Immunoglobulin for acquired hypogammaglobulinaemia secondary to haematological malignancies, or post-haemopoietic stem cell transplantation (HSCT)

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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.

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EXECUTIVE SUMMARY

Immunoglobulin for acquired hypogammaglobulinaemia secondary to haematological malignancies, or post-haemopoietic stem cell transplantation (HSCT)

Main issues for MSAC consideration

- *Trials were reported for patients with CLL, MM, and those who underwent HSCT. However, no adequate randomised trials were identified in patients with acute leukaemia, NHL, or 'other haematological malignancies'.*
- *It was however considered plausible that similar outcomes would be observed in AL, NHL and 'other' haematological malignancies, assuming the patients satisfied the criteria for hypogammaglobulinaemia and history of infections.*
- *It was not possible to evaluate the claim that IgG with or without antibiotics is superior to No IgG with or without antibiotics.*
- *The clinical evidence in the included studies support a claim of superior efficacy but inferior safety for IgG compared to no IgG (with antibiotic use defined as part of supportive care).*
- *This evaluation could not address:*
    - *Confirmation of a clinically active dose or frequency of dosing. Most studies included explored doses between 200 and 500 mg/kg.*
    - *Definition of adequate treatment response: a qualitative reduction in infections rate was usually taken as evidence of a response. Timeframes for assessment were highly variable.*
    - *Criteria for discontinuation. An initial patient response in terms of infections seemed to be adequate reason for ongoing IgG replacement which often lasted for some months or years.*
    - *Frequency of serum IgG monitoring as a basis for response assessment or a decision to discontinue.*
- *Given the underlying uncertainty associated with the estimates of IgG treatment effectiveness, the use of these estimates in the economic model is therefore also associated with uncertainty.*
- *A main assumption in the economic model structure allows for the development of bronchiectasis. The inclusion of such health states was based on a recent economic evaluation in Australian patients comparing SCIg to IVIg for acquired hypogammaglobulinaemia (Windegger et al. 2019). A significant increase in the incremental cost-effectiveness ratio (ICER)*

Main issues for MSAC consideration

is observed when transitions to bronchiectasis health states are not allowed. The resulting ICER from this sensitivity analysis is consistent with that observed in an older relevant economic model (Weeks, Tierney & Weinstein 1991) which did not model the development of bronchiectasis.

- *The financial implications for government health budgets associated with Ig include cost offsets due to a reduction in infections. As these are indirect cost-offsets, and assume a relative treatment effect of Ig in reducing the incidence of infections, these are associated with uncertainty.*

This contracted assessment is part of a pilot process to review the evidence to support funding of immunoglobulin (IgG) for patients with acquired hypogammaglobulinaemia, under the national blood arrangements. This indication is one of several 'diagnostic groups' of conditions eligible for funded IgG treatment under the National Blood Authority's *Criteria for Immunoglobulin Use in Australia, Version 3* [1](the *Criteria*).

ALIGNMENT WITH AGREED PICO CONFIRMATION

This contracted assessment of IgG for acquired hypogammaglobulinaemia addresses all of the PICO[2] elements that were pre-specified in the PICO Confirmation that was ratified by the Ig Review Reference Group. However, the Report needs to be interpreted in the context that there is a limited underlying scientific evidence base available to inform the assessment.

MEDICAL SERVICE

IgG replacement therapy (IgG-RT) is used to compensate for the low levels of serum IgG in patients with hypogammaglobulinaemia. It would be used in combination with standard care, which includes antibiotic use and treatment for the underlying conditions. IgG products are manufactured from pooled human donor plasma, and the IgG fraction formulated to contain the desired concentration of IgG as active substance. The IgG content represents a broad spectrum of human antibodies. Other immunoglobulins such as IgA, IgM and IgE may be present but are controlled as impurities.

IgG products may be administered by intravenous (IV), subcutaneous (SC) or intramuscular infusion, although intramuscular administration is out of scope for this evaluation, as it is rarely used in Australia.

[1] Criteria for Immunoglobulin Use in Australia version 3, National Blood Authority, 2018.

[2] Population, Intervention, Comparator, Outcomes

There are currently 17 IgG products that are registered on the Australian Register of Therapeutic Goods (ARTG). For more information, see Table 10, pg. 20.

The recommended dose on BloodSTAR is 0.4 g/kg. The majority of documentation reviewed cites a maintenance dose for IVIg of 0.4 g/kg every four weeks, however, doses lower than 0.4 g/kg may be used during titration.

PUBLIC FUNDING

This contracted assessment is to review the use of IgG for an indication which is currently funded under the National Blood Supply Arrangements. The products current funded are shown in Table 1.

Table 1 Ig products funded for this indication

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

IV=intravenous; SC=subcutaneous
Source: PICO Confirmation for MSAC 1565.

POPULATION

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

- Acute leukaemia
- Chronic lymphocytic leukaemia (CLL)
- Multiple myeloma (MM)
- Non-Hodgkin lymphoma (NHL)

- Other Haematological malignancy
  [Diagnosis of haematological malignancies should be according to the criteria of the current World Health Organization (WHO) classification[3].]
- Memory B cell deficiency secondary to HSCT.

The target population is identified by symptoms but covers different underlying haematological malignancies each characterised by low IgG levels. Patients with each condition will differ in clinical characteristics, treatments for underlying disease and prognosis. There are different baseline risks of infection (higher in acute leukaemia and post-HSCT patients) and consequently, a difference in infection treatments among the above conditions. In addition, the baseline risk of intensive care admission is greater for post-HSCT patients than for the other specific conditions. The way in which hypogammaglobulinaemia is diagnosed and treated (with or without access to IgG) is common across the patients in this indication.

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

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

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

COMPARATOR DETAILS

The comparator is defined in the ratified PICO Confirmation as 'No IgG access; with or without antibiotics'. The Ig Review Reference Group advised oral trimethoprim + sulfamethoxazole (sometimes called co-trimoxazole) would be the first line antibiotic for prophylaxis against infections. This combination has a very broad TGA indication and is available on the Pharmaceutical Benefits Scheme (PBS) (Table 2).

[3] WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, IARC Revised 4th Edition 2017

Table 2 Relevant trimethoprim + sulfamethoxazole listings on the PBS

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

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

CLINICAL MANAGEMENT ALGORITHM(S)

The clinical management algorithms for the current use of IgG and for the comparator arm (No IgG) are shown in Figure 1, pg. 28.

KEY DIFFERENCES IN THE DELIVERY OF THE PROPOSED MEDICAL SERVICE AND THE MAIN COMPARATOR

In the absence of IVIg or SCIg, patients with acquired hypogammaglobulinaemia are expected to have a higher rate of infections, and therefore a higher need for antibiotics and hospitalisation due to infections.

CLINICAL CLAIM

The clinical claim in the PICO Confirmation was 'IgG with antibiotics as required' is superior to 'no IgG with antibiotics as required' for reducing infections in patients with acquired hypogammaglobulinaemia secondary to haematological malignancies, or post-HSCT.

APPROACH TAKEN TO THE EVIDENCE ASSESSMENT

A systematic review of the published literature was undertaken. PubMed, Embase.com and the Cochrane Library were searched for papers published between 1990 and March 2019. Relevant articles and reviews had their reference lists pearled for studies which may have potentially been missed through the searches. Studies were included if they met criteria determined *a priori*, as summarised in Table 3.

Table 3 Population, Intervention, Comparator and Outcomes: Acquired Hypogammaglobulinaemia due to haematological conditions

Component	Description
Patients	Patients with acquired hypogammaglobulinaemia secondary to haematological malignancies, or post-haemopoietic stem cell transplantation (HSCT) who are currently eligible for immunoglobulin (Ig) treatment in Australia according to version 3 of the *Criteria for the clinical use of immunoglobulin in Australia.*
Intervention	Replacement IgG therapy with or without antibiotics, • including IgG by intravenous administration (IVIg) or

Component	Description
	• by subcutaneous administration (SCIg)
Comparator	No IgG therapy with or without antibiotics
Outcomes	*Safety Outcomes:* ○ Adverse events including development of disease or side effects *Clinical effectiveness outcomes:* ○ Number of infections ○ Change in quality of life, including anxiety ○ Mortality *Healthcare system resources utilisation* ○ Changes in health system resource utilisation associated with the intervention, for example ○ Ig products, ○ 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 use of hospital resources) ○ 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 ○ Change in health system resource utilisation associated with the comparators, for example ○ Comparator products ○ Resources to deliver the comparator ○ Hospitalisation ○ Management of adverse events ○ Follow-up and/or monitoring visits
Questions for evidence review	Is IgG replacement therapy (with or without antibiotics) more safe, effective and cost-effective than no IgG (with or without antibiotics)?

Two researchers independently reviewed the titles and abstracts, and the citations which looked relevant to either researcher were retrieved for evaluation of the full text article. Full text articles were assessed by one researcher. The included studies had their risk of bias evaluated according to checklists designed for their study designs. Randomised and non-randomised controlled trials and observational studies were assessed using the Scottish Intercollegiate Guidelines Network (SIGN) checklists, and case series were assessed using the Institute of Health Economics checklist. The overall body of evidence per outcome measure were evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) process.

CHARACTERISTICS OF THE EVIDENCE BASE

A total of 24 studies were included in this contracted assessment. Given that IgG treatment is current clinical practice for patients with acquired hypogammaglobulinaemia, it was expected there would be a large volume of evidence. However, this was not the case.

Overall, the studies included in the report were low level evidence consisting primarily of case series with a small number of randomised studies (several of which did not adequately report the primary efficacy outcome, infections).

RESULTS

Safety

In the included studies, safety data were limited to reports of systemic adverse events (AEs) directly related to the infusion, with the exception of a registry study reporting thromboembolic events (TEE) risk. Otherwise it was not feasible to consider long-term, rare or potentially unknown events. A number of the included studies reported no safety outcomes.

Overall, the included studies show that IgG has inferior safety to No IgG, due to infusion-related AEs and a small risk of TEE events (note that safety relates to unintended adverse events - benefits and risks due to infections are considered as part of effectiveness).

AEs associated with IgG infusion were frequent but generally mild (low grade) and were manageable with adjustments to infusion. Moderate AEs tended to be less frequent and were manageable with dose adjustment, cessation or corticosteroids. None of the included studies reported any AEs greater than Grade 3 severity, nor were there any deaths or anaphylaxis due to IgG.

The 'No IgG' comparator was typically observation, thus safety of IgG was worse than the comparator, associated with injection site effects and systemic infusion reactions (and noting that differing rates of infection are part of effectiveness rather than safety). Occasionally recurrent infusion reactions lead to discontinuation of treatment. Some of the older studies employed a sham injection of solution such as albumin or saline – these were also associated with infusion-related AEs, but at a lower rate than IgG.

A small number of studies compared IVIg and SCIg, which showed that SCIg is associated with different AEs (injection site reactions) but is generally more tolerable (fewer systemic infusion reactions). One study (Sundin et al. 2012) reported that patients with a history of AEs due to IVIg products had fewer or more manageable AEs with SCIg.

IgG products have been in use in this population for some decades, thus the safety profile is well understood, even as regards rare events. In lieu of adequate safety data from the included studies, the safety data contained within approved Product Information should provide a suitably comprehensive assessment of safety for IgG products. The most common AEs associated with IVIg infusion are chills, headache, dizziness, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and moderate low back pain. Serious AEs such as thromboembolic reactions and myocardial infarctions, stroke, pulmonary embolisms, or deep vein thrombosis are very rare.

Effectiveness

The key effectiveness measure determined *a priori* during development of the PICO confirmation, was the rate of infections. Overall, there is reasonable evidence that IgG is effective at reducing the

incidence of infections. The results are remarkably consistent despite the otherwise highly variable quality of the included studies.

The randomised trial evidence showed that the rate of major infections/life-threatening infections/ septicaemia was significantly lower in patients with acquired hypogammaglobulinaemia, who received IVIg (k=5), or SCIg (k=1) than those who did not receive Ig (incident rate ratio/IRR=0.14, 95%CI 0.05, 0.43). Those receiving IgG only had one seventh the incidence of serious infections that those being managed without IgG had over the same time period, which is highly clinically important. The difference in non-serious infections was less marked, but still significant (k=6; IRR=0.61, 95%CI 0.51, 0.72). These trial data were supported by nine before and after case series, which compared the rate of infections within patients prior to receiving IgG, and while receiving IgG. The incidence of serious infections/sepsis or pneumonia or infections requiring hospitalisation was only a quarter of the incidence recorded prior to IgG initiation (IRR=0.25, 95%CI 0.15, 0.43). Similar to the randomised trials, the incidence of non-serious infections was also significantly reduced by the use of IgG (IRR=0.64, 95%CI 0.49, 0.84). The limitations of the evidence mean that the risk ratios reported in these meta-analyses are highly uncertain.

Only one trial reported on the difference in mortality, which was not significantly different for the overall sample. However, in a subsample of patients aged over 20 who had undergone a bone marrow transplant (BMT) from HLA-identical donors, the cumulative incidence of non-relapse mortality was significantly higher in those who did not receive IVIg (46%) than those who did (30%, p=0.023) (Sullivan et al. 1990).

Quality of life on the SF-36 was reported to be statistically significantly higher in a sample of MM patients who were randomised to receive SCIg compared to no SCIg (Vacca et al. 2018).

Vacca et al. (2018) performed a trial in MM patients, randomised to either SCIg or no SCIg. Patients who received SCIg had far fewer days of antibiotic use (28 vs 217) and hospitalisation (8 vs 121) than those who did not receive SCIg. These differences were considered both statistically significant and clinically important.

The summary of evidence is shown in Table 4. On the basis of the benefits and harms reported in the evidence base it is suggested that, relative to No IgG replacement with antibiotics as required, the use of IgG products with antibiotics as required has **inferior safety** and **superior effectiveness** (where safety is based on unintended adverse events and effectiveness is based on rates of infections).

