IVIG		SCIG		
HGG Groups by underlying conditions	Full data	Predicted*	Full data	Predicted*	Criteria

B cell depletion therapy	Not Available	50,258	Not Available	5,311	V3
Solid organ transplantation	Not Available	60,014	Not Available	2,271	V3
Other	Not Available	118,584	Not Available	13,323	V3
Good Syndrome	Not Available	3,120	Not Available	0	V3
All Secondary HGG (excluding haematological malignancies)	209,611	231,977	12,526	20,905	V2/V3

Source: (NBA 2020a)

*Uses available criteria V3 distributions for the calendar year 2019 (where V3 was used for 81% of the Ig Use) applied to data on use across all Secondary HGG (excluding haematological malignancies) for 2018-2019 (V2 and V3)

Table 36: Number of Patients with Secondary HGG (excluding haematological malignancies or HSCT)

	2017 – 2018	2018 – 2019	2017 - 2018	2018 – 2019	
	IVIG (n patients)		SCIG (n patients)		
HGG Groups by underlying conditions	**Full data**	**Predicted***	**Full data**	**Predicted***	**Criteria**
B cell depletion therapy	Not Available	226	Not Available	28	V3
Solid organ transplantation	Not Available	271	Not Available	9	V3
Other	Not Available	477	Not Available	50	V3
Good Syndrome	Not Available	10	Not Available	0	V3
All Secondary HGG (excluding haematological malignancies)**	920	984	55	87	V2/V3

Source: (NBA 2020a)

*Uses available criteria V3 distributions in the calendar year 2019 applied to data on use across all Secondary HGG (excluding haematological malignancies) for 2018-2019 (V2 and V3)

** Overall total number of patients for 2018-2019 was lower than the separate addition of IVIG plus SCIG patient count (1045 vs. 1071, respectively)

Table 37: Ig Usage per Patient (Grams) with Secondary HGG (excluding haematological malignancies or HSCT)

	2017 – 2018	2018 – 2019	2017 - 2018	2018 – 2019	
	IVIG (g)		SCIG (g)		
HGG Groups by underlying conditions	**Full data**	**Predicted***	**Full data**	**Predicted***	**Criteria****
B cell depletion therapy	Not Available	222	Not Available	189	V3
Solid organ transplantation	Not Available	222	Not Available	266	V3
Other	Not Available	248	Not Available	265	V3
Good Syndrome	Not Available	318	Not Available	0	V3
All Secondary HGG (excluding haematological malignancies)***	228	236	228	240	V2/V3

Source: (NBA 2020a)

*Uses criteria V3 distributions across subgroups in the calendar year 2019 to estimate data on across HGG subgroups for the financial year 2018-19.

** 2018-19 data collected with two different versions (one where patients were classified into subpopulations V3 and one where patients are all grouped together V2).

***Overall total number of patients for 2018-2019 was lower than the separate addition of IVIG plus SCIG patient count (1045 vs. 1071, respectively)

There are several gaps on costs and healthcare utilisation (see Table 34). There is only data on how much Ig patients are receiving (and this is limited as we do not have individual level data on treatment duration), and no information on hospital use and other healthcare resources implications of this use.

In 2018-2019 Criteria V2 was used to record use for a large proportion of patients and thus they were grouped as "All secondary HGG (excl. haematological malignancies)" instead of being classified into the different subpopulation groups. Patients transitioned from Criteria V2 to Criteria V3 at different times from October 2018 until October 2019. Thus, to get a better estimate of overall trends and breakdown by subgroups we used monthly data on Ig use (NBA 2020b). With the monthly data we focus on Ig use in grams rather than the numbers of patients because with aggregate monthly data it is unknown the extent to which it is the same or different patients each month.

Figure 7 shows the monthly use of Ig (either with IVIG or SCIG) from July 2014 till March 2020 (NBA 2020b). The use is grouped by which Criteria (V2 or V3) it was listed under, and for Criteria V3 the subpopulation was indicated. We can see the transition from Criteria V2 to Criteria V3 occurring from October 2018 to October 2019, with most of this transition completed by July 2019. In general, the rate of growth of total Ig for all secondary HGG (excluding haematological malignancies) has been quite consistent over this period (with an approximate annual growth rate of 19.3%). There was a slight slowing of the growth rate coinciding with the introduction and transition to Criteria V3; however, from July 2019 to March 2020 the equivalent annual growth rate was 22.0%. Also, of note, there is a minimal seasonal impact on the use of Ig, which makes it easier to estimate equivalent annual growth rates based on limited monthly data.

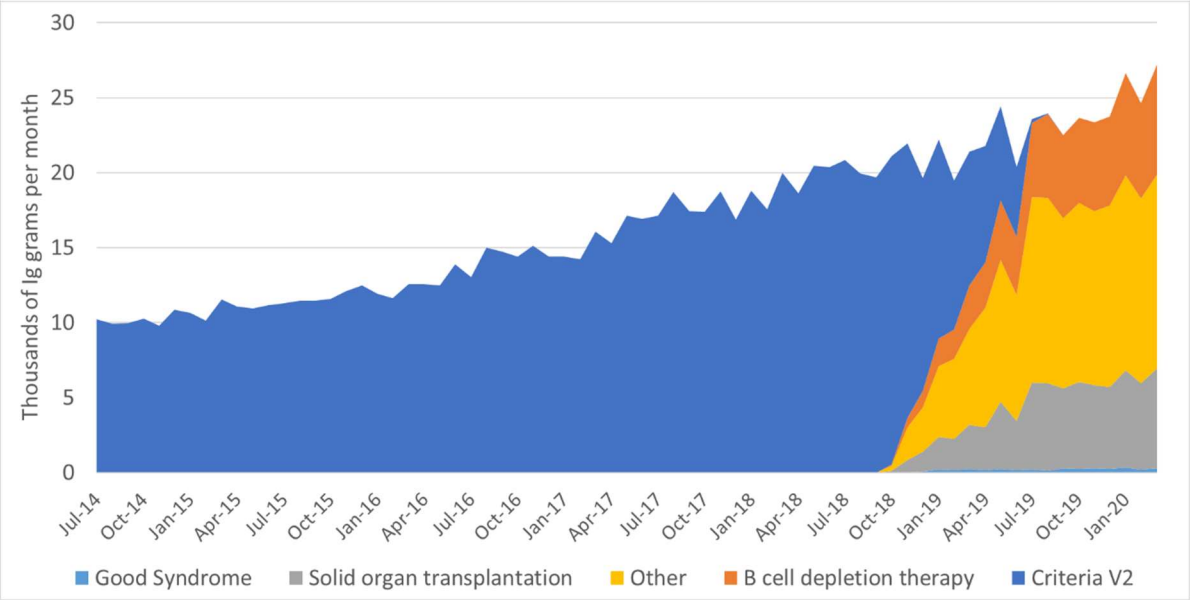

Figure 7. Monthly recorded Ig use (IVIG and SCIG) under each criterion and by subpopulation in V3
Source: (NBA 2020b)

E.2. USE AND COSTS OF IMMUNOGLOBULIN SECONDARY HGG (EXCLUDING HAEMATOLOGICAL MALIGNANCIES OR HSCT)

Projected Ig Use (grams)

From June 2014 to March 2020 there has been an annual growth rate of approximately 19.3%, based on the monthly use of Ig (grams) for all secondary HGG (excl. haem malignancies). The annual growth rates of Ig use (grams) – for IVIG and SCIG combined across each year (March to April) are presented in Table 38. We also include an estimate of the equivalent annual growth rate based on growth in the last nine months (July 2019 to March 2020) - after the transition to Criteria V3 had mostly been completed - as this gives us a potentially better guide to what growth rates may be expected in the future. For the last nine months we also estimated the annual equivalent growth rates by subpopulation. With Ig use (combined for IVIG and SCIG) for all Secondary HGG (excl. haem malignancies) we see a mostly consistent annual growth over all years; however, we do see a noticeable drop in Apr 2018 – Mar 2019 and Apr 2018 – Mar 2019, which coincided with the transition from Criteria V2 to Criteria V3. The current growth rate over the last nine months, however, shows a return back to a similar growth rate (22.0%) to that previously observed. Below we use this growth rate (22.0%) to extrapolate the likely use of Ig in the future.

Using the breakdown provided by Criteria V3 in the most recent nine-month period we can also see that there have been very different growth rates for Ig use in each subpopulation over this period. In particular, we have seen rapid growth in Ig use related to B-cell deletion therapies compared to more moderate growth for solid organ transplantation and the 'Other' group. The current extremely high growth rate in the use of Ig in the subpopulation with HGG following B cell depletion therapy is likely related to the current growth in the use of B cell depletion therapies in the wider population but it is unknown the extent to which this is likely to continue to grow in the future or when we may expect to see the use of B cell depletion therapies start to plateau and reach some steady state of growth.

Table 38 Annual growth rates of Ig use (grams) in Australia

	Apr 2015- Mar 2016	Apr 2016- Mar 2017	Apr 2017- Mar 2018	Apr 2018- Mar 2019	Apr 2019- Mar 2020	Jul 2019- Mar 2020**
Total Ig grams used (IVIG and SCIG combined)	139,686	170,437	212,006	245,775	285,952	219,354****
Annual (equivalent) growth rates						
Secondary HGG (excl.haem malignancies)*	N/A	22.0%	24.4%	15.9%	16.3%	22.0%
B-cell depletion therapy	N/A	N/A	N/A	N/A	N/A	61.8%

	Apr 2015- Mar 2016	Apr 2016- Mar 2017	Apr 2017- Mar 2018	Apr 2018- Mar 2019	Apr 2019- Mar 2020	Jul 2019- Mar 2020**
Solid organ transplantation	N/A	N/A	N/A	N/A	N/A	16.7%
Other	N/A	N/A	N/A	N/A	N/A	8.1%
Good Syndrome***	N/A	N/A	N/A	N/A	N/A	-16.5%

Source: (NBA 2020b, 2020a)
*Growth rates from 2015-2016 to 2019-2020 are annual growth rates from one year to the next.
** The annual equivalent growth for these nine months were obtained by fitting exponential growth curves to the monthly NBA data. Given the limited evidence of strong seasonal use of Ig fitting exponential growth curves to monthly data is likely to provide a reasonable approximation to the underlying growth rate during this short period of time.
**There was a change in Ig eligibility from Criteria V2 to Criteria V3 which started in July 2018 which may have impacted Ig annual growth within April 2018- March 2019 and may have also had an impact on the period April 2018- March 2019 given that V3 was not fully implemented until October 2019.
****Use in grams over nine months.