Table 4 Balance of clinical benefits and harms of IgG with antibiotics as required, relative to No IgG with antibiotics as required (GRADE assessment)

Outcomes (units) Follow-up	Participants (studies)	Quality of evidence (GRADE)	Relative effect	Comments
Safety	K=13 studies; N=1,342 (2 RCTs reported AEs for both IgG and No IgG; N=125)	⊕⊕⊙⊙ Low quality	IgG has worse safety than No IgG	Safety data were limited and sometimes absent for the included studies, focusing on infusion-related events only (key RCTs (Boughton et al. 1995; Chapel et al. 1994b)). No evidence was available for longer-term outcomes other than TEE risk. Adverse events reported were nevertheless consistent with the established safety profile for IgG products (discussed in Extended Assessment of Harms).
TEE risk (arterial or venous)	1 registry study N=10,759	⊕⊕⊕⊕ High quality	% Risk difference (95% CI), 1 yr IgG tx: 1.0 (-0.2, 2.7)	Only 1 included study, but very large, recent registry study. Control and intervention groups were balanced for cardiovascular risk. Selection bias which limits use of this study for infections is unlikely to affect cardiovascular safety (the main endpoint of this study) – high confidence in risk of TEE due to IgG.
Infections	K=20 studies, N=1,930 (15 in meta-analyses: 6 RCTs, 2 cohort, 7 case series; N=1,536)	⊕⊕⊙⊙ Low quality	Rate ratio (95% CI) 0.14 (0.05, 0.43) for reduction of serious infections with IgG compared to No IgG	The quality of evidence was poor overall and infections were both reported and defined in widely variable ways. Moderate confidence that IgG reduces serious infections in patients based on a meta-analysis, but effective dose range could not be identified with any confidence and evidence was absent or limited for some of the conditions such as HSCTs, AL and 'Other haematological malignancies'.
Transplant-related events	1 RCT (N=369) 1 supportive study (N=58)	⊕⊙⊙⊙ Very low quality	No conclusion drawn.	Only two studies investigated transplant-related outcomes. One study from 1990 may not be replicable with current standard of care for HSCTs and management of GVHD risk. A second supportive study could not be used.
Mortality	4 included studies (1 RCT, 1 cohort study, 1 registry and 1 retrospective case series) N=11,674	⊕⊙⊙⊙ Very low quality	No conclusion drawn.	Insufficient duration of follow-up and variability between patient disease stage and other clinical factors precluded any meaningful assessment.
QoL	1 RCT (N=46) 1 case series with small amount of before and after data (N=307)	⊕⊕⊙⊙ Low quality	IgG marginally improves QoL compared to No IgG	Only 2 of the 4 studies reported QoL for IgG versus no IgG.

[a] 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.

TRANSLATION ISSUES

The economic model presented is a cost-utility analysis, where Ig therapy is associated with a reduction in infection rates, but that is traded off against a reduced safety profile. Ig therapy is already in use in Australia and seven translation studies were conducted to address issues regarding the applicability, extrapolation and transformation of the evidence to the proposed setting. These are summarised in Table 5.

Table 5 Summary of results of pre-modelling studies and their uses in the economic evaluation

	Results used in the economic analysis	Results tested in sensitivity analyses
Applicability		
Patient demographics	Average patient ages and weights for patients who currently receive Ig for acquired hypogammaglobulinaemia were compared to those of patients enrolled in the randomised studies used to inform the economic analysis. Patient demographics were generally not well reported, though CLL patients in the studies tended to be older than those in current practice. The majority of the randomised evidence was published in the 1990s, however the treatment effect was observed to be reasonably consistent in the older and newer studies and across both randomised and non-randomised studies. Therefore the more recent Australian data from a mixed haematological malignancy population (Paxton, Hawkins & Crispin 2016) will be used to approximate the baseline infection rate in the absence of Ig. The pooled risk reductions estimated in Section B will then be applied to the baseline infection rate to model the treatment effect of Ig.	To explore the uncertainty around baseline infection rates modelled, infection rates from each of the included randomised studies were tested. To explore the uncertainty around the treatment effect of Ig, the 95% CI of the pooled estimates were tested, in addition to the pooled estimates derived from the non-randomised studies. Further, actual infection rates (with and without Ig) from each of the randomised studies were tested in scenario analyses.
Antibiotic use in the absence of Ig	Antibiotic use in the 'No Ig' arms of the randomised studies were compared to what would happen in Australian clinical practice in the absence of Ig. Prophylactic use was generally not allowed or did not change with Ig in the included randomised studies. One non-randomised study (Duraisingham et al. 2014) did however report a slight decrease in prophylactic antibiotic use with Ig (from 80% to 67%). This study supported a benefit of similar magnitude for Ig irrespective of whether prophylactic antibiotics were used in the comparator, however due to the study design and small patient numbers, this was not conclusive and is currently being tested in an ongoing Australian trial. In the absence of alternative evidence to i) suggest that rates of antibiotic prophylaxis would increase in the absence of Ig; and ii) that this increase in antibiotic use would affect the relative treatment effect of Ig, the economic analysis will assume no difference in prophylactic antibiotic across model arms – and so the relative treatment effect observed in the randomised studies was assumed to apply to the current setting.	A scenario analysis was presented based on the results of the Duraisingham et al. (2014) study. This analysis included the cost of antibiotic prophylaxis and modelled actual infection rates (before and after Ig initiation) observed when the proportion of patients who receive antibiotic prophylaxis decreased from 80% to 67%.
Dose of Ig	The Version 3 criteria suggest doses of 0.4 g/kg every 4 weeks or more frequently to achieve targeted IgG trough levels in patients with acquired hypogammaglobulinaemia. However it is also specified that the lowest dose possible that achieves the	A sensitivity analysis was presented increasing the dose to 0.4 g/kg. Trial-based scenario analyses were also presented that

	Results used in the economic analysis	Results tested in sensitivity analyses
	appropriate clinical outcome should be used. The weighted average doses observed in the BloodSTAR data ranged from 0.36 to 0.38 g/kg). The doses used in the randomised studies ranged from 0.3 g/kg to 0.8 g/kg every three to four weeks. Despite variations in the doses used in each of the studies, the relative treatment effect of Ig was observed to be reasonably consistent. Given the experience in use with Ig in current practice, it will be assumed that current dosing is appropriate to achieve the clinical outcome of preventing infections, and so the economic analysis will use actual doses from the BloodSTAR data under the assumption that this has no effect on the relative treatment effect of Ig as observed in the trials.	use the doses from the trials with the actual infection rates observed for each of the randomised studies.
Duration of Ig treatment	No data were available from BloodSTAR to inform average treatment durations in patients with acquired hypogammaglobulinaemia. The duration of Ig treatment in the studies included in Section B was reviewed. The randomised studies included most commonly reported an Ig treatment duration of 12 months which was generally fixed and not conditional on an assessment of treatment response. One non-randomised study was identified in Australian patients which reported a median treatment duration of 26 months. This source will be used in the base case analysis. The economic model in Section D will assume that while on Ig therapy, patients are at risk of infections, however after treatment cessation, it will be assumed that no new infections are modelled – in either model arm – after such time.	Sensitivity analyses were presented assuming varying alternate treatment durations, ranging from 1 to the model time horizon of 10 years.
Extrapolation		
Duration of treatment effect	Based on the continuing access criteria it is assumed that the direct treatment effect of Ig (reduced infection rate and severity) is maintained for the duration of treatment. No direct treatment effect occurs after this time, but there is a residual difference in survival and quality of life associated with the difference in the proportions of patients in the various health states at the end of the treatment period, between the treatment arms.	This is not tested in sensitivity analyses.
Natural history of recurrent infections	There is very little published information regarding the long term consequences of recurrent infections in patients with acquired hypogammaglobulinaemia. One narrative review (Brown, Baxendale & Floto 2011) was identified which described the association of secondary immune deficiencies with bronchiectasis. This study reported that patients with haematological malignancies (particularly MM and CLL) or post-HSCT were relatively commonly associated with bronchiectasis. This is consistent with a recent Australian economic evaluation in this population which modelled the development of bronchiectasis. Therefore, the model structure will include health states associated with bronchiectasis in the base case analysis.	The inclusion of these health states are tested in a sensitivity analysis.
Transformation		
Utilities	Utility weights were sourced from the published literature. Utilities reported in a relevant Australian population using the AQoL-6D instrument will be preferentially used in the model presented in Section D. The utilities related to infections were based on an alternative source as the Australian data do not allow for differences in infection severity to be quantified. A	Sensitivity analyses are presented using alternative assumptions regarding the utility weights used in the model.

	Results used in the economic analysis	Results tested in sensitivity analyses
	disutility is applied per IV infusion, however no disutilities have been assumed due to infusion-related AEs (which were generally mild and manageable).	

AE = adverse events; AQoL-6D = Assessment of Quality of Life, six dimension; CLL = chronic lymphocytic leukaemia; Ig = immunoglobulin; MM = multiple myeloma; post-HSCT = post- haemopoietic stem cell transplantation.

ECONOMIC EVALUATION

The clinical evaluation suggested that in patients with acquired hypogammaglobulinaemia secondary to haematological malignancies, relative to no Ig, Ig has inferior safety and superior effectiveness. On this basis, a modelled cost-utility analysis was presented.

One economic analysis was presented across the acquired hypogammaglobulinaemia indications. This is consistent with contemporary clinical and economic modelling studies which generally included patients with mixed haematological malignancies. As the purpose of Ig in acquired hypogammaglobulinaemia is to reduce the risk of infection and as the treatment effect of Ig was observed to be consistent across indications with respect to this outcome, this is considered to be a reasonable approach. Scenario analyses have been presented determining the cost-effectiveness per indication assuming the best estimates available.

Table 6 Summary of the economic evaluation

Perspective	Australian healthcare
Comparator	No Ig
Type of economic evaluation	Cost-utility and cost-effectiveness analyses
Sources of evidence	Systematic review presented in Section B
Time horizon	10 years
Outcomes	QALYs Infections avoided
Methods used to generate results	Markov model
Health states	Infection-free Infection Bronchiectasis Bronchiectasis, with infection Bronchiectasis, with chronic *Pseudomonas aeruginosa* infection Dead
Cycle length	1 week
Discount rate	5%
Software packages used	Microsoft Excel and TreeAge Pro

Ig = immunoglobulin; QALY = quality-adjusted life year.

Key structural assumptions of the model are:

- The risk of developing an infection varies depending on whether Ig is available and as such has been informed by the clinical evidence. Subsequent transitions were predominantly

based on those reported in Windegger et al. (2019), though some were adjusted according to infection severity, and so varied by model arm.

- Once patients develop bronchiectasis, they are not able to transition back to the infection-free health state. This is consistent with a previously published economic evaluation conducted by Windegger et al. (2019).

The results of the stepped economic analysis are presented in Table 7.

Table 7 Results of the stepped economic analysis

	Inc. cost	Inc. QALYs	ICER
Step 1 – Trial-based analysis. Applies the dose (0.4 g/kg), dose frequency (q4w), infection rates, time horizon (1 year) and Ig treatment duration (1 year) as per the Chapel et al. (1994b) study. This study was chosen on the basis that, of the randomised studies, this study had the most patient years of data and used a dose that was most consistent with those recommended in the Version 3 criteria.	$22,734	–0.0035	Dominated
Step 2 – Trial-based, extrapolated analysis Applies the dose, dose frequency and infection rates from the Chapel et al. (1994b) study, with the model time horizon extrapolated to 10 years, with the development of bronchiectasis to be modelled. Ig treatment duration is based on Paxton, Hawkins & Crispin (2016) (26 months).	$66,922	0.2556	$261,789
Step 3 – Modelled economic evaluation (base case) Applies the pooled IRRs estimated in Section B.6 to the best available source of baseline infection rates in Australia (based on Paxton, Hawkins & Crispin 2016), while assuming the weighted average dose from BloodSTAR data (0.37 g/kg).	**$41,011**	**0.4109**	**$99,803**
Sensitivity analyses for the cost per gram of Ig (base case: $60.41)			
High cost of Ig, $140.18	$117,335	0.4109	$285,543
Low cost of Ig, $44.94	$26,209	0.4109	$63,782
Weighted average cost of Ig, $94.51	$73,634	0.4109	$179,195

ICER = incremental cost-effectiveness ratio; Ig = immunoglobulin; QALY = quality-adjusted life years; IRR = incidence rate ratio.

In Step 1 of the analysis the ICER of Ig is observed to be dominated, with a net reduction in QALYs resulting from the inclusion of a disutility per IVIg infusion. In Step 2, the time horizon is extrapolated to 10 years and allows for the development of bronchiectasis which leads to a substantial improvement in the ICER. Further improvements in the ICER are observed when the best estimates of baseline infection rates, Ig treatment effect and dose are included in the modelling.

In the base case analysis, the cost of Ig was the main driver of the incremental cost, with offsets related to a reduction in the number of infections and costs associated with managing chronic *P. aeruginosa* infections. Incremental QALYs were primarily accrued in the infection-free health state. As Ig was associated with fewer infections of lower severity, less time was spent in the infection health state with Ig and therefore, patients had a lower risk of progressing to subsequent health states.

Key sensitivity analyses are presented in Table 8. The model is highly sensitive to the inclusion of the bronchiectasis health states. When these health states are excluded, the ICER significantly increases to $3 million per additional QALY gained. This result is consistent with that observed in Weeks, Tierney & Weinstein (1991), which also did not model the development of bronchiectasis. The inclusion of these health states had been justified based on the model structure used in a contemporary economic evaluation (Windegger et al. 2019) and that this was most consistent with the natural history of recurrent infections (Table 5). The modelled results were also sensitive to the selection of the time horizon, the relative treatment effect of Ig and baseline rates of infection.

Table 8 Key sensitivity analyses

	Inc. cost	Inc. QALYs	ICER	% change
Base case analysis	**$41,011**	**0.4109**	**$99,803**	**-**
Baseline annual infection rates (base case: Paxton, Hawkins & Crispin 2016, serious 0.43, non-serious 1.05)				
Molica et al. (1996): serious 0.29, non-serious 1.73	$50,160	0.3819	$131,328	32%
Chapel et al. (1994): serious 0.26, non-serious 1.75	$51,346	0.3653	$140,555	41%
Sullivan et al. (1990): serious 1.79, non-serious 3.79	$48,062	0.7121	$67,493	–32%
IRR of Ig treatment effect (base case: serious, 0.15; non-serious 0.61)				
Serious infections, 0.43	$52,526	0.3139	$167,315	68%
Non-serious infections, 0.72	$46,236	0.3523	$131,233	31%
Duration of Ig treatment (base case: 2.2 years)				
5 years	$84,261	0.5430	$155,168	55%
10 years	$125,097	0.5457	$229,233	130%
Exclude development of bronchiectasis	$41,213	0.0141	$2,927,525	2833%
Time horizon (base case: 10 years)				
2.2 years (as per Ig treatment duration)	$38,869	0.0322	$1,208,343	1111%
5 years	$39,552	0.1509	$262,086	163%
Transition probabilities (base case: adjusted)				
Transitions from infection health state, unadjusted	$45,309	0.3087	$146,792	47%
Transitions from infection and bronchiectasis, unadjusted	$29,927	0.2335	$128,154	28%
Cost of hospitalisation of serious infections (base case: $12,775)				
$52,961, based on AR-DRG R01A	$19,349	0.4109	$47,088	–53%

ICER = incremental cost-effectiveness ratio; Ig = immunoglobulin; IRR = incidence rate ratio; QALY = quality-adjusted life year.

ESTIMATED EXTENT OF USE AND FINANCIAL IMPLICATIONS

A market-based approach has been used to estimate the financial implications of Ig in acquired hypogammaglobulinaemia, based on current utilisation of Ig products in patients with acquired hypogammaglobulinaemia. As data available on utilisation were only available for use under the Version 2 Criteria, the impact of transitioning to the Version 3 Criteria were not able to be captured in the analysis. There is uncertainty as to whether trends observed in the past would continue to be observed.

It is also acknowledged that rapid technological development is occurring in this therapeutic area and this may also change clinical demand and Ig use in the future. For example, demand may increase if patients using new therapies (such as monoclonal antibodies, CAR-T cell therapy and BTK inhibitors) live longer with suppressed immune systems.