There is significant uncertainty around the expected growth rate of Ig use for secondary HGG (excluding haematological malignancies) given the recent changes in eligibility from the Criteria V2 (NBA 2016) to Criteria V3 (NBA 2019a) in October 2018. The Criteria V2 included patients with HSCT unrelated to haematological malignancy, whereas the Criteria V3 excluded all patients with HSCT. The specific indications for Ig use in the two versions of the Criteria differ slightly:

- Criteria V2: replacement therapy for life-threatening infection due to HGG related to other diseases, or medical therapy, including HSCT unrelated to haematological malignancy.
- Criteria V3: 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.

These changes may have lowered recent use and it is unclear whether they may have also impacted the future growth rate given we have only nine months of clean data to observe recent trends. In addition, the future growth in Ig use for all Secondary HGG (excl. haem malignancies) is likely to depend on the individual growth rate within each subpopulation. The current growth for all Secondary HGG (excl. haem malignancies) mostly reflects the growth rate for the 'Other' group (because it currently has the largest proportion of use), but if the use of Ig related to B-cell deletion therapies continues to grow at the current rate it will soon overtake the Ig use in the 'Other' group and may drive the overall growth rate of Ig for Secondary HGG (excl. haem malignancies) . However, these recent trends are based on limited data, so we consider this scenario in a sensitivity analysis to highlight that it may be worthwhile to continue to monitor these trends in the near future.

We note that for all secondary HGG (excl. haem malignancies) there has been a steady transition from IVIG to SCIG in the period between July 2014 and March 2020. Figure 8 shows the increase in SCIG from around 2% of total Ig use at the start of this period to close to 13% of overall use by the end this period. Also, we see an increase in the uptake of SCIG in February and March 2020, which may be related to COVID-19, and we may expect the transition to SCIG to further speed up during

the COVID-19 pandemic. The variability in growth for IVIG and SCIG also makes extrapolation of Ig use into the future difficult. It is unknown to what extent the current higher growth rates for SCIG are coming at the expense of growth in IVIG or whether greater access to SCIG may also encourage additional Ig use.

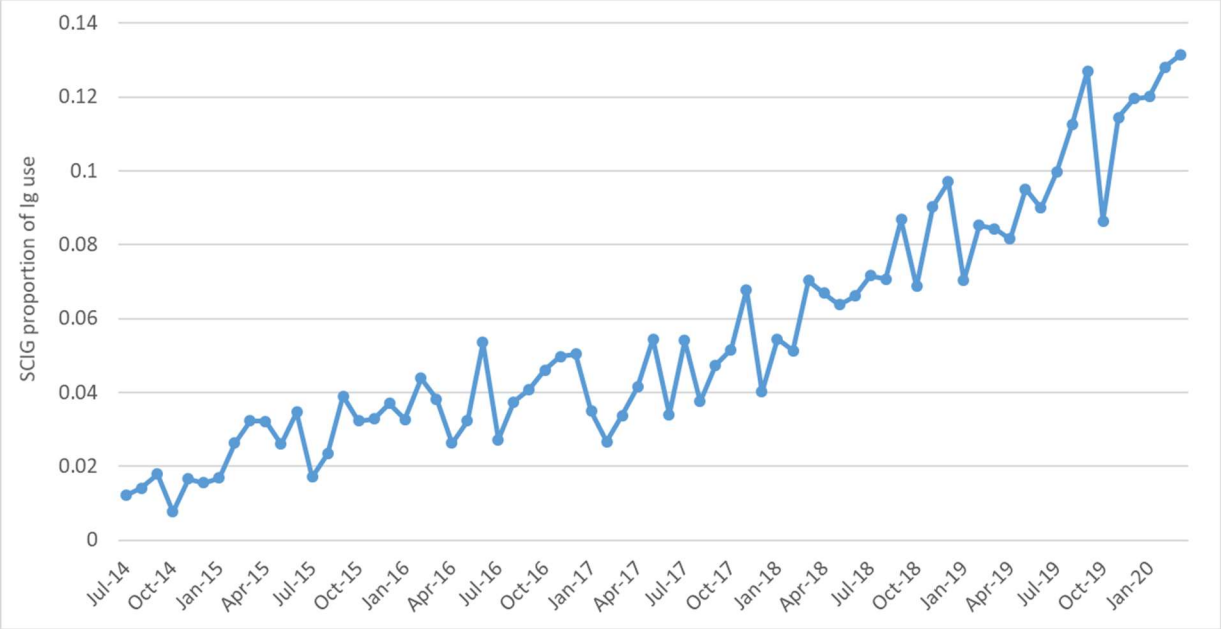

Figure 8. Proportion of Ig use (grams) in SCIG formulation
Source: (NBA 2020b)
Note that the IVIG proportion will be one minus the SCIG proportion.

We present the projected use (in thousands of grams) with secondary HGG (excluding haematological malignancies or HSCT) in Table 39 using the annual equivalent growth rate observed from July 2019 to March 2020 for the overall population 22.0% (which coincided with the approximate growth rate before the introduction and transition to Criteria V3). Based on this growth rate we expect the Ig use to increase from 252,882 grams used in the financial year 2018-2019 to 683,465 grams in the financial year 2023-2024.

Table 39: Projected Use (thousands of grams) within the Secondary HGG (excluding haematological malignancies or HSCT) population assuming a 22% growth rate

Total Ig Use (IVIG_+ SCIG) thousands of grams	2018-2019	2019-2020	2020-2021	2021-2022	2022-2023	2023-2024
All Secondary HGG (excluding haematological malignancies)*	252.9	308.5	376.4	459.2	560.2	683.5

Source: (NBA 2020b)
*All Secondary HGG (excluding haematological malignancies) includes all the subgroup of 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.

Patient numbers

With aggregate data and the recent changes in the Criteria it is difficult to track patient numbers. However, there is little evidence to suggest significant differences in the average yearly use per patient over time. We do observe a 3.5% increase in IVIG use and a 5.5% increase in SCIG use per

patient from 2017/18 to 2018/19 but we do not expect continued annual growth per patient (NBA 2020a). Thus, the increase in Ig use we observe most likely reflects additional patients rather than additional use per patient.

Total Ig Drug Costs

The cost per gram of Ig used in the base case analysis is $60.41. This cost was provided by the Applicant 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

We first present the estimated total costs based on the projected Ig use, using the recommended base case Ig costs across all indications ($60.41). This does not include administration costs. These results assume a 22% annual growth in Ig use (Table 40). We see total Ig costs 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. These results along with the implications of the alternative costs per gram are presented in Table 40.

Table 40 Ig projected costs (IVIG +SCIG) - All Secondary HGG (excl.haemat. malignancies)*

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: (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 subgroups of patients. Note that due to the very different growth rates within subpopulations and the limited data available to estimate these trends we only extrapolation into subpopulations using these trends in the sensitivity analysis (Table 41).

[a] Based on actual use.

It should be noted that if the considerable recent growth over the last nine months for Ig use in those with HGG related to B-cell depletion therapy continues, this will further increase the predicted Ig costs on top of those estimates. We estimate the potential implications of this in the sensitivity analysis in Section E.6 (Table 41). Given the bulk of the current cost is found for the subpopulation of

"other secondary HGG excluding haematological malignancies" the projected costs per year are also largest for this group ($12.1 million for IVIG and $1.4 million for SCIG), with Good Syndrome projected to cost the least ($0.3 million for IVIG and $0 for SCIG) by 2023-2024.

E.3. Changes in Use and Cost of Other Medical Services

We currently do not have enough information to make a prediction of changes in use and cost of other medical services.

We have very limited evidence on the number of hospitalisations due to infections (see Section C and Section D) and no other health care resource utilisation data (see Table 34). Therefore, it is not possible to calculate the cost offsets associated with a potential reduction in infections or transplant rejections for that subpopulation. Any prediction of those changes is likely to be unreliable.

E.4. Financial Implications for the MBS

Based on current available data, it will be impossible to make predictions on implications for MBS. For this to be done, more data relevant to our target population is needed.

E.5. Financial Implications for Government Health Budgets

Based on current available data, it will be impossible to make predictions on implications for Government Health Budgets.

Other Government Impacts

Currently not possible to estimate based on available data.

State and Territory Government Health Budgets

Currently not possible to estimate based on available data.

E.6. Identification, Estimation and Reduction of Uncertainty

There are a number of assumptions required to estimate the projected financial cost of Ig use. Here we explore the implications of extrapolating use based on recent growth in Ig use for each of the subpopulations.

Sensitivity analysis: extrapolation using recent (July 2019 to March 2020) growth rates by subpopulations; rather than 22% growth for All Secondary HGG (excluding haematological malignancies)

We use the base costs of ($60.41 per gram) to estimate the total predicted cost of Ig use. The results are presented in **Error! Reference source not found.**. If the recent subpopulation trends continue for the next 5 years, total Ig costs (including both IVIG and SCIG) could potentially reach $52.2 million by the year 2023 – 2024. We see the majority of these costs ($31.9 million) are predicted to be related to use within the B cell depletion therapy subpopulation, with the use in this subpopulation expected to overtake use in the 'Other' subgroup by 2021-2022. The future Ig use related to B-cell depletion therapy will depend on the further growth in the use of B-cell depletion therapies and the extent to which this further increase translates into Ig use. If the current trend continues and the B cell depletion subgroup becomes a significant population, further research investigating the effectiveness and cost effectiveness of Ig use in this population may be valuable.