The financial implications associated with funding Ig for acquired hypogammaglobulinaemia are summarised in Table 9.

Table 9 Net financial implications to government associated with Ig for acquired hypogammaglobulinaemia

	2019-20	2020-21	2021-22	2022-23	2023-24
Total cost of Ig	$98,136,389	$105,651,248	$113,166,107	$120,680,966	$128,195,825
Cost of Ig to the Commonwealth	$61,825,925	$66,560,286	$71,294,647	$76,029,008	$80,763,370
Cost of Ig to the States	$36,310,464	$39,090,962	$41,871,460	$44,651,957	$47,432,455
Cost of Ig administration to the States	$15,427,172	$16,394,813	$17,362,453	$18,330,093	$19,297,734
Total cost offsets due to a reduction in the number of infections	–$18,180,716	–$19,320,253	–$20,459,790	–$21,599,328	–$22,738,865
Offsets to the Commonwealth	–$671,936	–$714,051	–$756,167	–$798,283	–$840,399
Offsets to the States	–$17,508,780	–$18,606,202	–$19,703,623	–$20,801,045	–$21,898,466
Net cost	**$95,382,845**	**$102,725,807**	**$110,068,769**	**$117,411,732**	**$124,754,694**
Net cost to the Commonwealth	$61,153,989	$65,846,235	$70,538,480	$75,230,725	$79,922,971
Net cost to States	$34,228,856	$36,879,572	$39,530,289	$42,181,006	$44,831,723
Sensitivity analyses for the cost per gram of Ig (base case: $60.41)					
High cost of Ig $140.18	$224,969,664	$242,235,823	$259,501,981	$276,768,140	$294,034,299
Low cost of Ig, $44.94	$70,251,742	$75,670,273	$81,088,805	$86,507,336	$91,925,867
Weighted average cost of Ig, $94.51	$150,773,057	$162,357,562	$173,942,066	$185,526,570	$197,111,075

Ig = immunoglobulin.

CONSUMER IMPACT SUMMARY

Public consultation responses received during the PICO confirmation development stage were positive regarding the availability of IgG replacement therapy for patients with acquired hypogammaglobulinaemia. The benefits seen to patients were the reduced risk of infections, including life-threatening infections, normalisation of IgG levels, reduced risk of Graft Versus Host Disease (GVHD) for HSCT patients, reduced use of antibiotics, and less anxiety/stress/worry about risk of infections. Benefits to carers/family were the reduction of anxiety/stress/worry about the risk of infections. The side-effects of IgG treatment were acknowledged (phlebitis at cannula insertion site, side effects of Ig, hospital acquired infection).

Sponsor companies were also invited to provide submissions to the development of this contracted assessments and four responded with comments that have been considered in this report.

ACRONYMS AND ABBREVIATIONS

Abbreviation	Meaning
AA	aplastic anaemia (not a malignancy)
AE	adverse event
AIHW	Australian Institute of Health and Welfare
AL	acute leukaemia
ALL	acute lymphoblastic leukaemia (a type of AL)
AML	acute myeloid leukaemia (a type of AL)
ARCBS	Australian Red Cross Blood Service
ARTG	Australian Register of Therapeutic Goods
BMT	bone marrow transplant (a type of HSCT)
CI	confidence interval
CLL	chronic lymphocytic leukaemia
CML	chronic myeloid leukaemia (a type of 'other haematological malignancy')
CMV	cytomegalovirus
CVID	common variable immunodeficiency
DLBCL	diffuse large B-cell lymphoma (a type of NHL)
DVT	deep vein thrombosis
EMA	European Medicines Agency
EU	European Union
FL	follicular lymphoma (a type of NHL)
G-CSF	granulocyte colony stimulating factor (filgrastim)
GI	Gastrointestinal (tract)
GVHD	graft versus host disease
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HL	Hodgkin lymphoma (a type of 'other haematological malignancy')
HM	haematological malignancy
HR	hazard ratio
HRQoL	health-related quality of life
HSA	human serum albumin
HSCT	haemopoietic stem cell transplantation
HSV	Herpes simplex virus
HTA	health technology assessment
hypo-GG	hypogammaglobulinaemia
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
IgA	immunoglobulin A (alpha)
IgG	immunoglobulin G (gamma)
IgG-RT	IgG replacement therapy
IgM	immunoglobulin M (mu)
IRB	institutional review board (USA)
IRR	incidence rate ratio
IQR	interquartile range
IM	intramuscular
ITP	idiopathic thrombocytopenic purpura
IV	intravenous
IVIg	intravenous immunoglobulin
JMML	juvenile myelomonocytic leukaemia (a type of 'other haematological malignancy')
LLN	lower limit of normal (refers to laboratory reference range)
LRT	lower respiratory tract
MBS	Medicare Benefits Schedule
MCL	mantle cell lymphoma (a type of NHL)
MD	mean difference

Abbreviation	Meaning
MDS	myelodysplastic syndrome, also ‘pre-leukaemia’ (a type of ‘other haematological malignancy’)
MEPM	meropenem (carbapenem type antibiotic)
MM	multiple myeloma
MGUS	monoclonal gammopathy of undetermined significance (a precursor state but not a malignancy)
MSAC	Medical Services Advisory Committee
MZL	marginal zone lymphoma (a type of NHL)
NATA	National Association of Testing Authorities
NBA	National Blood Authority
NHL	non-Hodgkin lymphoma
NHMRC	National Health and Medical Research Council
NNH	number needed to harm
PAPS	primary antiphospholipid syndrome
PASC	PICO Confirmation Advisory Sub-Committee of the MSAC
PE	pulmonary embolism
PICO	Population, Intervention, Comparator, Outcome criteria
PID	primary immunodeficiency
QALY	quality adjusted life year
QoL	quality of life
RCT	randomised controlled trial
RT	replacement therapy
SC	subcutaneous
sd	standard deviation
SCIg	subcutaneous immunoglobulin
SEM	standard error of the mean
SID	secondary immunodeficiency
SLL	small lymphocytic lymphoma (similar to CLL)
S+T	sulfamethoxazole+trimethoprim
TEE	thromboembolic event
TGA	Therapeutic Goods Administration
tx	treatment
URT	upper respiratory tract
UTI	urinary tract infection
WM	Waldenström macroglobulinaemia (a type of ‘other haematological malignancy’)

SECTION A CONTEXT

This contracted assessment of human gamma immunoglobulin (IgG) for the treatment of *acquired hypogammaglobulinaemia secondary 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 public funding is sought in terms of their safety, effectiveness and cost-effectiveness, while taking into account 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. IgG in this indication is presently funded under the national blood supply arrangements but cost-effectiveness of this use has not previously been established.

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. The Department of Health has convened an Ig Review Reference Group to provide advice for evaluation of IgG funded by the National Blood Authority (NBA). The 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).

Adelaide Health Technology Assessment (AHTA) has been commissioned by the Australian Government Department of Health to conduct a systematic literature review and economic evaluation for MSAC referral application 1565. This assessment has been undertaken in order to inform MSAC's consideration of the cost-effectiveness of IgG as it currently funded for treatment of acquired hypogammaglobulinaemia secondary to haematological malignancies, or post-haemopoietic stem cell transplantation (HSCT).

The criteria for evaluation of IgG as it is currently funded for this indication in Australian clinical practice were outlined in a PICO Confirmation that was discussed at the IgG Review Reference Group (meeting of 7 February 2019) and ratified on 8th March 2019.

Appendix A provides a list of the people involved in the development of this assessment report.

A.1. ITEMS IN THE AGREED PICO CONFIRMATION

This contracted assessment addresses each of the PICO elements (that is, Population, Intervention, Comparator and Outcomes) in the ratified PICO confirmation (see summary in Table 14, Section A.9).

A.2. MEDICAL SERVICE REVIEWED

Hypogammaglobulinaemia (that is, low levels of gamma immunoglobulin, or IgG antibodies) may occur due to many different underlying conditions, both primary (due to congenital immune deficiencies) and secondary (due to conditions such as haematological malignancies). Patients with sustained low levels of gamma immunoglobulin are at high risk of recurrent and severe infections. Hypogammaglobulinaemia affects the full spectrum of IgG antibodies. It is distinct from defects in IgA or IgM levels and also different to abnormal levels of specific IgG paraproteins, each of which can be clinical signs of haematological malignancies.

Acquired hypogammaglobulinaemia in the context of MSAC application 1565 refers to a subset of patients where hypogammaglobulinaemia is due to haematological conditions. Defects in humoral immunity are due to the underlying disease (in CLL due to abnormal or malignant B cell activity) but may also be compounded by myelosuppressive chemotherapy or immunotherapy drugs used to treat the cancer. The most medically significant type of infections in these patients are respiratory, which can develop into pneumonia (Wadhwa & Morrison 2006). Repeated or severe pneumonia can lead to longer term complications such as scarring and bronchiectasis.

In Australia, patients with a clinical finding of hypogammaglobulinaemia, accompanied by risk or incidence of severe infections, must meet specifications for access to funded IgG laid out in the NBA document *Criteria for Immunoglobulin Use in Australia*[4] (*the Criteria Version 3*). *The Criteria* are periodically updated at which time eligibility criteria may be refined according to recommendations of the relevant NBA working group and subsequent approval by the Jurstictional Blood Committee.

IgG is given as replacement therapy, which may or may not be in combination with antibiotics. Antibiotic use may be prophylactic or in response to symptoms of infection. This is considered standard of care in Australia.

CURRENT FUNDING ARRANGEMENTS

IgG replacement therapy for certain haematological malignancies, has been funded since 2008 under the National Blood Arrangements as having an "Established Therapeutic Role". The indication considered in this referral to MSAC is one of several 'diagnostic groups' of conditions eligible for funded IgG treatment under the *Criteria Version 3*. The specific coverage of malignancies has been updated to reflect clinical data with each version of the NBA's Criteria.

[4] National Blood Authority, 2018. Available at https://www.blood.gov.au/igcriteria-version3

MARKETING STATUS OF IGG PRODUCTS

All IgG products that are registered on the Australian Register of Therapeutic Goods (ARTG), including the sponsor and route(s) of administration are listed in Table 10. Available strengths, ARTG numbers and text of the registered indications are in Attachment 1.

Table 10 IgG products registered on the ARTG for use in Australia

Product	Sponsor	Route of Administration	NBA Funded*?
Intragam 10	CSL Behring	IV	Yes
Privigen 10%	CSL Behring	IV	Yes
Hizentra	CSL Behring	SC	Yes
Gamunex 10%	Grifols	IV and SC	No
Flebogamma 10%	Grifols	IV	Yes
Flebogamma 5%	Grifols	IV	Yes
Intragam P	*CSL Behring*	*IV*	*Yes***
Evogam	CSL Behring	SC	No
Panzyga	Octaphama	IV	No
Hyqvia	Shire	SC	No
Intratect	Pfizer	IV	No
Intratect 5%	Pfizer	IV	No
Octagam	Octapharma	IV	No
Kiovig	Shire	IV and SC	No
Gammanorm	Octapharma	SC (and IM)	No
Cuvitru	Shire	SC	No
CSL Normal Immunoglobulin VF	*CSL Behring*	*IM*	*Out of scope*

* Indicates that Ig is currently funded for the indication sought in this application. Tendering arrangements may change products funded in the future.

**With the introduction of Intragram 10, Intragam P manufacturing ceased in 2017. Inventories of Intragam P were expected to be exhausted by between mid-March and mid-April 2017 and it is expected to be discontinued by the time this evaluation is completed. The Ig Review Reference Group has indicated it should be out of scope for this application.

IV – intravenous; SC – subcutaneous; IM – intramuscular

Source: Therapeutic Goods Administration (www.ebs.tga.gov.au), accessed January 2019

Not all these products are funded under the National Blood Supply Arrangements. Those that are funded for this indication (for application 1565) are given in Table 11, including prices per pack strength (current as of July 2019).

Table 11 Ig products funded for this indication

Product	Sponsor	Route of Admin.	Strength	NBA price
Intragam 10	CSL Behring	IV	2.5g/25mL 10g/100mL 20g/200mL	$145.57 $582.30 $1,164.59
Privigen 10%	CSL Behring	IV	5g/50mL 10g/100mL 20g/200mL 40g/400mL	$225.00 $450.00 $900.00 $1,800.00

Product	Sponsor	Route of Admin.	Strength	NBA price
Hizentra	CSL Behring	SC	1g/5mL 2g/10mL 4g/20mL 10g/50mL	$59.15 $118.31 $236.61 $591.53
Flebogamma 5%	Grifols	IV	0.5g/10mL 2.5g/50mL 5g/100mL 10g/200mL 20g/400mL	$22.50 $112.50 $225.00 $450.00 $900.00
Flebogamma 10%	Grifols	IV	5g/50mL 10g/100mL 20g/200mL	$225.00 $450.00 $900.00
Evogam	CSL Behring	SC	16% 0.8g/5mL 16%3.2g/20mL	$46.58 $186.33

IV=intravenous; SC=subcutaneous; IM=intramuscular
Source: Table 4, PICO Confirmation, updated from NBA price list July 2019

IgG products are manufactured from pooled human donor plasma, and the IgG fraction formulated to contain the desired concentration of IgG as active substance. Source plasma is normal human immunoglobulin not hyperimmune plasma. The IgG content represents a broad spectrum of human antibodies. Other immunoglobulins such as IgA, IgM and IgE may be present but are controlled as impurities.

IgG products may be administered by intravenous (IV) or subcutaneous (SC) infusion (IVIg and SCIg products respectively). IgG products for intramuscular (IM) administration are out of scope for this evaluation.

CURRENT CLINICAL PRACTICE

Provider and treatment setting

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

Assessment and processing of applications, and supply of IgG product is managed by the Australian Red Cross Blood Service under contract to the NBA. In terms of the level of information required and the opportunity for managing compliance with clinical eligibility criteria, the BloodSTAR process appears to be broadly similar to written applications for Section 100 Authority Required medicines on the Pharmaceutical Benefits Scheme.

IVIg administration requires a hospital or clinic with IV infusion facilities. For access to SCIg (in addition to requirements applicable for access to IVIg), the patient must be being treated by a

clinical specialist within a hospital based SCIg program[5], where the hospital provides access to all resources. The patient/carer must be trained in the procedure by a qualified nurse or technician to deliver SCIg in an out of hospital setting.

Management of treatment and dosing is described below. The specific criteria for patient eligibility are presented in *Section A.4 Population.*

Initial treatment

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

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

These are the specific requirements according to the *Criteria Version 3* but are subject to change in future versions which has not been taken into account in this evaluation.

Continuing treatment

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

- An increase in IgG levels (increase compared with baseline or stabilisation towards normal)
- An improvement in IgM levels (an indicator of humoral immune function)
- An improvement in IgA levels (an indicator of humoral immune function)
- An improvement in the number of acute episodes of bacterial infections followed by a sustained period with no infections in subsequent review periods

A trial cessation of IgG would be contraindicated on safety grounds (if the patient is receiving immunosuppressant medication or has neutropenia, active bronchiectasis, or suppurative lung

[5] Access to Subcutaneous Immunoglobulin

disease) or if severe hypogammaglobulinaemia persists where no significant improvement has occurred in the underlying condition. Where bronchiectasis and/or suppurative lung disease is cited as the reason for continuing IgG treatment, the diagnosis must be consistent with the guideline of the Thoracic Society of Australia and New Zealand.