Table 41: Projected Ig use (thousands of grams) and Cost ($million) within the Secondary HGG (excluding haematological malignancies or HSCT) population assuming continued recent growth by subpopulation

Total Ig Use (IVIG + SCIG) thousands of grams	**2018-2019***	**2019-2020**	**2020-2021**	**2021-2022**	**2022-2023**	**2023-2024**
Good Syndrome** (assumed growth - 16.5%)	N/A	2.7	1.8	1.5	1.2	1.0
B cell depletion therapy (assumed growth 61.8%)	N/A	77.1	124.7	201.7	326.4	528.1
Solid organ transplantation (assumed growth 16.7%)	N/A	71.7	83.6	97.5	113.9	132.9
Other (assumed growth 8.1%)	N/A	148.3	160.2	173.2	187.2	202.4
All secondary HGG (excl. haemat. malignancies)*	252.9	299.8	370.2	473.9	628.7	864.5
Total Ig Cost ($) (IVIG_+ SCIG)	**2018-2019***	**2019-2020**	**2020-2021**	**2021-2022**	**2022-2023**	**2023-2024**
Good Syndrome (assumed growth - 16.5%)	N/A	$200,000	$100,000	$100,000	$100,000	$100,000
B cell depletion therapy (assumed growth 61.8%)	N/A	$4,700,000	$7,500,000	$12,200,000	$19,700,000	$31,900,000
Solid organ transplantation (assumed growth 16.7%)	N/A	$4,300,000	$5,000,000	$5,900,000	$6,900,000	$8,000,000
Other (assumed growth 8.1%)	N/A	$9,000,000	$9,700,000	$10,500,000	$11,300,000	$12,200,000
All Secondary HGG (excluding	$11,400,000	$18,100,000	$22,400,000	$28,600,000	$38,000,000	$52,200,000

haematological malignancies)*						

Source: (NBA 2020b)
Limited breakdown available for the financial year 2018-19 with less than 40% of the Ig use recorded using Criteria V3.**Note that the Good Syndrome growth rate is based on low usage and therefore it likely to be very sensitive to small changes in use.
N/A= not available

E.7 GAPS IN DATA AND ASSUMPTIONS

A series of assumptions that were made due to the lack of data:

- Given the recent change in the Criteria from V2 to V3 there was limited clean data (approximately nine months where use of the V2 criteria was minimal) to assess trends in Ig use under the new Criteria or trends in the use by subpopulations.

- It is unknown the extent to which the recent large upward trend in Ig use related to B-cell depletion therapy will continue into the future, and resulting implications for the growth in Ig use in the overall population of secondary HGG excluding haematological malignancies are potentially large. The Ig use related to B-cell depletion therapy will depend on the extent of further growth in the use of B-cell depletion therapies and the extent to which this increase translates into Ig use. If the current trend continues and the B cell depletion subgroup becomes a significant population, further research investigating the effectiveness and cost effectiveness of Ig use in this population may be valuable.

- It is unknown to what extent the growth of Ig use administered as SCIG versus IVIG will continue into the future and the implications of this for the overall use of Ig and Ig related costs.

- It was not possible to estimate administration costs in our population due to the lack of data on treatment duration and treatment cycles per patient. The estimated cost per infusion used in the assessment MSAC 1565 (secondary HGG following haematological malignancies) was $253.42, estimated from Windegger 2019. The dataset only reported number of treatment episodes for the full secondary HGG (excl. haematological malignancies) population, but we do not know the number of infusions per patient for IVIG and SCIG.

- In addition, treatment patterns and utilisation may differ in each of the four subpopulations included (e.g. patients undergoing solid organ transplantation might only receive with Ig-RT for a more limited period of time than those with Good syndrome or B-cell depletion therapy). Differences between patients are also likely with subpopulations. The subgroup of patients classified as “Other” by the Criteria V3 had the current highest use of Ig in the population of secondary HGG excluding haematological malignancies. The lack of knowledge of the underlying conditions in this patient subgroup prevent us from estimating their treatment needs and thus developing financial estimates in this population.

APPENDIX A1 CLINICAL EXPERTS AND ASSESSMENT GROUP

CLINICAL EXPERT

Name	Expertise
Erica Wood	Haematology, Transfusion medicine
Zoe McQuilten	Haematology, Transfusion medicine
Alisa Higgins	Critical care research, health economics

ASSESSMENT GROUP

Name	Position
Sara Carrillo de Albornoz	Research Fellow
Karinna Saxby	Research Fellow
Maame Esi Woode	Research Fellow
Dennis Petrie	Associate Professor

Noted conflicts of interest

There were no conflicts of interest.

APPENDIX A2 INTERNATIONAL COMPARISONS IG USE

Table 42 International comparisons Ig use recommendations

	Australia[1]	England[3]	Scotland[4]	Atlantic Provinces (Canada)[5]	Alberta, Manitoba, Satskachewan (Canada)[6]	British Columbia (Canada)[7]	Ontario (Canada)
Condition Indication	Secondary HGG unrelated to Haematological malignancy or haematopoietic stem cell transplant (HSCT) Indication for Ig Use: Replacement therapy for recurrent or severe bacterial infections or disseminated enterovirus infection associated with HGG caused by a recognised disease process or B cell depletion therapy and/or immunosuppressant therapy. Specific Conditions: HGG following Solid organ transplantation HGG following B cell depletion therapy Thymoma-associated HGG (Good Syndrome) Other HGG unrelated to haematological malignancies or HSCT	Secondary antibody deficiency – long term use	Secondary antibody deficiency (any cause)	Secondary Immunodeficiency	HGG, secondary: Ig replacement is recommended for preventing recurrent, severe infection due to HGG (excl paraprotein) related to other diseases or medical therapy Separate recommendations for: - Acquired HGG secondary to haematological malignancies (incl. HSCT) - Kidney, active antibody-mediated rejection (ABMR) prevention and management - Solid organ (other than kidney) ABMR (see Table below for further details on solid organ transplantation)	Secondary immune deficiency	Secondary immune deficiency Separate recommendations for solid organ transplantation: - Kidney transplant from living donor to whom the patient is sensitized - Pre-transplant (heart) - Peri-transplant (heart, lung, kidney, pancreas) - Post-transplant (see Table below for further details on solid organ transplantation)
Criteria	A diagnosis must be made by any specialist. Serum IgG to be measured on two separate occasions (at least one hour apart and at least one sample taken when the patient does not have an active infection). Baseline serum levels of IgA and IgM should be provided to allow assessment of immune recovery at review. Significant HGG with serum IgG less than 4g/L (excluding paraprotein) regardless of the frequency and severity of infections; OR Serum IgG (excluding paraprotein) greater than 4g/L but less than the lower limit of the age-related reference range and at least one life-threatening infection in the last 12 months; OR Serum IgG (excluding paraprotein) greater than 4g/L but less the lower limit of the age-related reference range with at least two serious infections in the last six months	Underlying cause of HGG cannot be reversed or reversal is contraindicated; OR HGG associated with drugs, therapeutic monoclonals targeted at B cells and plasma cells (rituximab and other anti-CD20,CD19 agents, daratumumab etc) post-HSCT, NHL, CLL, MM or other relevant B-cell malignancy confirmed by haematologist; AND Recurrent or severe bacterial infection despite continuous oral antibiotic therapy for 6 months IgG < 4g/L (excl paraprotein) Documented failure of serum antibody response to	Underlying cause of HGG cannot be reversed or reversal is contraindicated; OR HGG associated with NHL, CLL, MM or other relevant B-cell malignancy confirmed by haematologist; AND Recurrent or severe bacterial infection despite continuous oral antibiotic therapy for 3 months IgG < 5 g/L (excl paraprotein) Documented failure of serum antibody response to	Adult: Patient has/had recent life threatening or recurrent clinically significant infection(s) related to low levels of polyclonal immunoglobulin Paediatric: Order must be in consultation with an Immunologist	HGG secondary to underlying disease or medical therapy (incl HCST) with all of the following: Serum IgG less than the lower limit of the reference range on two separate occasions; AND At least one of the following: One invasive or life-threatening bacterial infection (e.g., pneumonia, meningitis, sepsis) in the previous year; Recurrent, severe bacterial infections; Clinically active bronchiectasis confirmed by radiology; Assessment by a physician specializing in immunodeficiency indicating a significant antibody defect that would benefit from Ig replacement.	HGG (reduced total IgG or IgG subclasses) with recurrent bacterial infection Monitor IgG trough level as appropriate to achieve desired clinical outcome	Hypogammaglobulinemia (reduced total IgG or IgG subclasses) with recurrent bacterial infection

	Australia[1]	England[3]	Scotland[4]	Atlantic Provinces (Canada)[5]	Alberta, Manitoba, Satskachewan (Canada)[6]	British Columbia (Canada)[7]	Ontario (Canada)
	requiring more than standard courses of antibiotics (e.g. Hospitalisation, intravenous or prolonged antibiotic therapy); OR Evidence of impaired antibody production to vaccination in the context of persistent infections affecting long term function such as persistent purulent suppurative otitis media threatening long term hearing; AND Underlying cause of HGG cannot be reversed; OR Underlying cause of HGG is reversible but reversal is contraindicated A diagnosis of bronchiectasis and/or suppurative lung disease must be consistent with the Thoracic Society of Australia and New Zealand (Chang AB et al. 2014). Initial review is required within six months and ongoing reviews by a specialist at least annually to assess clinical benefit. Documentation of clinical effectiveness is necessary for continuation of Ig therapy. Cessation of Ig therapy should be considered at least after each 12 months of treatment. If serum IgM and IgA levels are trending upwards and near normal, this may suggest recovery of the immune system and a trial might be considered if the patient is well. Once the patient has normal IgA and IgM levels, the IgG is also likely to be normal and a trial off Ig therapy may be undertaken. Ig therapy should be extended as required to enable cessation of therapy in September/October, with repeat clinical and/or immunological evaluation before recommencement of therapy.	unconjugated pneumococcal or other polysaccharide vaccine challenge In these circumstances vaccine challenge may be omitted if it is considered inappropriate clinically. It is acknowledged that not all of the above criteria will need to be fulfilled for an individual patient. In patients developing HGG associated with B-cell aplasia as a consequence of Chimeric Antigen Receptor – T cell therapy (CAR-T cells) targeted against B cell antigens, the prophylactic use of Ig in the absence of a burden of severe infections and vaccine challenge may be appropriate. There is controversy regarding Ig replacement in adult patients with HGG post-HSCT for haematological malignancy. The American Society for Blood and Marrow transplantation and the Canadian Blood and Marrow Transplant group have recently stated as follows: Don't routinely give Ig replacement to adult HSCT recipients in the absence of recurrent infections regardless of the IgG level (Bhella et al. Choosing Wisely BMT. Biol Blood Marrow Transplant 2018;24:909-13)	unconjugated pneumococcal or other polysaccharide vaccine challenge				
Dosing	The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.	0.4-0.6g/kg/month modified to achieve an IgG trough level of at least the lower limit of the	0.4 g/kg/month modified to achieve an IgG trough level of	Adult: 0.4-0.6 g/kg every 4 weeks	Aim to use the dose that achieves a significant reduction in the number of bacterial infections.	Adult: 0.4-0.6 g/kg every 3-4 weeks	Adult: 0.4-0 .6 g/kg every 3-4 weeks