Dosing

The default dose in BloodSTAR is 0.4 g/kg. The majority of documentation reviewed cites a maintenance dose for IVIg of 0.4 g/kg every four weeks, however, doses lower than 0.4g/kg may be used during titration. A maximum IgG dose of up to 1 g/kg may be given. Dosing may be divided to give two or more infusions within the month. Dosing for SCIg is 0.1 g/kg per week (based on patient's lean or ideal body weight). Modification of infusion rate and/or administration of divided doses may be required to manage infusion reactions which are relatively common with this type of product.

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

Specialists may prescribe an initial loading dose of 0.4 g/kg (on top of monthly maintenance supply) and a one-off dose of 2 g/kg is for disseminated enterovirus infection. The Ig Review Reference Group confirmed that disseminated enterovirus infection should be considered a separate indication.

Monitoring

Cessation of Ig therapy should be considered at least after each twelve months of treatment. If serum IgM and IgA levels are trending upwards and near normal, this may suggest recovery of the immune system and a trial might be considered if the patient is well. Once the patient has normal IgA and IgM levels, the IgG is also likely to be normal and a trial off therapy may be undertaken.

Monitoring of IgG trough levels enables dose adjustments as described above though no frequency is defined by *the Criteria Version* 3.

OTHER INDICATIONS

According to *the Criteria*, the indication sought is separate to a similar indication "*Secondary hypogammaglobulinaemia unrelated to Haematological malignancy or HSCT"* (including patients with low plasma IgG due to B cell depletion or immunosuppressant therapies, or underlying health conditions such as thymoma). The distinction between the terms 'acquired' versus 'secondary' hypogammaglobulinaemia is specific to these diagnostic groups in *the Criteria Version 3*. Elsewhere, and in the scientific literature 'secondary hypogammaglobulinaemia' often includes conditions covered by both indications.

Other uses of IgG such as replacement therapy in patients with primary hypogammaglobulinaemia (due to Common Variable Immune Deficiency for example) and immune-modulatory uses (such as for myasthenia gravis) are funded separately under the National Blood Supply arrangements.

A.3. PUBLIC FUNDING

IgG replacement therapy for haematological conditions is already funded by the NBA and represents the standard of care in Australia. The proposal is to continue the current funding arrangements as administered by the NBA.

A.4. POPULATION

The NBA funds IgG replacement therapy for hypogammaglobulinaemia in patients with the following haematological conditions:

- Acute leukaemia[6]
- Chronic lymphocytic leukaemia (CLL)
- Multiple myeloma (MM)
- Non-Hodgkin lymphoma (NHL)[7]
- Other haematological malignancy[8]
- Also; memory B cell deficiency secondary to HSCT

Each of these conditions carries a different baseline risk of hypogammaglobulinaemia, infections, long-term prognosis, mortality and other factors. Of the conditions encompassed by this indication, hypogammaglobulinaemia is found in 25% of patients at diagnosis and will occur in up to 85% during the disease course (Sanchez-Ramon, Dhalla & Chapel 2016). In CLL patients for example, hypogammaglobulinaemia is more pronounced with advanced disease stage and disease duration: 50% to 60% of CLL patients will die from infectious complications (Wadhwa & Morrison 2006). When hypogammaglobulinaemia does occur secondary to haematological conditions, the diagnosis and clinical management of it is common across these patients.

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[6] Includes mainly acute lymphoblastic leukaemia (ALL)(ICD-10 C91.0) and acute myeloid leukaemia (AML)(C92.0, C92.3–C92.6, C92.8, C93.0, C94.0, C94.2, C94.4–C94.5), also other acute leukaemias (various codes within C93, C94 and C95).

[7] Conditions classified as NHL are ICD-10 codes C82–C86.

[8] 'Other haematological malignancies' are according to current AIHW reporting practices, including as follows (where not falling into CLL, MM and so on): ICD-10 codes C81–C96, and also ICD-10 codes D45–D46, D47.1 and D47.3–D47.5, which cover most of the myelodysplastic and myeloproliferative cancers but excludes the precursor condition monoclonal gammopathy of undetermined significance (MGUS).

The Criteria Version 3 provides for IgG supply as follows:

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

These qualifying criteria have evolved with each version of *the Criteria* and may change in future versions. For the purposes of the literature search, the target population is considered to be patients with acquired hypogammaglobulinaemia (secondary to the above haematological conditions) accompanied by incidence or high risk of severe/recurrent infections.

The Ig Review Reference Group advised that interpretation of age-related reference ranges for serum IgG would vary between pathology laboratories but would be acceptable if undertaken in a laboratory accredited by the National Association of Testing Authorities (NATA) for this testing.

The applicant proposes that a positive recommendation by MSAC would support the application of the prevailing version of *the Criteria* for patients to gain access to IgG treatment.

The Ig Review Reference Group advised that although treatment with IgG of disseminated enterovirus infection in these patients is currently permitted by *the Criteria Version 3*, it should be excluded from this evaluation.

Some guidelines suggest IVIg doses of 0.4 g/kg every three weeks, consistent with trial evidence that studied this regimen. However, four-weekly/monthly dosing with monitoring of trough levels and upward dose adjustment targeting the lower limit of the age-related IgG reference range is the prevailing recommendation.

For a 70 kg person, this represents a minimum the dose limits represent an annual dose of between 336 g and 840 g IgG. The applicant comments that the average grams per patient is much less than the maximum. Nevertheless, the average duration of Ig therapy for acquired hypogammaglobulinaemia is unknown and treatment duration is likely to vary between specific conditions due to varying mortality rates and varying remission and recovery rates following chemotherapy. Without information regarding the median and range of values for grams per patient and range of treatment durations it is not known what a typical dose is in a given month or year.

As a summary of incident patient numbers, the table produced for the PICO Confirmation has been updated with the 2017-18 data provided for this evaluation by the NBA (Table 12). Prevalent patient numbers were not readily available. The utilisation data available from the NBA describes total treated patients judged eligible according to the NBA Criteria.

Table 12 Numbers of patients receiving funded IgG for this indication (2017-18)

Condition	Patients diagnosed (2015)*	Total NBA-funded patients (2017-18)**	Mean episodes/ patient (2017-18)	Mean dose/ episode (g)(2017-18)**
CLL	1,597	1632	10.0	0.37
MM	1,885	1458	9.1	0.37
NHL	5,031	1651	10.1	0.36
Other Haem. Malignancy	Unknown	625	7.8	0.38
Post-HSCT	Unknown	443	7.6	0.37
Acute Leukaemia	1431*	[150-200 patients]**	5.5**	0.37**

*Notes for ACIM data: 2015 year data are the most recent in the ACIM books; ALL (n=389) and AML (n=1042) were used as a proxy for AL since this is not reported in the ACIM data as a group. Prevalent patients not calculated as data ACIM data do not include surviving+new patient statistics.

**Notes for NBA data: the most recent full year NBA data are for 2017-18 and do not include AL patient numbers; part year data for 2018-19 (until December) indicate patient numbers between 35-45% of the previous year, suggesting a full year total of ~150–200 AL patients based on n=68 for the part year; episode and dose data for AL are from the 2018-19 part year.

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

A.5. COMPARATOR DETAILS

The comparator is defined in the ratified PICO Confirmation as 'No IgG access; with or without antibiotics', given that the intervention is defined as 'IgG access; with or without antibiotics'. The utilisation of antibiotics was expected to be higher in the comparator arm.

The haematology expert on the Ig Review Reference Group advised oral trimethoprim + sulfamethoxazole would be the first line antibiotic. This has a broad TGA indication and is available on the Pharmaceutical Benefits Scheme (PBS) (Table 13).

Table 13 Relevant trimethoprim + sulfamethoxazole listings on the PBS

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

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

Patients already on chemotherapy for MM or CLL would likely be offered prophylactic antibiotics, however those not receiving chemotherapy are unlikely to be offered prophylaxis. The patients may be treated with purine analogues and anti-CD20 monoclonal antibodies, both of which are associated with increased incidence of infections (Sanchez-Ramon, Dhalla & Chapel 2016). The IgG

Review Reference Group considered that around 10% of MM or CLL patients would receive antibiotic prophylaxis.

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

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

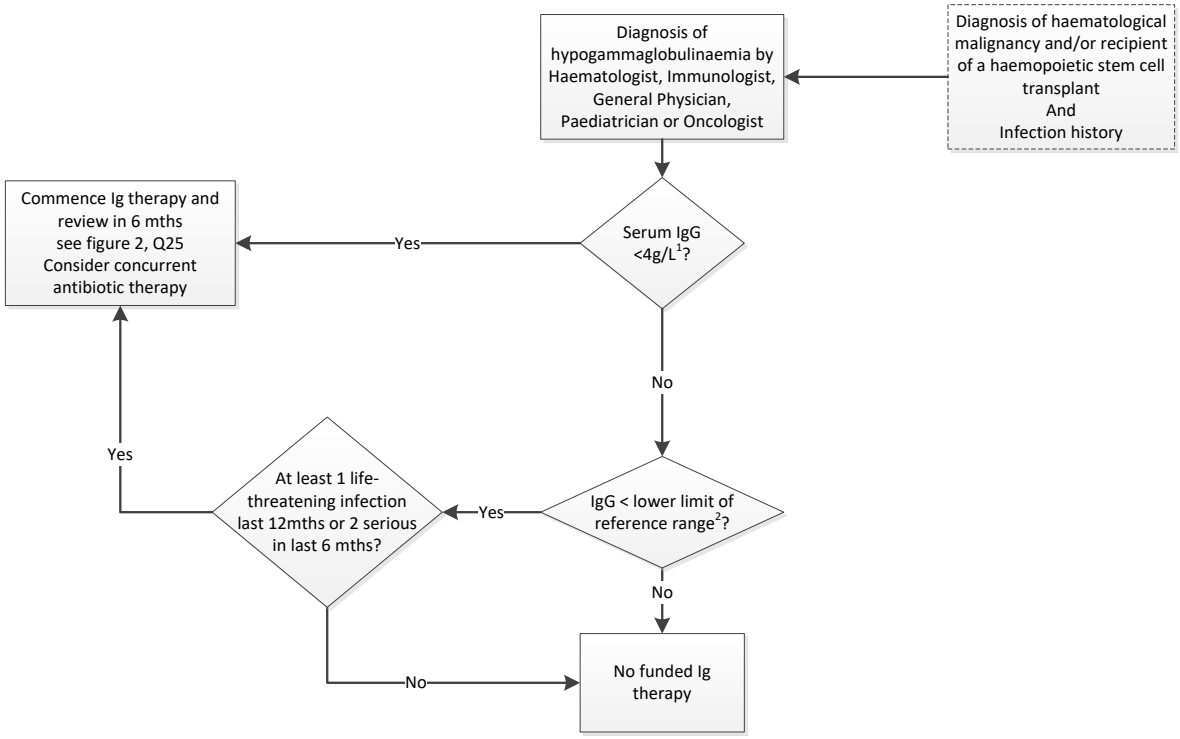
None of the studies returned by the literature search had considered antibiotics as a comparator or intervention, thus this evaluation considered the intervention 'IgG' versus the comparator 'No IgG'.

A.6. CLINICAL MANAGEMENT ALGORITHM(S)

The current treatment algorithm from the PICO Confirmation is presented in Figure 1. This algorithm represents treatment under the current NBA arrangements. As the purpose of this referral to MSAC is consider the cost-effectiveness of these arrangements, there is no 'proposed' treatment algorithm.

Figure 1 Treatment algorithm

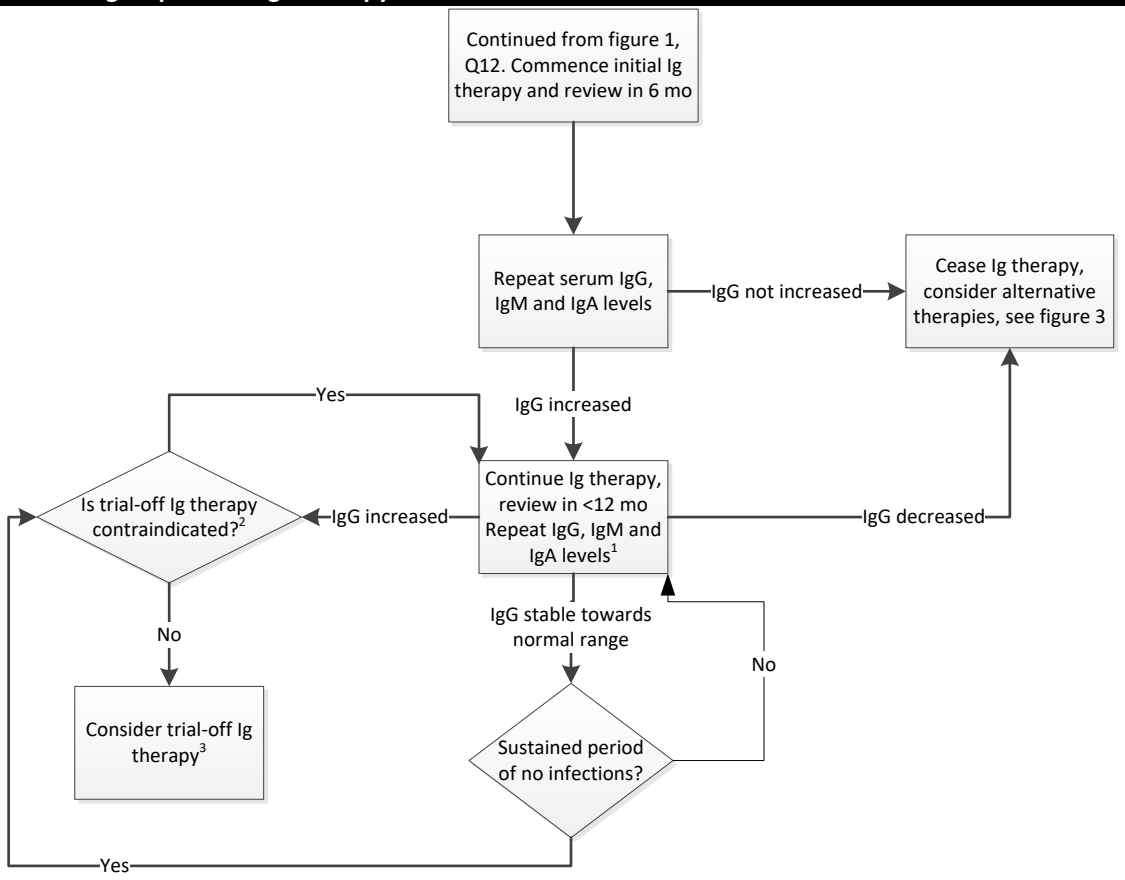
(A) Initial Access to IgG funded under the National Blood Arrangements



[1] Serum IgG levels should be measured on two separate occasions, at least one hour apart and at least one sample taken when the patient does not have an active infection.