	Australia[1]	England[3]	Scotland[4]	Atlantic Provinces (Canada)[5]	Alberta, Manitoba, Satskachewan (Canada)[6]	British Columbia (Canada)[7]	Ontario (Canada)
	Loading Dose (IVIG) - One loading dose of 0.4 g/kg in the first month of therapy (in addition to the maintenance dose) is permitted if the serum IgG level is <4 g/L. Disseminated Enterovirus Dose (IVIg) - One dose of 2g/kg at any stage is permitted (in addition to the maintenance dose) in the management of disseminated enterovirus infection. Maintenance Dose (IVIg) - 0.4–0.6g/kg every four weeks or more frequently, to achieve IgG trough level of at least the lower limit of the age-specific serum IgG reference range. More frequent dosing to achieve IgG trough level of up to 9 g/L is permitted if chronic suppurative lung disease is not adequately controlled at an IgG trough level at the lower limit of the age-specific serum IgG reference range. A total dose of up to 1 g/kg may be given over any 4-week period. Supplementary Dose (IVIg) - One additional dose of 0.4 g/kg is permitted at any stage (in addition to the maintenance dose) if the serum IgG level is <4 g/L. Loading Dose (SCIg) - One loading dose of 0.4 g/kg in the first month of therapy (in addition to the maintenance dose) is permitted if the serum IgG level is <4 g/L. Disseminated Enterovirus Dose (SCIg) - One dose of 2g/kg at any stage is permitted (in addition to the maintenance dose) in the management of disseminated enterovirus infection. Maintenance Dose (SCIg) - 0.1-0.15g/kg every week or more frequently, to achieve IgG trough level of at least the lower limit of the age-specific serum IgG reference range. More frequent dosing to achieve IgG trough level of up to 9 g/L is permitted if chronic suppurative lung disease is not adequately controlled at an IgG trough level at the lower limit of the age-specific serum IgG reference range. A	age-specific serum IgG reference range	at least the lower limit of the age-specific serum IgG reference range	Paediatric: 0.3-0.6 g/kg every 4 weeks	Maintenance: 0.4 to 0.6 g/kg adjusted body weight IVIg every 4 weeks, or SCIg 0.1 to 0.5 g/kg adjusted body weight weekly, modified to achieve an IgG trough level of at least the lower limit of the age-specific serum IgG reference range, or as needed to achieve clinical effectiveness. Loading: One additional dose of 0.4 g/kg adjusted body weight may be given in the first month of therapy if the serum IgG level is markedly reduced. Chronic suppurative lung disease: 0.4 to 0.8 g/kg adjusted body weight IVIg or equivalent SCIg dose may be given if chronic suppurative lung disease is not adequately controlled at an IgG trough level at the lower limit of the age-specific serum IgG reference range.	Paediatric: 0.3-0.6 g/kg every 4 weeks	Paediatric: 0.3-0 .6 g/kg every 3-4 weeks Doses or frequency to be adjusted by experts according to desired trough level (more than 500 mg/dL and ideally 700 mg/dL) and according to individual patient clinical needs.

	Australia[1]	England[3]	Scotland[4]	Atlantic Provinces (Canada)[5]	Alberta, Manitoba, Satskachewan (Canada)[6]	British Columbia (Canada)[7]	Ontario (Canada)
	total dose of up to 1 g/kg may be given over any 4-week period. Supplementary Dose (SCIg) - One additional dose of 0.4 g/kg is permitted at any stage (in addition to the maintenance dose) if the serum IgG level is <4 g/L.						
Review / Clinical Outcome Measures	Initial review is required within six months and ongoing reviews by a specialist at least annually to assess clinical benefit. Documentation of clinical effectiveness is necessary for continuation of Ig therapy. Cessation of Ig therapy should be considered at least after each 12 months of treatment. If serum IgM and IgA levels are trending upwards and near normal, this may suggest recovery of the immune system and a trial might be considered if the patient is well. Once the patient has normal IgA and IgM levels, the IgG is also likely to be normal and a trial off Ig therapy may be undertaken. Ig therapy should be extended as required to enable cessation of therapy in September/October, with repeat clinical and/or immunological evaluation before recommencement of therapy On review of the initial authorisation period: Monitoring of serum immunoglobulin levels (IgG, IgM and IgA) and infection history; AND There should be regular consideration of a trial period of cessation of Ig for the purposes of immunological evaluation unless medically contraindicated on safety grounds (for example active bronchiectasis and/or suppurative lung disease, neutropenia, or ongoing immunosuppressant medication) or where there is persistence of the underlying condition that would result in severe HGG in the absence of Ig replacement therapy. Trial cessation is best commenced in September or October. When IgA and IgM are trending upwards and close to normal and the patient is well, a trial	Reduction in number of infections and days in hospital (Database parameters will include entry of number of infections and days in hospital pre-treatment and 6 monthly thereafter)	Reduction in number of infections and days in hospital. Database parameters will include entry of number of infections and days in hospital pre-treatment and 6 monthly thereafter.	n/a	Continued use of Ig should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of treatment and at least annually thereafter by a physician specializing in immunodeficiency disorders. If clinical effectiveness has not been achieved, Ig treatment should be discontinued. Cessation of Ig treatment may be possible depending on the status of the underlying disease.	n/a	n/a

	Australia[1]	England[3]	Scotland[4]	Atlantic Provinces (Canada)[5]	Alberta, Manitoba, Satskachewan (Canada)[6]	British Columbia (Canada)[7]	Ontario (Canada)
	off therapy (in September or October) is considered to allow immunological re-evaluation, or is unless medically contraindicated. On review of a continuing authorisation period: Monitoring of trough or serum immunoglobulin levels (IgG, IgA and IgM) and any history of infection; AND There should be regular consideration of a trial period of cessation of Ig for the purposes of immunological evaluation unless medically contraindicated on safety grounds (for example active bronchiectasis and/or suppurative lung disease, neutropenia, or ongoing immunosuppressant medication) or where there is persistence of the underlying condition that would result in severe HGG in the absence of Ig replacement therapy. Trial cessation is best commenced in September or October. When IgA and IgM are trending upwards and close to normal and the patient is well, a trial off therapy (in September or October) is considered to allow immunological re-evaluation, or is medically contraindicated. A diagnosis of bronchiectasis and/or suppurative lung disease must be consistent the guideline of the Thoracic Society of Australia and New Zealand (Chang AB et al. 2014).						
Alternative treatments	Antibiotic therapy may be indicated in addition to Immunoglobulin therapy.	Many patients with secondary antibody deficiency will achieve protection from bacterial infections with prolonged antibiotic prophylaxis. Ig is reserved for those patients in whom antibiotic prophylaxis proves to be ineffective. Since infection susceptibility in patients with haematological malignancies is frequently	n/a	n/a	n/a	n/a	

	Australia[1]	England[3]	Scotland[4]	Atlantic Provinces (Canada)[5]	Alberta, Manitoba, Satskachewan (Canada)[6]	British Columbia (Canada)[7]	Ontario (Canada)
		multifactorial, the reduction in overall burden of infections with long term Ig replacement may be variable. For this reason annual reviews of treatment are recommended. In patients with seasonal preponderance of infections, it may be appropriate to consider temporary cessation of Ig in the summer.					

Abbreviations: CLL= Chronic lymphocytic leukaemia, HGG=hypogammaglobulianemia, HSCT=haematopoietic stem cell transplantation, Ig=immunoglobulin,IVIG=intravenous immunoglobulin, MM=multiple myeloma, NHL=non-Hodgkin lymphoma, SCIG=subcutaneous immunoglobulin
Sources: (Alberta Ministry of Health 2018; European Medicines Agency 2018; New Zealand Blood Service 2016; NHS England 2018; NHS Scotland 2012; British Columbia Provincial Blood Coordinating Office 2019; Nova Scotia Provincial Blood Coordinating Team 2018; NBA 2019a; Ontario Regional Blood Coordinating Network 2018).

Table 43 Separate Ig use recommendations for solid organ transplantation

Country/region	Solid organ transplantation	Recommendations	Dose
Ontario	Kidney transplant from living donor to whom the patient is sensitized	IVIG is recommended to decrease donor-specific sensitization.	2 g/kg/month for 4 months.
	Pre-Transplant (heart)	For desensitization in selected heart transplant recipients who are highly sensitized, medically urgent and unlikely to receive a transplant otherwise – this should be preceded by discussion at the transplant program level.	Suggested dose is up to 1 g/kg/month until transplant.
	Peri-Transplant (heart, lung, kidney, pancreas)	Solid-organ transplant recipient with donor-specific antibodies identified at time of transplant surgery (heart, lung, kidney, pancreas) on virtual crossmatch –first-line agent.	Suggested dose 1 g/kg, can give as divided doses if in association with a course of plasmapheresis.
	Post-Transplant	Acute antibody-mediated rejection in a solid-organ transplant recipient – first-line agent. Chronic antibody-mediated rejection in a solid-organ transplant recipient.	1 g/kg/dose, can give as divided doses if in association with a course of plasmapheresis. 1 g/kg/month.
Alberta, Manitoba, Satskachewan	Kidney, active antibody-mediated rejection (ABMR) prevention and management	Pre-transplant: IVIG is recommended when an antibody or antibodies might preclude transplantation (e.g., donor specific anti-human leukocyte antigen (HLA) antibody or anti-blood group	IVIG with plasma exchange: 0.1 g/kg adjusted body weight after each plasma exchange, to a maximum total dose of 2 g/kg.

Country/region	Solid organ transplantation	Recommendations	Dose
		antibody). IVIG may be continued for up to 3 months post-transplant. Post-transplant: IVIG may be used to treat active ABMR1 when other therapies are ineffective. Patient response to each treatment cycle should be documented according to objective measures of effectiveness established at the outset of treatment.	IVIG alone: 2 g/kg adjusted body weight divided over 2 to 5 days. When IVIG is used alone, further doses may be indicated every 4 weeks for a further 3 cycles, depending on clinical response or biopsy findings. Thereafter, additional treatment cycles (often together with other treatment modalities) may be indicated, but only when biopsy findings and/or clinical response demonstrate ongoing/recurrent active ABMR or chronic active ABMR.1 Demonstration of ongoing/recurrent active ABMR or chronic active ABMR should precede each treatment cycle. Note: Some sucrose-stabilized formulations of IVIG have shown nephrotoxicity and are best avoided in patients with pre-existing kidney impairment.2 Some nephrologists recommend that IVIG infusions be capped at 140 g/day to reduce the risk of nephrotoxicity.
	Solid organ (other than kidney) ABMR	IVIG is recommended in addition to plasma exchange. Where appropriate, biopsy evidence of rejection should be sought. Patient response should be documented according to objective measures of effectiveness established at the outset of treatment.	0.1 g/kg adjusted body weight after each plasma exchange, to a maximum dose of 2 g/kg total.

Source: (Ontario Regional Blood Coordinating Network 2018; Alberta Ministry of Health 2018)

APPENDIX B SEARCH STRATEGIES

BIBLIOGRAPHIC DATABASES

Electronic database	Time period searched
Embase	No time limit
Medline	No time limit
Cochrane Central	No time limit

ADDITIONAL SOURCES OF LITERATURE

Source
Australian New Zealand Clinical Trials Registry
ClinicalTrials.gov
WHO International Clinical Trials Registry Platform
National Guideline Clearinghouse
National Institute for Health Research Journals Library
Canadian Agency for Drugs and Technologies in Health

Table 44 Search terms used (Ovid platform)

Element of clinical question	Search terms
Population	((immunoglobulin or antibody or gammaglobulin or Ig) adj (deficienc$ or defect$)).mp. hypogammaglobulin?emia.mp. or exp hypogammaglobulinemia/ secondary immunodeficienc$.tw. OR/1-3 exp hematologic neoplasm$/t ((hematological or hematologic) adj (malignanc$ or neoplasm)).mp (myeloma or leukemia or lymphoma).mp. or/5-7 "bone marrow transplant$".mp. ("stem cell transplant$" or "peripheral blood stem cell transplant$").mp. or/9-10 4 not 8 not 11
Intervention	((immunoglobulin or gammaglobulin or Ig$) adj (infusion$ or replacement$)).mp. (Ig$ adj replacement).mp IGRT.mp ((intravenous or subcutaneous) adj (immunoglobulin$ or gammaglobulin$ or Ig$)).mp. exp IMMUNOGLOBULIN/ (privigen or hizentra or flebogamma or evogam or intragam or cuvitru or panzyga or gamunex or hyqvia or intratect or kiovig or octagam or gammanorm).mp or/13-19 12 AND 20
Limits	limit 21 to human limit 22 to english language case reports/ or comment.pt. or editorial.pt. or letter.pt.

Element of clinical question	Search terms
	23 NOT 24 remove duplicates from 25

APPENDIX C STUDIES INCLUDED IN THE SYSTEMATIC REVIEW

Table 45 Profiles of studies on secondary HGG (excluding haematological malignancies and HSCT) included in the systematic literature review

Authors Publication Year		Study design	Level of evidence[a]/ Risk of bias[b]	Location Setting Length of follow-up	Study population characteristics / *Population of interest*	Description of Intervention	Description of Comparator	Relevant outcomes assessed	Measurement of relevant outcomes and methods of analysis*
	Transplant								
Carbone 2012		Retrospective study	Level III-2 Serious	Spain Single centre 18 months	Heart transplant patients (n=110)/ *Secondary HGG (Ig<600 mg/dL) post heart transplant + severe infections (n=55)*	IVIg (Flebogamma 5%) 300-400 mg/kg/month to reach Ig>750 mg/dL Min 3 infusions at 2-3wk intervals (given to all HGG patients) IVIG started after diagnosis of severe infections	Patients without HGG	Severe infections/ infections before-after IVIg	t-test or Mann-Whitney
Carbone 2007		Retrospective study (1996-2005)	Level III-2 Serious	Spain Single centre 51 months (mean), range 1-124months	Heart transplant patients (n=123)/ *Secondary HGG (Ig<600 mg/dL) post heart transplant + severe infections (n=29)*	IVIg (Flebogamma 5%) 400 mg/kg every 21 days to reach Ig>700 mg/dL (given to all HGG patients)	Patients without HGG	Infections Rejection Cancer Mortality	NA
Claustre 2015		Retrospective study (1998-2010)	Level III-2 Serious	France Single centre 2.8 years (median)	Lung transplant patients (n=84)/ *Secondary HGG (Ig<600 mg/dL) post lung transplant* *N= 29*	IVIg (Tegeline/Clairyg) 400 mg/kg per month every 3 months (given to all HGG patients) IVIG started 3.5m after transplant and lasted for 4.5m	Patients without HGG	Infections Rejection Survival	NA
Farmer 2013		Retrospective study (2007-2011, 8-week duration)	Level III-2 Serious	USA Database review 8 weeks	Intestinal transplant patients (n=34)/ *Secondary HGG (Ig< 95% CI of the mean Ig for age, <639 mg/dL in adults) post intestinal transplant (n=20)*	IVIg (Privigen) 500 mg/kg single or multiple dose (every 12 days to 13 patients), given to 85% (n=17) HGG patients 42 times	Patients without HGG	Infections Time to infection Rejection Time to rejection	NA

Authors Publication Year		Study design	Level of evidence[a]/ Risk of bias[b]	Location Setting Length of follow-up	Study population characteristics / *Population of interest*	Description of Intervention	Description of Comparator	Relevant outcomes assessed	Measurement of relevant outcomes and methods of analysis*
						Mean time to IVIG was 20.4 days			
Kawut 2005		Retrospective study (2002-2003)	Level III-2 Critical	USA Single centre (up to 2 years)	Lung transplant patients (n=57) *Secondary HGG (Ig <700 mg/dL) post lung transplant (n=34)* *Only separate results for severe HGG (<400 mg/dL) (n=8)*	NR	Patients with normal or mild HGG (NA)	Infections Mortality	NA
Lederer 2014		RCT cross-over PBO-controlled (2005-2008)	Level II Moderate	USA Single centre Two 12wk treatment periods separated by 12wk washout	Patients with secondary HGG (Ig <500 mg/dL) post lung transplant (n=11) Median time from transplant to enrolment was 187days	IVIg (Gamunex) 400 mg/kg every 4 weeks, 3 doses given	No treatment with IVIg	Infection Rejection Hospitalisation Ig levels AEs	Generalised estimating equations and logit used to estimate odds ratios for infections and hospitalisation. Models included fixed effects for drug and period Least squares means for continuous variables (Ig)
Lichvar 2018		Retrospective study (2007-2011)	Level III-2 Serious	USA Single centre 5 years	Lung transplant patients (n=484)/ *Secondary HGG (Ig <700 mg/dL) post lung transplant (n=408, 216 treated/ 192 untreated)*	On-demand IVIg to 195 (90.3%) patients (Gammagard 500mg/kg every 4 weeks) or SCIg to 21 (9.7%) patients (Hizentra weekly) to reach Ig>700 mg/dL Start of IVIG at a median of 323.5 days after transplant	No treatment with IVIg	CLAD Rejection Infection Survival	t-test or ANOVA for normally distributed data Wilcoxon rank sum, Mann-Whitney or Kruskal-Wallis for non-normally distributed data Kaplan-Meier with logrank comparisons for freedom-from-event analyses
Noell 2013		Retrospective study (2008-2011)	Level III-2 Critical	USA Single centre 612 days (mean)	Lung transplant patients (n=263)/ Secondary HGG (Ig <700 mg/dL) post lung transplant (n=192)	NR	Patients without HGG	Infection Rejection Mortality	NA

Authors Publication Year		Study design	Level of evidence[a]/ Risk of bias[b]	Location Setting Length of follow-up	Study population characteristics / *Population of interest*	Description of Intervention	Description of Comparator	Relevant outcomes assessed	Measurement of relevant outcomes and methods of analysis*
Sarmiento 2016		Prospective study (2011-2014)	Level III-2 Serious	Spain Single centre 6 months (range 137-193 days)	Secondary HGG (Ig<500 mg/dL) post heart transplant (n=25)	IVIg (Flebogamma) 200 mg/kg every 2 weeks followed up by up to 5 doses of 300 mg/kg if Ig<750 mg/dL at days 30, 60, 90 and 120 IVIG started 15.4d after transplant	No treatment with IVIg	Severe infection Time to infection Freedom from severe infection Rejection Mortality Hospital stay Hospital readmission AEs	Mann-Whitney for continuous variables Chi square for proportions Kaplan Meier to assess freedom from severe infection. Cox model to estimate the effect size
Shankar 2013		Prospective study (2009-2010)	Level III-3 Critical	USA Single centre 12 months	Secondary HGG (Ig<750 mg/dL) post lung transplant + recurrent infections or Ig<500 (n=10)	IVIg (Gammagard) 400 mg/kg/ month loading dose followed by SCIg (Vivaglobin, Hizentra) 100 mg/kg/wk (70% of patients had prior IVIg treatment)	None	Ig levels AEs	None *t-test and mean differences for Ig levels before/after Ig-RT calculated during the preparation of this report*
	Surgery								
Rhodes 2014		Retrospective study (2010-2011)	Level III-3 Critical	USA Single centre NR	CPB infants (n=47) *Secondary HGG (Ig<2SD of mean preoperative levels) post CPB (n=25)*	Ig-RT NR	Patients without HGG	Length of PICU stay Infection Mortality	NA
Yamani 2006		Retrospective study (1999-2004)	Level III-3 Critical	USA NR	VAD+heart transplant patients (n=76) *Secondary HGG (Ig<700 mg/dL) post VAD implantation and pre-heart transplant (n=20)*	Ig-RT NR	Patients without HGG	Infection Rejection Survival	NA
	Rituximab treatment in Rheumatoid arthritis								
Boleto 2018		Prospective study (2005-2017)	Level III-3 Serious	France Multicentre 64 months (mean)	Patients with RA treated with Rituximab (n=134)/	Ig-RT NR	Patients without HGG	Severe infection	NA

Authors Publication Year		Study design	Level of evidence[a]/ Risk of bias[b]	Location Setting Length of follow-up	Study population characteristics / *Population of interest*	Description of Intervention	Description of Comparator	Relevant outcomes assessed	Measurement of relevant outcomes and methods of analysis*
					Secondary HGG (Ig<600 mg/dL) after rituximab treatment (n=23)				
	Good Syndrome								
Sun 2015		Retrospective case series (2001-2015)	Level III-3 Serious	China Single centre (NR)	Good's syndrome (HGG<500mg/dL) hospitalised for moderate to severe infections (n=12)	IVIg + antibiotics (n=10) Antibiotics or supportive care (n=2)	None	Remission from infection Mortality	None
Zaman 2019		Retrospective case series (2009-2018)	Level III-3	UK UKPID Registry	Good's syndrome (HGG<600mg/dL), (n=78)	Ig-RT given to all patients (no details)	None	Clinical course Mortality	NA

AEs: adverse events, CLAD: chronic lung allograft dysfunction, CPB=cardiopulmonary bypass, HGG=hypogammaglobulinaemia, Ig-RT=immunoglobulin G replacement therapy, IVIG=intravenous immunoglobulin G, NA=not applicable, NR=not reported, PBO=placebo, RCT=randomised controlled trial, SCIG=subcutaneous immunoglobulin G, VAD=ventricular assisted device