[2] Reference range should be age related.

(B) Monitoring response to IgG therapy

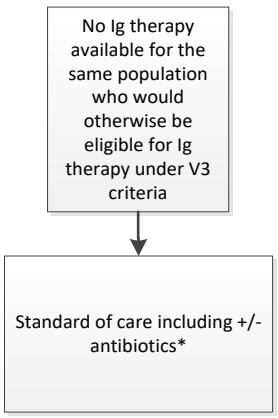


[1.] If serum IgM and IgA levels are trending upwards and near normal, IgG is also likely to be normal, this may suggest recovery of the immune system and a trial-off Ig therapy might be considered.

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

[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.

(C) Treatment pathway when IgG is not an option



A.7. KEY DIFFERENCES IN THE DELIVERY OF THE MEDICAL SERVICE AND THE MAIN COMPARATOR

This evaluation was unable to compare the intervention and comparator as defined in the PICO Confirmation due to limitations of the clinical evidence, which did not include any studies reporting the safety or efficacy of antibiotics used with IgG either as part of intervention or comparator arms.

For the purpose of this evaluation therefore, antibiotic prescribing was considered part of supportive care. This is highly variable, depending on (for example) the patient's status (inpatient/outpatient), whether the infection required hospitalisation and if not whether infections would be managed in the community (by a GP for example in a patient in remission) or by the treating specialist at an outpatient clinic. HSCT patients would most likely be inpatients until engraftment/neutropenic recovery which could be some months. These factors would not differ between intervention and comparator, though rate of antibiotic prescribing and rate of hospitalisations (or duration of the same) could be expected to be higher in the comparator/'No IgG' patients.

A.8. CLINICAL CLAIM

The clinical claim in the PICO Confirmation was 'IgG with antibiotics as required' is superior to 'no IgG with antibiotics as required' for reducing infections in patients with acquired hypogammaglobulinaemia secondary to haematological malignancies, or HSCT.

A.9. SUMMARY OF THE PICO

The summary PICO from the PICO Confirmation is presented in Table 14.

Table 14 Population, Intervention and Comparator: Acquired Hypogammaglobulinaemia due to haematological conditions

Component	Description
Patients	Patients with acquired hypogammaglobulinaemia secondary to haematological malignancies, or post-haemopoietic stem cell transplantation (HSCT).
Intervention	Replacement IgG therapy with or without antibiotics. Subgroups: intravenous administration (IVIg), subcutaneous administration (SCIg).
Comparator	No IgG replacement therapy; with or without antibiotics.
Outcomes	<u>Patient-relevant outcomes</u> Effectiveness • mortality • infections, including severe and/or recurrent infections (or infections requiring hospitalisation • antibiotic use (not including prophylaxis) • hospitalisations (all cause), including duration of hospital stay or time to discharge • Quality of Life (QoL) including anxiety • IgG trough levels Safety • serious infusion reactions (including anaphylaxis)

Component	Description
	• other serious adverse events (such as thrombotic/veno-occlusive events, renal insufficiency, haemolytic anaemia, aseptic meningitis) • venous damage • antibiotic allergy • antibiotic resistance • development of bronchiectasis/lung disease • graft versus host disease (GVHD). Healthcare system outcomes • cost, cost effectiveness • financial implications (financial impact, healthcare resource use, etc.)
Questions for evidence review	Is IgG replacement therapy (with or without antibiotics) more safe, effective and cost-effective than no IgG (with or without antibiotics)?

Several issues relevant to this PICO arose during this evaluation. Due limitations of the evidence, the intervention, comparator and some of the outcomes could not be evaluated as defined in the PICO Confirmation. This evaluation considered 'IgG' as intervention and 'No IgG' as comparator. This is discussed in Section B.4 Characteristics of the Evidence Base.

A.10. CONSUMER IMPACT STATEMENT

Public consultation responses received during the PICO confirmation development stage were positive regarding the availability of IgG replacement therapy for patients with acquired hypogammaglobulinaemia. The benefits seen to patients were the reduced risk of infections, including life-threatening infections, normalisation of IgG levels, reduced risk of Graft Versus Host Disease (GVHD) for HSCT patients, reduced use of antibiotics, and less anxiety/stress/worry about risk of infections. Benefits to carers/family were the reduction of anxiety/stress/worry about the risk of infections.

Feedback from the public consultation process raised concern about whether measurement of IgA and IgM as a requirement of the current NBA *Criteria*. Only a few studies reviewed included monitoring of IgA and IgM. Nevertheless, it was evident that these provide a useful measure of immunoglobulin recovery in hypogammaglobulinaemic patients. In comparison, measuring serum IgG may only inform the treating physician whether dosing with IgG products is adequate as replacement therapy may mask endogenous IgG recovery.

There was little evidence to support a threshold serum IgG<6g/L level, proposed by one respondent, in the absence of a documented history of infections. Most of the clinical evidence supported the approach of establishing a baseline risk of serious infections based on both medical history of recent infections and serum IgG below the lower limit of normal.

Sponsor Consultation

On 21 May 2019, sponsors of Ig were contacted and given an opportunity to provide input to the development of this contracted assessment, specifically information relevant to the utilisation, efficacy, safety and cost-effectiveness of Ig. Submissions received from four companies were provided to the contracted HTA group for consideration in the development of this report. The sponsor submission provided information and comments on:

- the PICO
- patient benefits associated with new SCIg formulations
- products that should be included/excluded from the assessment, and the interchangeability of products
- changes to the criteria for Ig access for the treatment of acquired hypogammaglobulinaemia
- estimating the prevalence of acquired hypogammaglobulinaemia, and estimating the utilisation of Ig for the treatment of acquired hypogammaglobulinaemia
- published data on effectiveness
- the public health implications associated with antibiotic use
- the likely impact of new oncology treatments on Ig demand and the impact that access changes may have on the value of immune-modulating oncology therapies.

Sponsors also provided comments on management of the Ig supply and access to SCIg, and the process for the Ig Review. Sponsors did not provide any unpublished clinical trial data that would inform the contracted assessment.

SECTION B CLINICAL EVALUATION

B.1. LITERATURE SOURCES AND SEARCH STRATEGIES

The medical literature was searched during March 2019 to identify relevant studies and systematic reviews published during the period 1990 onwards.

Searches were conducted of databases and with search terms as described in Appendix B.

B.2. RESULTS OF LITERATURE SEARCH

A PRISMA flowchart (Figure 2) shows the flow of the literature search results and application of the PICO criteria (above) in selecting the included studies (Liberati et al. 2009; Moher et al. 2009). Studies were selected independently by two reviewers. Where study relevance was in doubt, the two reviewers discussed the merits of inclusion/exclusion to agree an outcome.

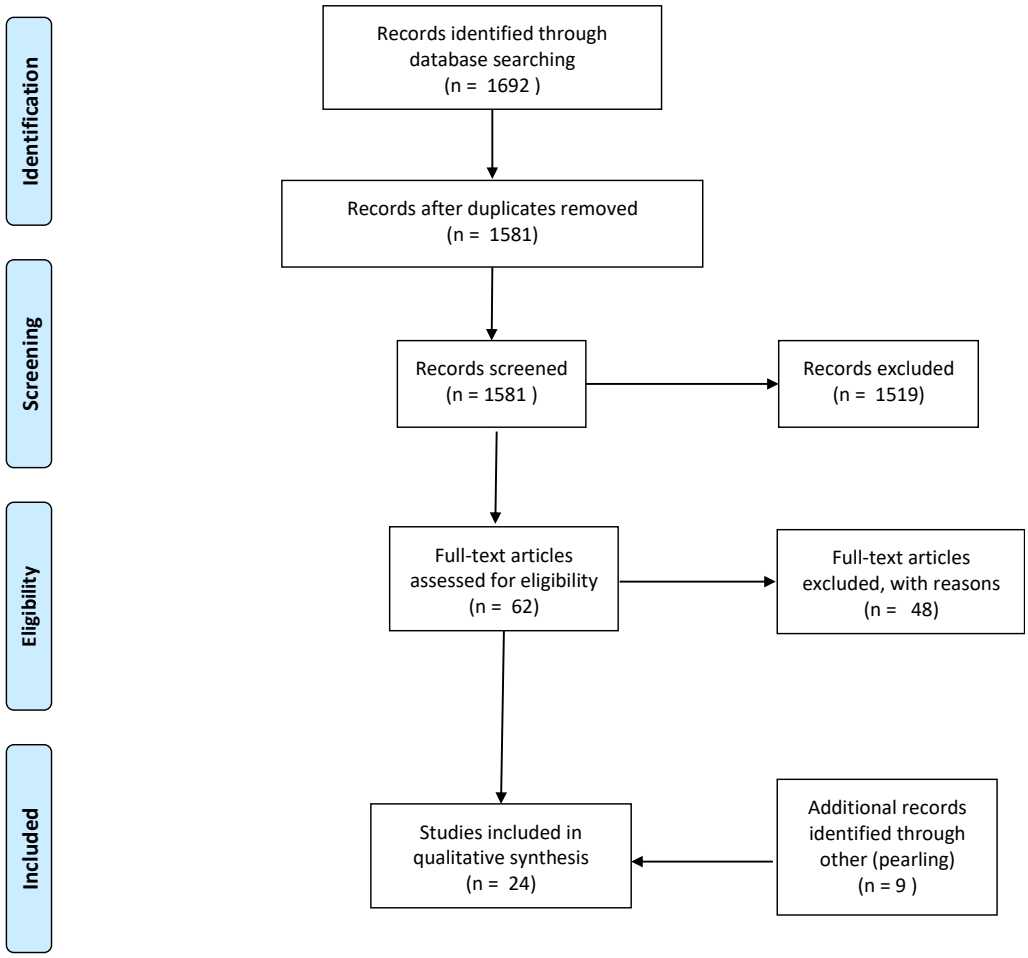


Figure 2 Summary of the process used to identify and select studies for the assessment

Studies that could not be retrieved or that met the inclusion criteria but contained insufficient or inadequate data for inclusion are listed as Excluded Studies in Appendix E. All other studies that met the inclusion criteria are listed in Appendix C.

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

APPRAISAL OF THE EVIDENCE

Appraisal of the evidence was conducted in 3 stages:

Stage 1: Appraisal of the risk of bias within individual studies included in the review.

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. A meta-analysis was undertaken for the primary efficacy outcome, infections, in spite of variability in how infections were defined and reported between the studies.

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-B.8)

B.3. RISK OF BIAS ASSESSMENT

Three of the eight included RCTs were at moderate risk of bias due to the way events were pooled for reporting (Boughton et al. 1995; Molica et al. 1996; Musto, Brugiatelli & Carotenuto 1995), and, for the former two, due to the open-label, three-stage crossover design. The other RCTs had a low risk of bias.

For the remaining non-randomised studies with direct evidence (IgG versus No IgG), two retrospective cohort studies were at high risk of bias based on the marked difference in infection risk at baseline between intervention and comparator groups due to selection bias (Blombery et al. 2011; Paxton, Hawkins & Crispin 2016). The other cohort studies and case series were generally at moderate risk of bias, with the exception of one recent case study with low risk (Benbrahim et al. 2019) and not including the four supportive studies (that is, with no direct evidence) which could not be used for a comparison of IgG with No IgG.

In addition to the individual studies, the overall body of evidence was assessed for the key outcomes using GRADE (Guyatt et al. 2011).

B.4. CHARACTERISTICS OF THE EVIDENCE BASE

An overview of the included studies is provided in Table 15. More details are in Appendix C (Table 77, full citations) and Appendix D (study profiles). Also in Appendix C is a breakdown of which of the included studies can be considered applicable to the NBA-funded conditions (Table 78).

The search strategy returned 25 articles representing 24 studies (k=24). Six of the eight included RCTs dated from the early-to-mid 1990s. There were two recent RCTs; one from 2018 investigating SCIg (which was also the only RCT in the clinical evidence that studied SCIg)(Vacca et al. 2018) and a second from 2014 investigating a carbapenem antibiotic with or without IVIg (the only study identified that explicitly studied an antibiotic with IgG)(Kobayashi et al. 2014). The recent literature is otherwise notable for the absence of eligible RCTs in this population. Four of the included studies were not applicable to any of the NBA indications due to insufficient patient numbers.

Four other comparative studies comprised one large US registry study of over 10,000 CLL and MM patients (Ammann et al. 2016) and three cohort studies (Blombery et al. 2011; Paxton, Hawkins & Crispin 2016; Van Winkle et al. 2018) the former two of which were in Australian patients.

The remainder of the evidence is case series or before/after time series.

Overall, the studies included in the report were low level evidence consisting primarily of case series with a small number of randomised studies (several of which did not adequately report the primary efficacy outcome, infections).

Four of the included studies were designed as comparative studies of different routes of IgG administration (Sundin et al. 2012; Windegger et al. 2019) or different dosing of IgG (Chapel et al. 1994a; Stump et al. 2017). These four studies were included as case series of IgG, but offered no direct comparison of IgG with No IgG and can be considered supportive.

Pearling indicated only a small number of studies published prior to 1990 that were excluded as prior to the search cut-off date, all in the more commonly studied indications, and which were considered unlikely to have changed the conclusions of this evaluation had they been included.

Many studies returned by the search evaluated patients *at risk of* hypogammaglobulinaemia, but who did not have *symptomatic hypogammaglobulinaemia*, that is, documented low IgG levels accompanied by a history of infections. This was the main reason for excluding studies that investigated IgG in patients with haematological malignancies. Studies were excluded (see reasons for exclusion in Appendix E) that presented neither the patient's infections history nor the serum IgG levels at baseline, or where it was not known what proportion of patients had these clinical features.

In some cases, baseline IgG levels showed patients in the excluded studies had normal or only moderately low IgG levels without any information regarding prior infections, or baseline data for these features was lacking altogether (see Table 83, Appendix E). This led to exclusion of a number of HSCT and paediatric studies (noting also for HSCTs that it was not clear whether the baseline serum IgG levels in HSCT recipients predicted post-transplant levels), so there is much less evidence to support use in these groups than might have been expected.

The majority of studies identified in the searches were in patients with CLL, followed by MM, NHL and HSCT. HSCT from peripheral blood was not in routine use prior to 2000 or so – in earlier studies patients received bone marrow transplants (BMT). There were few data for patients with AL other than ALL. One RCT included children with ALL and a small number of AML patients (Kobayashi et al. 2014). The most common approach was for a clinic or group of centres to recruit every patient indicated for IgG according to their institutional policy for IgG eligibility. Many studies had thus enrolled a mixed population of patients with different haematological malignancies, each at a different stages of disease course and treatment cycle. In these, patients were usually in single digits who had malignancies such as types of NHL (such as follicular lymphoma (FL) or diffuse large B-cell lymphoma (DLBCL)), AL, or other malignancies (myelodysplastic syndrome (MDS) or Hodgkin lymphoma (HL)).