*Not applicable to our review, statistical methods in the study used to compare HGG to non-HGG

[a] source: see NHMRC hierarchy of evidencehttps://bmcmedresmethodol.biomedcentral.com/articles/10.1186/1471-2288-9-34/tables/1),[b] risk of bias described in section B.3

Table 46 Antimicrobial treatment in studies included in the systematic literature review

Study	Antibiotic	Antiviral	Antifungal/Antimalarial
Transplant			
Carbone 2012	• Cephazolin 2g IV first day after transplant (AT) • Trimethoprim-sulfamethoxazole oral 160-180g twice weekly during the first year AT	• IV ganciclovir or vanganciclovir to CMV-positive patients	• Nystatin 500,000U oral during the first month AT
Carbone 2007		• IV ganciclovir 5mg/kg twice a day during 14 days AT for CMV-seropositive patients	
Claustre 2015	NR	• Oral ganciclovir 100 days AT in CMV-positive patients • Valaciclovir during 3 months AT in CMV-negative patients	• Posaconazole daily for 100 days AT • Pyrimethamine-sulfadoxine for 1 year AT
Farmer 2013	NR	NR	NR
Kawut 2005	NR	• IV ganciclovir or vanganciclovir 6-12 months AT depending on CMV serology	• Amphotericin B during the hospital phase • Oral fluconazole or voriconazole post-hospital based on fungal culture results
Lederer 2014	NR	NR	NR
Lichvar 2018	NR	NR	NR
Noell 2013	NR	NR	NR
Sarmiento 2016	• Cephazolin first day after transplant (AT) • Trimethoprim-sulfamethoxazole oral twice daily twice week during the first year AT • Oral norfloxacine twice daily during the first month AT	• IV ganciclovir or oral vanganciclovir to CMV-positive patients	• Itraconazole in patients with risk factors for invasive aspergillosis
Shankar 2013	NR	NR	NR
Surgery			
Rhodes 2014	NR	NR	NR
Yamani 2006	NR	NR	NR
Rituximab treatment in rheumatoid arthritis			
Boleto 2018	NR	NR	NR
Good Syndrome			
Sun 2015	NR	NR	NR
Zaman 2019	NR	NR	NR

AT=after transplant, IV=intravenous, NR=not reported

These are all the details on antimicrobial therapy reported in the studies. None of the studies reported antimicrobial treatment by HGG group

APPENDIX D EVIDENCE PROFILE TABLES

Table 47 Evidence profile table for the key effectiveness outcomes (IVIG vs. no IVIG)

Outcome (follow-up)	No. of studies & study design	Risk of bias	Inconsistency[a]	Indirectness	Imprecision	Other considerations[b]	No. of patients in intervention arms	No. of patients in comparator arms	Relative effect (95%CI)	Absolute effect (95%CI)	Quality
Infections											
Infections (12w-5y)	N=2 1 RCT 1 Observational	Serious[1]	Very serious[2]	Not serious	Very serious[3]	None	227	203	Not estimable	Not estimable	Very low
Severe infections (6m)	N=1 Observational	Serious[1]	Serious[4]	Not serious	Serious[5]	None	12	13	RR 0.33 (0.12, 0.91)	RD -0.52 (-0.85, -0.18)	Very low
Bacterial infections (12w-6m)	N=2 1 RCT 1 Observational	Serious[1]	Very serious[2]	Not serious	Very serious[3]	None	23	24	Not estimable	Not estimable	Very low
CMV infection (6m)	N=1 Observational	Serious[1]	Serious[4]	Not serious	Serious[5]	None	12	13	RR 0.10 (0.01, 1.60)	RD -0.38 (-0.66, -0.11)	Very low
Viral infections	N=1 RCT	Moderate	Serious[9]	Not serious	Very serious[3]	None	11	11	OR 0.8 (0.1, 5.9)	RD *0.00 (-0.32, 0.32)*	Very low
Transplant rejection											
Acute rejection	N=2 1 Observational 1 RCT	Serious[1]	Not serious	Not serious	Very serious[3]	None	23	24	Not estimable	Not estimable	Very low
A-grade rejection score	N=1 Observational	Serious[1]	Serious[4]	Not serious	Not serious	None	216	192	NR	NR	Very low
5-year Severe CLAD (Grade 2)	N=1 Observational	Serious[1]	Serious[4]	Not serious	Not serious	None	145	177	RR 0.51 (0.28, 0.94)	RD -0.09 [-0.16, -0.01]	Very low
5-year Severe CLAD (Grade 3)	N=1 Observational	Serious[1]	Serious[4]	Not serious	Not serious	None	145	177	RR 1.44 (0.78, 2.64)	RD 0.04 (-0.03, 0.11)	Very low

Outcome (follow-up)	No. of studies & study design	Risk of bias	Inconsistency[a]	Indirectness	Imprecision	Other considerations[b]	No. of patients in intervention arms	No. of patients in comparator arms	Relative effect (95%CI)	Absolute effect (95%CI)	Quality
Survival											
1-year survival	N=1 Observational	Serious[1]	Serious[4]	Not serious	Not serious	None	216	192	75% vs 88.0%, p<0.006	Not estimable	Very low
2-year survival	N=1 Observational	Serious[1]	Serious[4]	Not serious	Not serious	None	216	192	64.8% vs. 81.3% p<0.001	Not estimable	Very low
5-year survival	N=1 Observational	Serious[1]	Serious[4]	Not serious	Not serious	None	216	192	56.0% vs. 67.2% p<0.006	Not estimable	Very low
Mortality rate (6m)	N=1 Observational	Serious[1]	Serious[4]	Not serious	Not serious	None	11	12	*25% vs.23%* p=0.91	Not estimable	Very low
1-year CLAD-free survival	N=1 Observational	Serious[1]	Serious[4]	Not serious	Serious[8]	None	216	192	74.6% vs. 78.2%	Not estimable	Very low
2- year CLAD-free survival	N=1 Observational	Serious[1]	Serious[4]	Not serious	Serious[8]	None	216	192	52.53% vs. 52.53%	Not estimable	Very low
Hospitalisations											
Hospitalisation (12w-6m)	N=2 1 RCT 1 Observational	Serious[1]	Very serious[2]	Not serious	Very serious[6]	None	23	24	Not estimable	Not estimable	Very low
Length of hospital stay, days (6m)	N=1 Observational	Serious[1]	Serious[4]	Not serious	Serious[7]	None	11	12	NR, p=0.57	Not estimable	Very low

[a] It was not possible to pool the data across the studies and conduct a meta-analysis, thus statistical measures of heterogeneity are not available to determine inconsistency. An assessment of the difference in the magnitude of effects across studies and direction of effect was done instead.

[b] Other considerations: Particular design features of extremely rigorous well-conducted observational studies may warrant consideration for rating up quality of evidence

[1] Downgraded by one for high risk of bias

[2] Downgraded by 2 due to differing direction of effect across the studies

[3] Downgraded by 2 due to small number of patients, lack of power, CI in the studies include no effect or clinically meaningful benefits or harms

[4] Downgraded by one as this was a single observational study

[5] Downgraded by one due to the small number of patients
[6] Downgraded by 2 due to small number of patients, lack of power, wide CI in one study, no effect estimate in the other study
[7] Downgraded by 1 due to lack of effect estimate
[8] Downgraded by 1 due poor reporting of statistical analysis
[9] Downgraded by 1 as this is only a small RCT
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

APPENDIX E EXCLUDED STUDIES

Table 48 Excluded studies and reasons for exclusion

Exclusion: Population (n=31)
Abdou, N. I., C. A. Greenwell, R. Mehta, M. Narra, J. D. Hester and J. F. Halsey (2009). "Efficacy of intravenous gammaglobulin for immunoglobulin G subclass and/or antibody deficiency in adults." International Archives of Allergy & Immunology 149(3): 267-274.
Anonymous (2017). "Home-based subcutaneous infusion of immunoglobulin for primary and secondary immunodeficiencies: A health technology assessment." 17(16).
Barmettler, S., M. S. Ong, J. R. Farmer, H. Choi and J. Walter (2018). "Association of Immunoglobulin Levels, Infectious Risk, and Mortality With Rituximab and Hypogammaglobulinemia." JAMA Network Open 1(7): e184169.
Berlana, D., A. Vidaller, R. Jodar, E. Fort, A. Domingo and L. Pasto (2005). "Changes in biochemical, hematological and immunological profiles after low-dose intravenous immunoglobulin administration in patients with hypogammaglobulinemia." Transfusion Clinique et Biologique 12(6): 433-440.
Cabanillas, F., I. Liboy, O. Pavia and E. Rivera (2006). "High incidence of non-neutropenic infections induced by rituximab plus fludarabine and associated with hypogammaglobulinemia: a frequently unrecognized and easily treatable complication." Annals of Oncology 17(9): 1424-1427.
Cherin, P., C. Belizna, O. Cartry, G. Lascu-Dubos, C. de Jaeger, J. C. Delain, J. C. Crave and E. Hachulla (2016). "Long-term subcutaneous immunoglobulin use in inflammatory myopathies: A retrospective review of 19 cases." Autoimmunity Reviews 15(3): 281-286.
Frenzel, W., S. Wietek, T. E. Svae, A. Debes and D. Svorc (2016). "Tolerability and safety of Octagam (IVIG): a post-authorization safety analysis of four non-interventional phase IV trials." International journal of clinical pharmacology and therapeutics 54(11): 847-855.
Gardulf, A., L. Hammarstrom and C. I. E. Smith (1991). "Home treatment of hypogammaglobulinaemia with subcutaneous gammaglobulin by rapid infusion." Lancet 338(8760): 162-166.
Hoffmann, F., B. Grimbacher, J. Thiel, H. H. Peter, B. H. Belohradsky, W. Ebell, B. Gruhn, G. Jacobs, B. Kindler, M. Kindler, W. Mannhardt-Laakmann, O. Peters and I. Schuize (2010). "Home-based subcutaneous immunoglobulin G replacement therapy under real-life conditions in children and adults with antibody deficiency." European Journal of Medical Research 15(6): 238-245.
Hoskote, A. U., R. N. Ramaiah, C. M. Cale, J. C. Hartley and K. L. Brown (2012). "Role of immunoglobulin supplementation for secondary immunodeficiency associated with chylothorax after pediatric cardiothoracic surgery." Pediatric Critical Care Medicine 13(5): 535-541.
Kado, R., G. Sanders and W. J. McCune (2017). "Diagnostic and therapeutic considerations in patients with hypogammaglobulinemia after rituximab therapy." Current Opinion in Rheumatology 29(3): 228-233.
Keswani, A., N. M. Dunn, A. Manzur, S. Kashani, X. Bossuyt, L. C. Grammer, D. B. Conley, B. K. Tan, R. C. Kern, R. P. Schleimer and A. T. Peters (2017). "The Clinical Significance of Specific Antibody Deficiency (SAD) Severity in Chronic Rhinosinusitis (CRS)." The Journal of Allergy & Clinical Immunology in Practice 5(4): 1105-1111.
Kirch, W., M. Stangel, D. Pittrow, U. Baumann, M. Fasshauer, D. Huscher, M. Hensel, M. Reiser, R. Gold and M. Borte (2012). "Immunoglobulins for primary or secondary immunodeficiency or for immunomodulation in neurological autoimmune diseases: Insights from the prospective SIGNS registry." Journal of Public Health (Germany) 20(3): 289-296.
Lalan, S., H. Dai and B. A. Warady (2017). "Hypogammaglobulinemia in infants receiving chronic peritoneal dialysis." Pediatric Nephrology 32(3): 503-509.
Lamari, F., N. K. Karamanos, E. Papadopoulou-Alataki, F. Kanakoudi-Tsakalidou, G. Dimitracopoulos and E. D. Anastassiou (2000). "Monitoring of two intravenous immunoglobulin preparations for immunoglobulin G subclasses and specific antibodies to bacterial surface antigens and relation with their levels in treated immunodeficient patients." Journal of Pharmaceutical and Biomedical Analysis 22(6): 1029-1036.
Lindberg, K., R. Gustafson, A. Samuelson and B. Rynnel-Dagoo (2001). "Impact of Ig replacement therapy and antibiotic treatment on the colonization of non-encapsulated Haemophilus influenzae in the nasopharynx in patients with hypogammaglobulinaemia." Scandinavian Journal of Infectious Diseases 33(12): 904-908.

Exclusion: Population (n=31)
Perazzio, S. F., A. Granados, R. Salomao, N. P. Silva, M. Carneiro-Sampaio and L. E. C. Andrade (2016). "High frequency of immunodeficiency-like states in systemic lupus erythematosus: A cross-sectional study in 300 consecutive patients." Rheumatology (United Kingdom) 55(9): 1647-1655.
Pettit, S. J., H. Bourne and G. P. Spickett (2002). "Survey of infection in patients receiving antibody replacement treatment for immune deficiency." Journal of Clinical Pathology 55(8): 577-580.
Ramirez, E., J. A. Romero-Garrido, E. Lopez-Granados, A. M. Borobia, T. Perez, N. Medrano, C. Rueda, H. Y. Tong, A. Herrero and J. Frias (2014). "Symptomatic thromboembolic events in patients treated with intravenous-immunoglobulins: results from a retrospective cohort study." Thrombosis Research 133(6): 1045-1051.
Remvig, L., V. Andersen, N. E. Hansen and H. Karle (1991). "Prophylactic effect of self-administered pump-driven subcutaneous Ig infusion in patients with antibody deficiency: A triple-blind cross-over study comparing P-Ig levels of 3 g l⁻¹ versus 6 g l⁻¹." Journal of Internal Medicine 229(1): 73-77.
Roifman, C. M., H. Levison and E. W. Gelfand (1987). "High-dose versus low-dose intravenous immunoglobulin in hypogammaglobulinaemia and chronic lung disease." Lancet 1(8541): 1075-1077.
Shemer, A., S. Kivity and Y. Shoenfeld (2018). "Clinical indications for intravenous immunoglobulin utilization in a tertiary medical center: a 9-year retrospective study." Transfusion 58(2): 430-438.
Skull, S. and A. Kemp (1996). "Treatment of hypogammaglobulinaemia with intravenous immunoglobulin, 1973-93." Archives of disease in childhood 74(6): 527-530.
Snowden, N., A. Moran, J. Booth, M. R. Haeney and D. R. Swinson (1999). "Defective antibody production in patients with rheumatoid arthritis and bronchiectasis." Clinical Rheumatology 18(2): 132-135.
Spadaro, G., A. Vultaggio, A. Alberto Bosi, D. Reichert, J. Janssen, D. Lamacchia, L. Nappi, A. Pecoraro, C. Milito, A. Ferraro, A. Matucci, F. Bacchiarri, V. Carrai, A. Hibbeler, E. Speckman, C. Guarnieri, S. Bongiovanni and I. Quinti (2017). "Rapid infusions of human normal immunoglobulin 50 g/l are safe and well tolerated in immunodeficiencies and immune thrombocytopenia." International immunopharmacology 44: 38-42.
Stubbs, A., C. Bangs, B. Shillitoe, J. D. Edgar, S. O. Burns, M. Thomas, H. Alachkar, M. Buckland, E. McDermott, G. Arumugakani, S. Jolles, R. Herriot and P. D. Arkwright (2018). "Bronchiectasis and deteriorating lung function in agammaglobulinaemia despite immunoglobulin replacement therapy." Clinical & Experimental Immunology 191(2): 212-219.
van Kessel, D. A., T. W. Hoffman, H. van Velzen-Blad, P. Zanen, J. C. Grutters and G. T. Rijkers (2017). "Long-term Clinical Outcome of Antibody Replacement Therapy in Humoral Immunodeficient Adults With Respiratory Tract Infections." EBioMedicine 18: 254-260.
Viallard, J. F., P. Agape, V. Barlogis, G. Cozon, C. Faure, F. Fouyssac, C. Gaud, M. P. Gourin, M. Hamidou, C. Hoarau, F. Husseini, M. Ojeda-Uribe, M. Pavic, I. Pellier, A. Perlat, N. Schleinitz and B. Slama (2016). "Treatment with Hizentra in patients with primary and secondary immunodeficiencies: A real-life, non-interventional trial." BMC Immunology 17(1).
Wijetilleka, S., C. Mukhtyar, D. Jayne, A. Ala, P. Bright, H. Chinoy, L. Harper, M. Kazmi, S. Kiani-Alikhan, C. Li, S. Misbah, L. Oni, F. Price-Kuehne, A. Salama, S. Workman, D. Wrench and M. Y. Karim (2019). "Immunoglobulin replacement for secondary immunodeficiency after B-cell targeted therapies in autoimmune rheumatic disease: Systematic literature review." Autoimmunity Reviews 18(5): 535-541.
Windegger, T. M., C. A. Lambooy, L. Hollis, K. Morwood, H. Weston and Y. L. Fung (2017). "Subcutaneous Immunoglobulin Therapy for Hypogammaglobulinemia Secondary to Malignancy or Related Drug Therapy." Transfusion Medicine Reviews 31(1): 45-50.
Windegger, T. M., S. Nghiem, K. H. Nguyen, Y. L. Fung and P. A. Scuffham (2019). "Cost-utility analysis comparing hospital-based intravenous immunoglobulin with home-based subcutaneous immunoglobulin in patients with secondary immunodeficiency." Vox Sanguinis 114(3): 237-246.
Exclusion: Wrong Intervention (n=6)
Doron, S., R. Ruthazer, B. G. Werner, A. Rabson and D. R. Snydman (2006). "Hypogammaglobulinemia in liver transplant recipients: incidence, timing, risk factors, and outcomes." Transplantation 81(5): 697-703.
Dupin, C., S. Marchand-Adam, O. Favelle, R. Costes, P. Gatault, P. Diot, L. Grammatico-Guillon and L. Guilleminault (2016). "Asthma and Hypogammaglobulinemia: an Asthma Phenotype with Low Type 2 Inflammation." Journal of Clinical Immunology 36(8): 810-817.

Exclusion: Population (n=31)
Florescu, D. F., A. C. Kalil, F. Qiu, W. Grant, M. C. Morris, C. M. Schmidt, M. C. Florescu and J. A. Poole (2014). "Does increasing immunoglobulin levels impact survival in solid organ transplant recipients with hypogammaglobulinemia?" Clinical Transplantation 28(11): 1249-1255.
Goldfarb, N. S., R. K. Avery, M. Goormastic, A. C. Mehta, R. Schilz, N. Smedira, L. Pien, M. T. Haug, S. M. Gordon, L. K. Hague, J. M. Dresing, T. Evans-Walker and J. R. Maurer (2001). "Hypogammaglobulinemia in lung transplant recipients." Transplantation 71(2): 242-246.
Poole, J. A., F. Qiu, A. C. Kalil, W. Grant, D. F. Mercer and D. F. Florescu (2016). "Impact of Immunoglobulin Therapy in Intestinal Transplant Recipients With Posttransplantation Hypogammaglobulinemia." Transplantation Proceedings 48(2): 479-484.
Yamani, M. H., R. Avery, S. Mawhorter, J. B. Young, A. McNeill, D. J. Cook, N. B. Ratiff, P. McCarthy and R. C. Starling (2001). "Hypogammaglobulinemia after heart transplantation: Impact of pre-emptive use of immunoglobulin replacement (CytoGam) on infection and rejection outcomes." Transplant Infectious Disease 3(SUPPL. 2): 40-43.
Exclusion: Outcomes (n=9)
Patel, K., J. Akhter, L. Kobrynski, M. A. Benjamin Gathmann, O. Davis, K. E. Sullivan and C. International DiGeorge Syndrome Immunodeficiency (2012). "Immunoglobulin deficiencies: the B-lymphocyte side of DiGeorge Syndrome." Journal of Pediatrics 161(5): 950-953.
Rehman, S., D. Bytnar, J. W. Berkenbosch and J. D. Tobias (2003). "Hypogammaglobulinemia in pediatric ICU patients." Journal of Intensive Care Medicine 18(5): 261-264.
Roberts, D. M., R. B. Jones, R. M. Smith, F. Alberici, D. S. Kumaratne, S. Burns and D. R. Jayne (2015). "Immunoglobulin G replacement for the treatment of infective complications of rituximab-associated hypogammaglobulinemia in autoimmune disease: a case series." Journal of Autoimmunity 57: 24-29.
Yip, N. H., D. J. Lederer, S. M. Kawut, J. S. Wilt, F. D'Ovidio, Y. Wang, E. Dwyer, J. R. Sonett and S. M. Arcasoy (2006). "Immunoglobulin G levels before and after lung transplantation." American Journal of Respiratory and Critical Care Medicine 173(8): 917-921.
Aguiar, R., C. Araujo, G. Martins-Coelho and D. Isenberg (2017). "Use of Rituximab in Systemic Lupus Erythematosus: A Single Center Experience Over 14 Years." Arthritis care & research 69(2): 257-262.
Marco, H., R. M. Smith, R. B. Jones, M. J. Guerry, F. Catapano, S. Burns, A. N. Chaudhry, K. G. Smith and D. R. Jayne (2014). "The effect of rituximab therapy on immunoglobulin levels in patients with multisystem autoimmune disease." BMC Musculoskeletal Disorders 15: 178.
Reboursiere, E., H. Fouques, G. Maigne, H. Johnson, S. Chantepie, A. C. Gac, O. Reman, M. Macro, K. Benabed, X. Troussard, G. Damaj and S. Cheze (2016). "Rituximab salvage therapy in adults with immune thrombocytopenia: retrospective study on efficacy and safety profiles." International Journal of Hematology 104(1): 85-91.
Sarmiento, E., N. del Pozo, A. Gallego, J. Fernandez-Yanez, J. Palomo, A. Villa, M. Ruiz, P. Munoz, C. Rodriguez, J. Rodriguez-Molina, J. Navarro, K. Kotsch, E. Fernandez-Cruz and J. Carbone (2012). "Decreased levels of serum complement C3 and natural killer cells add to the predictive value of total immunoglobulin G for severe infection in heart transplant recipients." Transplant Infectious Disease 14(5): 526-539.
Schwartz, H. J., R. W. Hostoffer, E. R. McFadden, Jr. and M. Berger (2006). "The response to intravenous immunoglobulin replacement therapy in patients with asthma with specific antibody deficiency." Allergy & Asthma Proceedings 27(1): 53-58.
Exclusion: Study design (n=8)
Florescu, D. F. (2014). "Solid organ transplantation: hypogammaglobulinaemia and infectious complications after solid organ transplantation." Clinical & Experimental Immunology 178 Suppl 1: 54-56.
Fricker, P. A., W. A. McDonald, M. Gleeson and R. L. Clancy (1999). "Exercise-associated hypogammaglobulinemia." Clinical Journal of Sport Medicine 9(1): 46-48.
Ledford, D. K. (2016). "Hypogammaglobulinemia without Infection." The Journal of Allergy & Clinical Immunology in Practice 4(4): 790.
Leitao Filho, F. S., S. Won Ra, A. Mattman, R. S. Schellenberg, N. Fishbane, G. J. Criner, P. G. Woodruff, S. C. Lazarus, R. Albert, J. E. Connett, M. K. Han, F. J. Martinez, J. M. Leung, S. F. P. Man, S. D. Aaron, R. M. Reed and D. D. Sin (2017). "Serum Ig and risk of exacerbations and hospitalizations in chronic obstructive pulmonary disease." Journal of Allergy & Clinical Immunology 140(4): 1164-1167.e1166.