A search of clinical trials showed that a protocol has been registered for a head to head study of IgG and antibiotics. An Australian multi-centre head-to-head clinical trial of IgG versus S+T[9] is underway in this population, funded by the NBA, and due to complete at the end of 2019. It is likely that this study is not powered to report a difference in efficacy between groups based on infection outcomes. The registered trial is described as a Phase II feasibility study, the primary endpoint for which is the proportion of patients remaining alive on assigned study treatment at the end of 12 months.The NBA advised that the purpose of this trial is to inform the sample size needed for a Phase III study powered to report infection as the primary outcome and adverse events of IgG compared with antibiotics in this population.

Given that infections incidence was quite variable between studies, no conclusions could be drawn regarding different approaches to dose level, frequency or duration. These aspects of the evidence have not been discussed in detail with the results in B.6. Thus, details dosing and duration for each of the studies are included in the overview of the included studies in Table 15 for reference.

[9] ACTRN12616001723471

Table 15 Key features of the included studies

Study	Type	Risk of Bias	N	Patients	Dosing	Tx duration	Outcomes	Favours IgG?
Randomised studies – IVIg vs No IVIg								
Boughton et al., 1995	RCT	RoB: moderate (SIGN)	N=42	CLL	18g total IVIg 3-weekly 12 months	12 month protocol	Infections, serious infections, tx outcome (<3 infections [success] or ≥3 infections [failure])	Yes
Chapel et al., 1991	RCT cross-over	RoB: low (SIGN)	N=12	CLL, NHL (separate numbers not given)	400 mg/kg IVIg 3-week 12 mo tx in 24 mo study	12+12 mo crossover	Incidence of infections.	Yes
Chapel et al., 1994	RCT	RoB: low (SIGN)	N=83	MM	400mg/kg IVIg 4-weekly 12 months	12 month protocol	Incidence and type of infections; adverse reactions including death; time to infection; infections in an immunised sub-set	Yes
Kobayashi et al., 2014	RCT	RoB: low (SIGN)	N=61	ALL(34); AML(12); other leukaemia(2); NHL(2); solid tumours(11)	100 mg/kg per day (max 5g/day) for 72h	72h	Tx success/failure; adverse events; infection-related death	Unclear
Molica et al., 1996	RCT cross-over	RoB: moderate (SIGN)	N=42	CLL	300mg/kg IVIg 4-weekly 6 months (+12+6 mo)	6+12+6 mo crossover	Infections (incidence, type, severity)	Yes
Musto et al., 1995	RCT cross-over	RoB: moderate (SIGN)	N=25	MM	300mg/kg IVIg 4-weekly 6 months (+12+6 mo)	6+12+6 mo crossover	Minor infections; serious infections.	Yes
Sullivan et al., 1990	RCT	RoB: low (SIGN)	N=382 (369 evaluable)	BMT	IVIg 500mg/kg weekly (d-7 to d90); then monthly to d360	12 months protocol	Acute GVHD, systemic infections, local infections, interstitial pneumonia, actuarial survival, non-relapse mortality.	Yes
Randomised studies – SCIg vs No SCIg								
Vacca et al., 2018	RCT	RoB: low (SIGN)	N=46	MM	SCIg: 0.4-0.8 g/kg/month Mean dose 80mg/kg/week	6 mo initial tx mean duration tx 18 mo (range 10–28)	Annual rate of severe infections; days of hospitalisation due to severe infections; days of treatment with antibiotics; improvement of HRQoL (SF-36). AEs were reported though not defined as an endpoint.	Yes

Study	Type	Risk of Bias	N	Patients	Dosing	Tx duration	Outcomes	Favours IgG?
Other comparative studies – IVIg vs No IVIg								
(Ammann et al. 2016)	Registry study	RoB: moderate (IHE)	N= 10,759	CLL (76%), MM (24%)	Not reported (variable). Any Ig IVIg, SCIg or IMIg.	Not reported (variable)	TEEs; NNH, mortality, hospitalisations due to infection.	No
(Blombery et al. 2011)	Cohort study	RoB: high (SIGN)	N=240	MM+HSCT (autologous)	400mg/kg IVIg single dose given to 123 of 130 patients (94.6%)	Single dose study	Infections in 30 days HSCT (days of IV antimicrobial agents, number of febrile days); survival post-ASCT	No
Paxton et al., 2016	Cohort study	RoB: high (SIGN)	N=92	CLL (42); MM (18); NHL (27); other (5)	IVIg. Dose not reported (variable).	Median 26 mo (range 3-79)	Rate of serious infections, defined as those requiring hospital admission. Hospitalisation compared before and after HSCT.	No
Van Winkle et al., 2018	Cohort study	RoB: moderate (SIGN)	N=118	ALL	IVIg 400mg/kg monthly Mean 10.5 doses (range 1-31)	Not reported (mean ~10.5 mo tx duration inferred from doses)	Infectious complications before and during maintenance tx (including episodes of infection; hospitalisations and days of hospitalisation)	No
Non-comparative studies – IVIg case series								
Besa, 1992	Case series	RoB: moderate (IHE)	N=23	CLL	400mg/kg IVIg; 3-weekly; 12 months	12 month protocol; 3 yrs maintenance reported	Lymphocyte counts; leukaemic response. Infections not reported as outcome; but as a complication/ prognostic variable	Yes
Brenner, 1996	Time series	RoB: moderate (IHE)	N=54 (n=26 SID; n=28 PID)	CLL(22), MM(4); ITP(20); PAPS(8)	400mg/kg IVIg 4-weekly ~6 months	~6 month protocol	Adverse events; infections; infections requiring hospitalisation	Yes
Günther & Dreger 2013	Case series	RoB: moderate (IHE)	N=10	CLL(5), FL(2), plasmacytoma; WM(1), MDS(1)	0.35 g/kg IVIg 3–4 weekly [no duration specified]	Median 54 mo (range 23–114)	Incidence of bacterial infections; non-bacterial infections; antibiotic/anti-infective use; adverse events including death.	Yes
Jurlander et al., 1994	Time series	RoB: moderate (SIGN)	N=15	CLL	10g total IVIg 3-weekly [No duration specified]	Median 19.5 infusions (or ~13 mo)	Serum IgG levels; infection status; antibiotic use; hospital admission for infection; febrile episodes	Yes
Non-comparative studies – SCIg case series								
Dimou et al. 2018	Before/after time series	RoB: moderate (SIGN)	N=33	CLL(25); MM(3); NHL(3); HL(1)	*0.4-0.8 g/kg/mo SCIg dose every 3-4 weeks.	12 month protocol	Incidence of infections; adverse reactions	Yes

Study	Type	Risk of Bias	N	Patients	Dosing	Tx duration	Outcomes	Favours IgG?
Any IgG (IVIg and SCIg) case series								
Benbrahim et al., 2018 (preliminary report)	Case series (prospective)	RoB: low (IHE)	N=231	MM(64), CLL(84), NHL(71), AL(6); HL(6)	385mg/k/mo IVIg 99 mg/kg/wk SCIg	Reported in Benbrahim 2019	Reported in Benbrahim 2019.	–
Benbrahim et al., 2019 (Follow-up report)	Case series (prospective)	As above.	N=160	MM(54), CLL(54), aggressive NHL(19), indolent NHL(29), HL(4)	IVIg dose 387±78mg/kg/mo 97±45mg/kg/wk SCIg (equals 388mg/kg/mo)	12 month protocol Mean exposure 8.4±4.0 mo (median 8.8 mo).	Change in serum IgG from baseline; annual incidence of infections. Also infections requiring antibiotics, requiring IV antibiotics, and requiring hospitalisation. Incidence of WHO grade >2 infections	Yes
Duraisingham et al., 2014	Case series (PID vs SID)	RoB: moderate (IHE)	N=39 SID patients, of which 15 had HM	CLL(1), MM(1), NHL(11); MDS(1); MGUS(1)	Median IgG dose 0.53g/kg (range 0.35–1.03) 4-weekly, 12 mo SID patients had IVIg (n=13, 33%) or SCIg (n=26, 67%)	12 month observation (median tx, 1 yr [range <1-9] – incl. existing patients)	Patient demographics, causes of immunodeficiency, diagnostic delay, clinical and laboratory features, infection frequency	Yes
Reiser et al., 2017	Case series	RoB: moderate (IHE)	N=307	CLL(130); MM(43); NHL(99); other(35)	Variable. Median (IQR) 4-weekly dose: IVIg (n=287); 163mg/kg (116-258) SCIg (n=20); 330mg/kg (255-420)	Duration of on-study treatment (mean, median or total months) not described.	Infection rate; serious bacterial infections; IgG trough levels; side-effects; QoL; mortality; IgG utilisation	Yes
Non-comparative studies – IVIg v SCIg case series								
Sundin et al., 2012	Case series (IVIg v SCIg cohort study design)	RoB: moderate	N=58, of which 26 had HM	HSCT	IVIg: 0.3–0.5 g/kg, every 2-4 weeks, OR SCIg: 0.1–0.2g/kg every 1-2 weeks	SCIg: Median 9 (range 6-20 months) IVIg: Median 5 months (range 3-47 months)	Rate of infections, IgG trough levels, GVHD; adverse events	Comparison not possible
Windegger et al. 2019	Before/after time series	RoB: moderate (IHE)	N=13 (N=84 for QoL survey)	Haem. malignancy (undefined)	IVIg 4 weekly: mean: 29.46g/mo followed by SCIg weekly: mean: 31.15g/mo	12 months each IVIg then SCIg crossover	Utilities associated with disease and infections	Comparison not possible

Study	Type	Risk of Bias	N	Patients	Dosing	Tx duration	Outcomes	Favours IgG?
Other (IVIg and SCIg) – dosing studies								
Chapel, Dicato et al. 1994	Case series	RoB: low	N=34	CLL	500mg/kg or 250 mg/kg	12 month protocol	Incidence of infections; adverse reactions	Comparison not possible
Stump et al., 2017	Case series	RoB: high	N=79 (209 infusions)	CLL(74); AL(65); MM(26); NHL(32); HL(7); CML(5)	Dose levels not reported. Comparison of actual vs ideal BW dosing.	30 months or 2.5 years; median doses per patient 1 (range 1-18; mean 2.6) during this period	Primary outcome was infection rate within 30 days of IVIg administration; Secondary outcomes incl. 60-day infection rate, IgG-level response (>400mg/dL), realised and potential IVIg savings.	Comparison not possible

Risk of Bias was assessed using the SIGN checklist for randomised trials (for RCTs only); the SIGN checklist for cohort studies, and the IHE checklist for case series.

*Notes: Units conversion: 100mg/dL (units used in older studies) equals 1g/L; Benbrahim et al., 2018 – 23% of all patients had received auto-HSCT, mostly MM patients (31/64 MM patients had HSCT). See study profile for definition of aggressive vs indolent NHL. Dimou et al., 2018 – the dose units quoted in the paper should be 'g/L' not 'mg/L' – Maria Dimou (pers. comm., May 2019). Günther & Dreger 2013 – the plasmacytoma case was IgA-secreting which is most likely not included in the WHO definition of MM depending on other clinical features (if solitary or extramedullary), thus is an 'other haematological malignancy'; FL is included in the WHO definition of NHL; the case of WM (described by authors as an IgM-secreting immunocytoma) is an 'other haematological malignancy'; Paxton et al., 2016 – 5 patients with 'other' malignancies were AML(1), amyloidosis(1), T-cell NHL(3); Reiser et al., 2017 – NHL total was reported as 22 NHL patients and 77 indolent lymphoma (the latter is most likely FL, a type of NHL), 'Other': HIV(7), post-transplant(7), leukaemia (not CLL)(4), HL(2), 15 other malignant and non-malignant conditions (e.g. MGUS, MDS, AA, haemolytic anaemia, COPD); Sundin et al., 2012 – underlying diagnoses were ALL(11); AML(7); JMML(3); NHL(2); MDS(3); other 1° / 2° causes of hypo-GG.

Abbreviations: AA=aplastic anaemia; AEs=adverse events; AML=acute myeloid leukaemia; BMT=bone marrow transplant; BW=body weight; CLL=chronic lymphocytic leukaemia; CML=chronic myeloid leukaemia; CMV=cytomegalovirus; COPD=chronic obstructive pulmonary disease; FL=follicular lymphoma; G-CSF=granulocyte colony stimulating factor (filgrastim); GVHD=graft versus host disease; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HM=haematological malignancy; HR=hazard ratio; HRQoL=health-related quality of life; HSCT=haematopoietic stem cell transplant; hypo-GG=hypogammaglobulinaemia; IgA=alpha immunoglobulin; IgG=gamma immunoglobulin; IgM=mu immunoglobulin; IMIg=intramuscular immunoglobulin; IQR=interquartile range; IRB=institutional review board (USA); ITP=idiopathic thrombocytopenic purpura; IVIg=intravenous immunoglobulin; JMML=juvenile myelomonocytic leukaemia; LLN=lower limit of normal (laboratory reference range); MDS=myelodysplastic syndrome; MGUS=monoclonal gammopathy of undetermined significance; MM=multiple myeloma; NHL=non-Hodgkin lymphoma; NNH=number needed to harm; PAPS=primary antiphospholipid syndrome; QoL=quality of life; RCT=randomised controlled trial; SCIg=subcutaneous immunoglobulin; sd=standard deviation; SID=secondary immunodeficiency; S+T=sulfamethoxazole+ trimethoprim; tx=treatment; TEEs= thromboembolic events; URT=upper respiratory tract; WHO=World Health Organization; WM=Waldenström macroglobulinaemia.

B.5. OUTCOME MEASURES AND ANALYSIS

Study profiles in Appendix D include details on the outcomes measured in the included studies, along with the statistical methods used to analyse the results.

The principal outcomes reported by the included studies were limited to incidence or rates of infections. Infections were assessed, defined, analysed and reported in a wide range of ways in the studies included. A large proportion of these studies also reported resource use (or infections outcomes that are relevant to resource use), for example, hospitalisations due to infection, infections requiring antibiotics, days of hospitalisation, or similar. Consideration of transplant related outcomes such as GVHD and virus reactivation was limited by the small number of eligible HSCT studies that could be included in the evaluation.

Of those studies reporting IgG use, only a subset reported safety data, often limited to systemic AEs observed in the intervention arm, but not in the comparator. AEs were also typically reported immediately following the infusion and only in a few studies were longer term outcomes such as risks considered.

Retrospective studies relied on the completeness of physician's notes and medical records for adequacy of all outcomes data.

As well as calculating infection rates per patient per month where possible, this evaluation undertook a meta-analysis of infection rates observed in the comparative studies (presented as a forest plot). This approach gave a relative risk of benefit in terms of infection with or without IgG. This provided a qualitative comparison of the included comparative studies given that each study defined and reported different types of infections and also evaluation of infections rates in each case suggests a wide variation in baseline risk of infection between studies.

B.6. RESULTS OF THE SYSTEMATIC LITERATURE REVIEW

IS IT SAFE?

Summary – Is IgG replacement therapy more safe, effective and cost-effective than no IgG?