Exclusion: Population (n=31)
Matthews, W. J., Jr., M. Williams, B. Oliphint, R. Geha and H. R. Colten (1980). "Hypogammaglobulinemia in patients with cystic fibrosis." New England Journal of Medicine 302(5): 245-249.
Ruffner, M. A., T. R. Aksamit, B. Thomashow, R. Choate, A. DiMango, G. M. Turino, A. E. O'Donnell, M. M. Johnson, K. N. Olivier, K. Fennelly, C. L. Daley, K. L. Winthrop, M. L. Metersky, M. A. Salathe, M. R. Knowles, M. L. A. Daniels, P. G. Noone, G. Tino, D. E. Griffith and K. E. Sullivan (2017). "Frequency of untreated hypogammaglobulinemia in bronchiectasis." Annals of Allergy, Asthma, & Immunology 119(1): 83-85.
Sacco, K. A. and R. S. Abraham (2018). "Consequences of B-cell-depleting therapy: hypogammaglobulinemia and impaired B-cell reconstitution." Immunotherapy 10(8): 713-728.
Sarmiento, E., J. J. Rodriguez-Molina, J. Fernandez-Yanez, J. Palomo, R. Urrea, P. Munoz, E. Bouza, E. Fernandez-Cruz and J. Carbone (2006). "Ig monitoring to identify the risk for development of infection in heart transplant recipients." Transplant Infectious Disease 8(1): 49-53.
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APPENDIX F HGG VS NO-HGG COMPARISON

The comparison between HGG (with Ig-RT or with Ig-RT not reported) and no-HGG was beyond the scope of this review and these data were not presented in the previous sections, but here we provide a top line summary of the findings across the included studies for the key outcomes below. This information may provide important information on the natural history of outcomes in patients with and without HGG and thus give an indication of the capacity to benefit from Ig-RT. It is important to note this comparison was not part of our systematic review and studies were not systematically identified to inform this question; instead, this is only an ad-hoc overview of those papers included through the current search criteria. It should be noted that no studies were found where it was explicitly reported that the HGG cohort had not been treated with Ig-RT. Overall, results vary widely across the studies, which is not surprising given the high level of heterogeneity in the included studies:

- Infections and severe infections: some studies did not find any significant differences between HGG and non-HGG patients (Lichvar et al. 2018; Sarmiento et al. 2016; Claustre et al. 2015; Farmer et al. 2013), suggesting that IVIG confers a protective effect in HGG patients, whereas Carbone 2007 found a significantly higher number of infections in IVIG-treated HGG patients compared to those without HGG. Others also found that HGG patients were at a significant higher risk of infections than non-HGG patients, but it was unclear if the HGG patients were treated with IVIG (Yamani et al. 2006; Boleto et al. 2018; Kawut et al. 2005).

- Transplant rejection: none of the studies reported significant differences between HGG treated with Ig-RT and non-HGG patients (Sarmiento et al. 2016) (Claustre et al. 2015; Noell, Dawson, and Seethamraju 2013; Carbone et al. 2007; Carbone et al. 2012; Farmer et al. 2013; Yamani et al. 2006). No significant differences between HGG and non-HGG groups for the outcome of transplant rejection were also found in two cohort studies where Ig-RT status was not reported (Noell, Dawson, and Seethamraju 2013; Yamani et al. 2006). Only Lichvar 2018 found a significantly higher freedom from allograft dysfunction in patients without HGG compared to those with HGG, irrespective of IVIG treatment, and their multivariate analysis showed that secondary HGG significantly increased the risk of CLAD development (Lichvar et al. 2018).

- Survival: some studies reported better survival in patients without HGG than in those with HGG treated with IVIG (Lichvar et al. 2018; Carbone et al. 2007) and those with HGG but unknown Ig-RT status ((Kawut et al. 2005). However, the majority of studies did not find any significant survival differences between non-HGG and HGG patients treated Ig-RT (Carbone

et al. 2012; Sarmiento et al. 2016; Claustre et al. 2015), and HGG patients with unknown Ig-RT status (Yamani et al. 2006; Noell, Dawson, and Seethamraju 2013; Rhodes et al. 2014).

- Hospitalisations: Sarmiento 2016 found no significant differences in hospital readmission between patients with HGG treated with IVIG and those without HGG, but length of hospital stay was shorter in patients without HGG (Sarmiento et al. 2016). No differences in length of ICU stay were found in heart transplant patients with HGG who received Ig-RT and those without HGG (Carbone et al. 2007), but Rhodes 2014 found a significantly higher length in ICU in their population of neonates with HGG (Ig-RT not reported) compared to those without HGG (Rhodes et al. 2014).

APPENDIX G ECONOMIC ANALYSIS (WINDEGGER 2019)

Windegger 2019 (Windegger et al. 2019) conducted a cost-utility analysis (CUA) comparing -based IVIG to home-based SCIG in patients with secondary HGG following malignancies. The study used a Markov cohort simulation model with six health states, 1-week cycles and 10-year time horizon. The model outcomes of included:

- Cost to the healthcare system
- Health outcomes
    - QALYs
- Clinical outcomes
    - Incidence of infection at home or in the hospital
    - Development of bronchiectasis with or without infections
    - Development of bronchiectasis with chronic pseudomonas aeruginosa infection
    - Mortality

The model population was a cohort of adult patients with secondary HGG following malignancies, including 8 females and 5 males with an average age of 62.5 years [39-76]. During their study period, patients did not develop bronchiectasis nor die. However, 4 patients developed bronchiectasis during the observation period while 2 patients died 2 years post study period. The 13 patients were treated at the Sunshine Coast Hospital and Health Services (SCHHS) in Queensland. QALY information was also collected from patients at the Gold Coast University Hospital (GCUH) in Queensland during the setting up of their SCIG programme. The model included 6 health states (Figure 9)

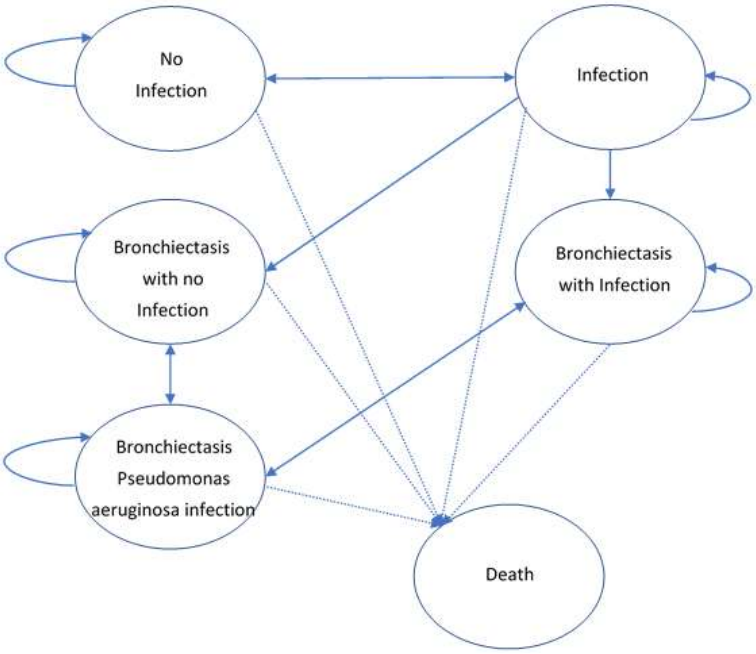

Figure 9: Economic model in patients with secondary HGG following malignancies
Source: (Windegger et al. 2019)

QALYs were measured using the Assessment of Quality of Life 6 (AoQL-6D). Transition probabilities were derived from clinical data of the patient cohort, except for data on pseudomonas infection or death, which were estimated from existing literature in patients with bronchiectasis (not patients with SID). Life table on all-cause mortality and from the cohort of 13 patients. A weekly cycle was used over a 10-year period. Probabilistic sensitivity analysis was conducted over 50 000 iterations.

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