AEs associated with IgG infusion were frequent but generally mild (low grade) and were manageable with adjustments to infusion. Moderate AEs tended to be less frequent and were manageable with dose adjustment, cessation or corticosteroids. None of the included studies reported AEs greater than Grade 3 severity, nor were there any deaths or anaphylaxis due to IgG.

Safety data were limited to reports of systemic AEs directly related to the infusion, with the exception of a registry study reporting TEE risk. Otherwise it was not feasible to consider long-term, rare or potentially unknown events. A number of the included studies reported no safety outcomes (Table 21).

The included studies did not adequately describe antibiotic use thus adverse events arising from antibiotic use could not be evaluated as specified in the PICO.

Given that the 'No IgG' comparator was typically no intervention, safety of IgG was worse than the comparator, associated with injection site effects and systemic infusion reactions. Occasionally recurrent infusion reactions lead to discontinuation of treatment. Some of the older studies employed a sham injection of solution such as albumin or saline – these were also associated with AEs, but at a lower rate than IgG.

A small number of studies compared IVIg and SCIg, which showed that SCIg is associated with different AEs (injection site reactions) but is generally more tolerable (fewer systemic infusion reactions).

IgG products have been in use in this population for some decades, thus the safety profile is well understood, even as regards rare events. In lieu of adequate safety data from the included studies, the safety data contained within approved Product Information should provide a suitably comprehensive assessment of safety for IgG products. According to core safety text for IgGs in Europe, adverse reactions due to IgG are (in decreasing frequency):

- chills, headache, dizziness, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and moderate low back pain
- reversible haemolytic reactions; especially in those patients with blood groups A, B, and AB and (rarely) haemolytic anaemia requiring transfusion
- (rarely) a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration
- (rarely) transient cutaneous reactions (including cutaneous lupus erythematosus - frequency unknown)
- (very rarely) thromboembolic reactions such as myocardial infarction, stroke, PE, DVT
- cases of reversible aseptic meningitis
- cases of increased serum creatinine level and/or occurrence of acute renal failure
- cases of Transfusion Related Acute Lung Injury (TRALI)

SYSTEMIC AND OTHER AEs INCLUDING INFUSION REACTIONS

The majority of included studies reported AEs either in the time immediately after infusion or limited to the study period. Two of the randomised studies (Chapel et al. 1991; Molica et al. 1996) reported few or no AEs. One RCT of IVIg in combination with an antibiotic reported AEs specific to the antibiotic and none associated with IVIg. Only one cohort study presented AE data (Van Winkle et al. 2018). Studies presenting no safety data are discussed further below (see Table 21).

A small number of studies monitored renal (Benbrahim et al. 2019; Chapel et al. 1994b) and liver function (Boughton et al. 1995; Brenner 1996; Sullivan et al. 1990), but each reported that there were no changes related to IgG treatment in these markers and presented few or no data.

AEs reported in the included studies were typical of infusion reactions – fever, chills, headache/pains and nausea. These events, though mild in nature, often recurred and led to discontinuation in small numbers of patients.

Systemic and other AEs – comparative studies

Comparative studies presenting systemic AEs including infusion reactions and other general AEs are summarised in Table 16 (IVIg) and Table 17 (SCIg).

Table 16 Comparative studies presenting systemic AE outcomes – IVIg vs No IVIg

Study, Indication	Outcome	Intervention	Comparator
RCTs			
Boughton et al., 1995	**AEs (N=42)**	**IVIg (n=24)**	**No IVIg (albumin) (n=18)**
CLL	• Pyrexia	11	2
	• Lethargy	3	0
	• Rigors	2	1
	• Sweating	2	0
	• Inflamed cannula	1	0
	• Hypothermia	1	0
	• Rigor	1	0
	• Headache	0	1
	Total patients with AEs	21	4
***Chapel et al., 1994**	**AEs and Discontinuations (N=83)**	**IVIg (n=42)**	**No IVIg (albumin) (n=41)**
MM	Evaluable patients	42	41
	Patients completing 12 mo study	30	31
	Withdrawals and deaths	12 (8)	10 (5)
	• recurrent infusion reactions	2	0
	• life threatening infections	0	3 (1)
	• disease progression	9 (7)	5 (3)
	• other*	1 (1)	2 (1)
	Mild AEs		
	• lethargy/malaise	14	7
	• shivers	7	6
	• headaches	6	1
	• felt cold	9	5

	• nausea/vomiting/diarrhoea • epigastric pain • drowsy • fever • blurred vision • tingling tongue • joint pain *Total mild AEs*	3 5 3 1 1 1 0 *50*	1 0 0 0 0 0 1 *21*
	Moderate AEs • Rigors and vomiting • Hypotension *Total moderate AEs*	 2 1 *3*	 1 0 *1*
	*Total AEs (% of infusions)	53 (12)	23* (5)
Kobayashi et al., 2014	**AEs (N=61; 146 episodes)**	**MEPM+IVIg (n=62 episodes)**	**MEPM alone (n=84 episodes)**
ALL, AML, others	Patients with liver dysfunction Deaths due to invasive fungal infection	2 0	4 2
Molica et al., 1996	**Withdrawals due to AEs (N=42)**	**IVIg therapy phase (N=21+21)**	**Empirical phase (N=21+21)**
CLL	Patient withdrawn due to AEs (chills, fever and back pain)	2	0
Sullivan et al., 1990	**AEs (N=369)**	**IVIg (n=184)**	**No IVIg (n=185)**
BMT	Total infusions	2226	0
	Infusions with AEs, n (%) • Chills • Fever • Headache • Pruritus • Flushing	14 (0.6%) 10 1 1 1 1	— - - - - -
Cohort studies			
Van Winkle et al., 2018	**AEs (N=118)**	**IVIg (n=36)**	**No IVIg (n=82)**
ALL	Total infusions Infusions with no AEs Patients with AEs, n/N (%) (1 Grade 3 event; none >Grade 3)(AEs were fever, nausea/ vomiting, headache or chills).	306 296 (96.8%) 10/36 (27.8%)	— n.r. n.r.

*Notes: Chapel et al., 1994 – placebo AE totals reported by the authors do not match mild and moderate AE totals. *Other patient withdrawals: IVIg - 1 cardiac amyloidosis death. Placebo - 1 unrelated cardiac death, 1 moved away. Kobayashi et al., 2014 – patient numbers not reported for the two groups, only episodes of febrile neutropenia; all instances of liver dysfunction were in patients receiving the higher 120mg/kg/day MEPM dose; liver dysfunction was Grade 2 in 5 patients and Grade 3 in 1 patient. Molica et al. 1996 – no AEs described other than representative AEs in these withdrawing patients. Sullivan et al., 1990 & Van Winkle et al., 2018 – in both studies, 'No IVIg' patients were untreated and received no placebo injection.

AEs=adverse events; ALL=acute lymphoblastic leukaemia; AML=acute myeloid leukaemia; BMT=bone marrow transplant; CLL=chronic lymphocytic leukaemia; IVIg=intravenous immunoglobulin; MEPM=meropenem; MM=multiple myeloma; mo=month.

Of the RCTS, only two reported AEs for both IgG and No IgG arms. Both investigated IVIg versus a sham injection.

One, a 1995 study in 42 CLL patients in the UK (Boughton et al. 1995) reported that AEs were mostly mild, although one patient withdrew due to a 'tolerance concern' (infusion-related pyrexia). Three patients died in the study due to disease progression. AEs were higher in the IVIg group than the placebo which was an albumin sham injection (still associated with a low rate of AEs). No serious AEs were reported.

The second study was in 83 MM patients also in the UK (Chapel et al. 1994b). The albumin placebo recipients experienced 5% AEs compared to the IVIg group who had a 12% rate of AEs. AEs were generally mild though where patients experience reactions, these tended to recur. One IVIg patient had nine reactions in 13 infusions; similarly, one placebo patient had seven reactions in 13 infusions. Moderate reactions (in two patients with IVIg and one receiving albumin placebo) were managed with dose rate adjustment and hydrocortisone. Three IVIg patients in the study withdrew due to recurrent infusion reactions (although tabulated figures suggest it was only two patients). This did not include one further IVIg patient who did not complete the first infusion, due to a moderate reaction which led to their immediate withdrawal.

Two patients in the Chapel et al study developed renal failure and were found on emergency unblinding to be in the IVIg group, resulting in the study being on clinical hold for 3 weeks. The study resumed after both cases of renal failure were considered to have been caused in one patient by light chain disease and, in the second, by septicaemia complicated by pre-existing (undetected) renal insufficiency. Serum creatinine was monitored prior to all remaining infusions (in addition to monitoring in patients with existing renal impairment), however found no change greater than 20 µmol/L during the study period (data not shown).

The remaining RCTs reported variable amounts of safety data. One investigated IgG in combination with an antibiotic (meropenem) in Japanese children who had failed first line antibiotic prophylaxis (Kobayashi et al. 2014). AEs due to IVIg were not reported. The study reported liver AEs due to meropenem use, as this was the target organ of toxicity for this antibiotic. These AEs were not representative of the safety profile or event rate from other antibiotics used in combination with IgG as each class of molecules will have its own toxicological characteristics. The authors considered the liver toxicity observed with meropenem as marginally preferable to renal toxicity observed with vancomycin, a potential alternative in this line of treatment.

An RCT of BMT recipients in the USA (Sullivan et al. 1990) recorded AEs occurred in 14 of 2226 (0.6%) IVIg infusions, noting only that 'toxicity of IVIg was minimal'.

A recent cohort study in US ALL patients (Van Winkle et al. 2018) concluded that IVIg was safe, based on no reactions in 98.6% of infusions with the remaining eight events either minor or (in one case) due to underlying causes. The authors further noted that no patients with reactions required corticosteroids or epinephrine.

Table 17 Comparative studies presenting systemic and other AE outcomes – SCIg vs No SCIg

Study, Indication	Outcome	Intervention		Comparator
Vacca et al., 2018	**Event, number of patients (%) (N=46)**	**SCIg (n=24)**	**SCIg (n=24)**	**No SCIg (n=24)**
MM	AEs	Grade 3/4	Grade 1/2	—
	• Allergic skin reaction	1 (4)	0	-
	• Oedema of the injection site	0	15 (62)	-
	• Oedema and erythema	0	8 (33)	-
	• Oedema and pain	0	5 (21)	-

	• Oedema and pruritus	0	3 (12)	-
	• Skin induration and pain	2 (8)	3 (12)	-
	Discontinuations due to AEs (%)		3 (12.5)	–

*Note: Vacca et al., 2018 – AEs only reported for SCIg and not for control group.
AEs=adverse events; MM=multiple myeloma; SCIg – subcutaneous immunoglobulin.

One RCT compared SCIg to No SCIg in the clinical evidence (Vacca et al. 2018). The authors reported that three patients (3/24 [12.5%]) with Grade 3/4 events discontinued infusions and withdrew from the SCIg arm: two due to injection site reactions; one had an extensive allergic skin reaction after the second infusion that resolved with steroids and anti-histamines. Otherwise AEs due to SCIg were mild.

Systemic and other AEs – case series

Case series presenting safety data for IgG without a comparator group are summarised in Table 18 (comparator indicated 'N/A' – these are studies that presented comparisons for efficacy outcomes based on untreated control patients or before/after data from IgG patients). Other case studies presenting AEs from two IgG intervention groups are in Table 19.

Table 18 Studies presenting systemic and other AE outcomes for IgG case series

Study, Indication	Outcome	Intervention	Comparator
Non-comparative studies – IVIg case series			
***Brenner, 1996**	**Total AEs (N=54)(SID=26; PID=28 patients)**	**IVIg (N=54)**	**N/A**
CLL(22), MM(4)	No. of infusions with AEs (%) (N=301 infusions)	41 (16%)	–
	Infusions with mild AEs	35 (65%)	-
	Infusions with moderate AEs	6 (11%)	-
	Infusions with severe AEs	0	-
	Infusions with most common AE – fever	12 (4%)	-
	Infusions with AE – chills	10 (3%)	-
	Infusions with AE – nausea	n.r. (1.5%)	-
	Infusions with AE – headache	n.r. (1.5%)	-
	Other AEs*	<0.7%	-
	Types of AEs reported	66	-
	AEs in CLL only (n=22 patients, 167 infusions)	29 (17%)	–
	AEs in MM only (n=4 patients, 18 infusions)	1 (6%)	–
Günther & Dreger 2013	**Adverse Events (N=10)**	**n events or n/N patients**	**N/A**
(various)*	AEs related to IVIg (n patients) (none of these were judged serious AEs)	8 (in 5/10 patients)	–
	• Patients with shivering and fever	2/5	-
	• Patients with shivering and fever, concomitant pruritus	1/5	-
	• Patients with shivering, headache and nausea	1/5	-
	• Patients with arthralgia	1/5 (on 3 occasions)	-
	Patients with SAEs due to underlying disease (splenectomy[1]; renal failure[2]; death due to disease progression[5]; death during unrelated surgery[1])	8 (in 6/10 patients)	-
Jurlander et al. 1994	**AEs (N=15 patients)**	**During study Median 14mo (range 3-20)(N=14)**	**N/A**
CLL (N=15)	Total infusions	225	-
	Total n events (%)	5 (2.2%)	-
	• Chills (in 3 patients), n (%)	4 (1.8%)	-
	• Dizziness, headache and heat sensation (single	1 (<1%)	-

Study, Indication	Outcome	Intervention	Comparator
	episode), n (%)		
	Discontinuations due to AE (n/N=15 patients)	1/15 (7%)	-
	12 months during study (median 14 mo, range 3-20) (n=14)		-
Non-comparative studies – SCIg case series			
Dimou et al. 2018	**Adverse Events, patients with event n/N (%)**	**During SCIg (N=33)**	**N/A**
CLL(25), MM(3) NHL(3), HL(1)*	Mild (grade 1) AEs (low grade fever and headache after the 1st and/or 2nd infusion)	3/33 (9%)	-
	**Other AE: recurrent unilateral scrotal oedema (transient, no severity described)	1/33(3%)	-
	Discontinued SCIg due to AE	1/33 (3%)	-
	**Late AEs (not attributed to SCIg)	2/33 (6%)	-

*Notes: Brenner, 1996 – N=54 patients included CLL (22); MM (4); ITP (20) and PAPS (8). Other AEs: dizziness, weakness, back pain, excessive salivation, sleepiness, palmar erythema, itching, flushing, chest pain or pressure, mild hypotension and mild hypertension, palpitations, vomiting, cold sweats, and dry cough. Günther & Dreger 2013 – underlying disease types: CLL (5), FL (2), WM (1), IgA-plasmacytoma (1), MDS (1)]. Jurlander et al., 1994 – 1 of 15 patients discontinued after 4 infusions and is not included, thus N=14. Dimou et al., 2018 – the individual haematological malignancy totals do not add up to N=33. Scrotal oedema recurred in 1 patient after SCIg infusions (each time resolving within 24h) until timing changed to evening infusion; Discontinuation was due to rare rash, mucinosis, most likely irrelevant to SCIg; late AEs were 1 episode DVT after 1 yr of tx (patient was also receiving erythropoietin), and 1 maculopapular pruritic rash on abdomen + buttocks 3 days after 6th infusion.

AEs=adverse events; CLL=chronic lymphocytic leukaemia; DVT=deep vein thrombosis; FL=follicular lymphoma; HL=Hodgkin lymphoma; ITP=idiopathic thrombocytopenic purpura; IVIg=intravenous immunoglobulin; MDS=myelodysplastic syndrome; MM=multiple myeloma; NHL=non-Hodgkin lymphoma; n.r.=not reported; PAPS=primary antiphospholipid syndrome; PID=primary immunodeficiency; SAE=serious adverse event; SCIg=sub-cutaneous immunoglobulin; SID=secondary immunodeficiency; tx=treatment; WM=Waldenström macroglobulinaemia.

A sponsor-funded study (Brenner 1996) of the efficacy and safety of an IVIg product, Octagam (Octapharma) studied 54 patients in the USA with haematological malignancies (CLL and MM) or primary immunodeficiency. The author found that AEs were similar to other IVIg products, most commonly fever and chills, and that reactions were generally mild or manageable with dose adjustment and medication.

A small sponsor-funded study in Germany of post-market experience with Alphaglobin/Flebogamma in 10 patients (Günther & Dreger 2013) reported 1.44% of infusions associated with at least one AE (8/556 infusions). None of the AEs related to the IVIg product was considered serious.

A Danish study in 15 CLL patients (Jurlander, Geisler & Hansen 1995) reported 5 AEs in 15 patients who had received 225 IgG infusions; one patient discontinued due to AEs.

A Greek study of 33 patients switching from IVIg to SCIg (Dimou et al. 2018) reported four AEs during the study period, one of which led to discontinuation. The authors noted with interest that two patients who had had moderate AEs on IVIg (headache, chills, low grade fever after every infusion) tolerated SCIg without reactions.

Table 19 Case series presenting systemic and other AE outcomes for more than one IgG group

Study, Indication	Outcome	Intervention 1	Intervention 2
Non-comparative studies – Any IgG (IVIg and SCIg) case series			
Benbrahim et al., 2019	**Tolerability of IgG-RT (N=160)**	**IVIg (n=50)**	**SCIg (n=110)**
MM(54), CLL(54 NHL(48), HL(4)	Serious AEs	0	0

Study, Indication	Outcome	Intervention 1	Intervention 2
	Patients with other AEs		
	• Pneumonia*	1 (2%)	0
	• Itching/swelling/redness	0	2 (1.8%)
	• Blood pressure increase	1 (2%)	0
	• Rash	0	1 (0.9%)
	• Cold sensation/asthenia	0	1 (0.9%)
	Total patients with AEs	2 (4%)	4 (3.6%)
	Discontinuation due to tolerance concern n=1 (group not reported)	n.r.	n.r.
Reiser et al., 2017	**On-study AEs (N=307)**	**IVIg (n=287)**	**SCIg (n=20)**
CLL(130); NHL(99); MM(43); other(35)	*Total on-study AEs (all in IVIg patients)	15	—
	Serious AEs (leading to hospitalisation)	4	
	Non-serious AEs	11	
Non-comparative studies – IVIg v SCIg case series			
Sundin et al., 2012	**Side effects (N=58)**	**IVIg (N=46) N with event/N(%) *n=24 haem. malignancy***	**SCIg (N=12) N with event/N(%) *n=2 haem. malignancy***
HSCT	• Allergic reaction	6/46 (16.2%)	0
	• Headache	40/46 (54.1%)	0
	• Hypertonia	1/46 (2.7%)	0
	• Local infection/reaction	0	2/12 (16.7%)
	• Other	1/46 (2.7%)	0
	No. patients with any side effect	31/46 (67.4%)	2/12 (16.7%)
Other (IVIg and SCIg) – dosing studies			
Chapel, Dicato et al. 1994	**AEs (N=34 patients; 378 infusions)**	**High dose IVIg 500mg/kg (n=16)**	**Low dose IVIg 250 mg/kg (n=18)**
CLL	Serious AEs	0	0
	Mild AEs (chills, fever, back pain) (events only; number of patients n.r.)	2	8

*Notes: Benbrahim et al., 2019 – the finding of pneumonia was reported as an AE rather than an infection; Reiser et al., 2017 – AEs specified as: allergic reactions (2), chill (5), back pain (1), thoracic pain (1), (severe) nausea (3), pleuritis (1), dizziness (1) and mild proctitis (1). Of these, the 4 AEs leading to hospitalisation were not identified. 'Other' underlying conditions were: HIV(7), post-transplant(7), leukaemia (not CLL)(4), HL(2), 15 other malignant and non-malignant conditions (e.g. MGUS, MDS, AA, haemolytic anaemia, COPD).

AA=aplastic anaemia; AEs=adverse events; CLL=chronic lymphocytic leukaemia; COPD=chronic obstructive pulmonary disease; FL=follicular lymphoma; HIV=human immunodeficiency virus; HL=Hodgkin lymphoma; HSCT=haematopoietic stem cell transplant; IVIg=intravenous immunoglobulin; IgG-RT=immunoglobulin gamma replacement therapy; MDS=myelodysplastic syndrome; MGUS=monoclonal gammopathy of undetermined significance; MM=multiple myeloma; NHL=non-Hodgkin lymphoma; n.r.=not reported; SAE=serious adverse event; SCIg=subcutaneous immunoglobulin; WM=Waldenström macroglobulinaemia.

A sponsor-funded study in 160 French patients published this year (Benbrahim et al. 2019) compared two of the company's products, IVIg, Octagam, and SCIg, Gammanorm (both Octapharma). The authors reported that no serious AEs were observed and IgG was well-tolerated by both routes of administration.

A German registry study of 307 patients with a range of haematological malignancies only reported those AEs that were recorded in patient records (Reiser et al. 2017). Four patients experienced AEs that required hospitalisation (median follow-up was 10.8 months). The authors reported that "*In view of the low drop-out rate in the study it can be assumed that IVIG and SCIG substitution therapies were overall well tolerated*". Actual numbers of discontinuations were not reported.

One Swedish case series (Sundin et al. 2012) reported AEs for SCIg versus IVIg in 58 children who had received HSCTs. Similar to the Greek study above (Dimou et al. 2018) the authors noted that three patients with a history of headaches due to IVIg infusions found these events resolved with the switch to SCIg.

A UK study compared two doses of IgG in in 34 CLL patients (Chapel et al. 1994a). No serious AEs were observed of 378 infusions, and of ten mild AEs that occurred, eight were in low dose patients and only two in the high dose IVIg group.

THROMBOEMBOLIC EVENTS (TEEs)

A US registry study in over 10,000 patients with CLL or MM (Ammann et al. 2016) investigated the risk of both arterial and venous thromboembolic events (TEEs) associated with IgG administration during 12 months of follow-up (Table 20).

Table 20 Studies presenting TEE outcomes – Ammann et al., 2016

Study, Indication	Outcome	Results			
Ammann 2016	**Event rate differences (propensity matched data) – 12 mo of monthly IVIg**	**% 1-yr incidence (cumulative) in unexposed**	**HR, d0-30 after IgG (95% CI)**	**% Risk difference (95% CI), 1 yr tx**	**NNH (95% CI), 1 yr tx**
CLL MM	Arterial TEE (AMI or ischaemic stroke)	1.8	1.38 (0.89, 2.14)	0.7 (-0.2, 2.0)	150 (50, ∞)
	Venous TEE (DVT or PE)	1.1	1.27 (0.67, 2.41)	0.3 (-0.4, 1.5)	340 (66, ∞)
	Composite end point (arterial or venous TEE)	2.9	1.36 (0.95, 1.96)	1.0 (-0.2, 2.7)	98 (37, ∞)

Notes: Amman et al., 2016 – the study included patients receiving any of IVIg, SCIg and IMIg (proportions not reported).
AMI=acute myocardial infarction; CI=confidence interval; d=day; DVT=deep vein thrombosis; HR=hazard ratio; IVIg=intravenous immunoglobulin; NNH=number needed to harm; PE=pulmonary embolism; TEE=thromboembolic event; tx=treatment; yr=year.

Investigation of TEE risk was the primary objective of this study – risks due to TEE were considered in the context of a 30 day treatment cycle. The number needed to harm (NNH) for arterial and venous TEEs are given in Table 20 above – the composite NNH for any TEE was 98 (37, ∞), noting that patients in the studied cohort were older and with a relatively high burden of risk factors for TEEs.

The authors concluded: *"For the primary endpoint, arterial TEE, we observed a transient increased risk of TEE during the day of an IVIg infusion and the day afterward (HR 3.40; 95% CI: 1.25-9.25); this risk declined over the remainder of the 30-day treatment cycle. When considered in terms of absolute risk averaged over a 1-year treatment period, the increase in risk attributable to IVIg was estimated to be 0.7% (95% CI: -0.2 – 2.0%) compared with a baseline risk of 1.8% for the arterial TEE end point."*

The authors reported an overall increased risk of 1.0% (95% CI -0.2%, 2.7%) for a composite endpoint of arierial and venous TEE during 12 months' IgG treatment.

A recent study in Greece described above (Dimou et al. 2018) also reported one DVT 'late' adverse event after one year of SCIg in a CLL patient who was also receiving erythropoietin. DVT is more often associated with the latter product than IgG – only erythropoietin was discontinued. The

patient received 3 months of low molecular weight heparin and continued SCIg, remaining event-free 15 months after the DVT occurred. The authors concluded this could not be attributed to SCIg.

STUDIES PRESENTING NO SAFETY DATA

The studies in Table 21 only considered the effect of IgG products on infections and reported few or no safety outcomes. A number of these were retrospective studies were limited by the information contained in patients records.

Table 21 Included studies presenting no AE data

Study	Indication	N	Comments regarding on-study AEs including death
Ammann et al., 2016	Various (undefined)	N= 10,759	TEE events reported only, no systemic AEs or other IgG-related outcomes.
Benbrahim et al., 2018	MM, NHL, CLL, HL	231	Preliminary report only – see Benbrahim et al., 2019 for AEs.
Besa, 1992	CLL	23	No mention of on-study AEs or infusion tolerability.
Blombery et al., 2011	MM+HSCT	240	No mention of on-study AEs or infusion tolerability.
Chapel et al., 1991	CLL, NHL	12	Paper presents data from two studies, but only presents AEs for a similar earlier study (Gale et al., 1988). No mention of on-study AEs or infusion tolerability.
Duraisingham et al., 2014	CLL(1), MM(1), NHL(11); MDS(1); MGUS(1)	39 (SID group)	No mention of on-study AEs, infusion tolerability, deaths or discontinuations.
Musto et al., 1995	MM	25	"*No relevant adverse effect due to the infusion of IVIg was observed*". No discontinuations due to infusion were reported.
Paxton et al., 2016	CLL (42); MM (18); NHL (27); other (5)	92	No mention of on-study AEs or infusion tolerability.
Stump et al., 2017	CLL(74); AL(65); MM(26); NHL(32); HL(7); CML(5)	209 infusions (N=79 patients)	*"[O]f the 26 IVIG encounters excluded for death within 30 days [the observation period], 17 (65%) were for treatment of a pre-existing infection, and 9 (35%) were for infection prevention secondary to hypogammaglobulinemia."*
Windegger et al. 2019	(undefined HM)	N=13	*"No serious adverse events requiring hospitalization due to [IgG] were reported in our cohort."* *"No patient developed bronchiectasis or died within the 24 months [study] period."*

AE=adverse event; AL=acute leukaemia; CLL=chronic lymphocytic leukaemia; CML=chronic myeloid leukaemia; HL=Hodgkin lymphoma; HM=haematological malignancy; HSCT=haematological stem cell transplant; IVIg=intravenous immunoglobulin; MM=multiple myeloma; NHL=non-Hodgkin lymphoma

IS IT EFFECTIVE?

Summary – Is IgG replacement therapy more safe, effective and cost-effective than no IgG?

Six randomised trials reported that patients with acquired hypogammaglobulinaemia who received IVIg (k=5) or SCIg (k=1) had fewer infections than those who did not have IgG therapy. These trials were in patients whose underlying conditions were CLL (k=3), MM (k=2); and those who underwent HSCT (k=1). Those patients who were randomised to receive IgG had significantly fewer infections than those who did not receive IgG. The difference in the number of severe/serious and life-threatening infections was large (weighted IRR=0.14; 95%CI 0.05, 0.43), whereas there was less difference in mild or moderate infections (weighted IRR=0.61; 95%CI 0.51, 0.72). These data were supported by before-and-after studies, where infection rates were available for patients prior to, and receiving IgG infusions (weighted IRR=0.64; 95%CI 0.49, 0.84).

One randomised trial compared transplant-related outcomes in patients who had undergone HSCT, with or without IVIg. In those who received allografts, the rate of GVHD and interstitial pneumonia was significantly less in those who received IVIg than those who did not receive IVIg. One cohort study compared the rate of GVHD in patients who received IVIg versus those who received SCIg. The rate of acute and chronic GVHD was higher in the IVIg group, however, given the study design, selection bias may have influenced these results.

IVIg did not appear to influence overall survival in a single trial and three observational studies identified. However, in the subgroup of patients randomised to IVIg, who were over 20 years old, and had HLA-identical bone marrow transplantation, the cumulative incidence of non-relapse mortality was significantly higher in those who did not receive IVIg (46%) than those who did (30%; p=0.023).

Five observational studies reported that patients who received Ig therapy were also more likely to be hospitalised due to infections. The selection bias inherent in the study design mean that the influence of Ig on hospitalisation risk cannot be determined.

One trial randomised MM patients with hypogammaglobulinaemia to receive SCIg or no SCIg. They graphically reported that quality of life on the SF-36 was significantly higher in those receiving SCIg for the domains of general health, physical functioning, role-physical, vitality, social functioning, role-emotional and mental health. The only domain which was not significant, was pain.

Infection risk characteristics and definitions of infections for all included studies are summarised in Table 22. Policies for antibiotic use in each study are described in Table 84, Appendix F.

Table 22 Baseline risk of infection in the included studies: serum IgG and history of infections

Study Indication	Definition of hypo-GG	Hypo-GG inclusion criterion?	Infections inclusion criterion?	Baseline IgG values	IgG values during study	Prior infection history	Infections definitions
Randomised studies – IVIg vs No IVIg							
Boughton et al., 1995 CLL	Hypo-GG: serum IgG <5.5g/L Severe hypo-GG: IgG <3.0g/L (normal range: 8-18g/L)	Yes.	Yes.	Mean serum IgG±sd, g/L: IVIg: 3.5±0.7 No IVIg: 3.6±0.6	Measured 3-weekly for study duration.	(all patients had history of infections)	History of infections: ≥2 documented infections in the preceding 12 months. Life threatening infections such as septicaemias and pneumonias which required hospital admission for intravenous antibiotics, were classified as serious.
Chapel et al., 1991 CLL, NHL	serum IgG <50% of LLN (LLN defined as 6.4g/L)	Yes (OR 1 prior major infection).	Yes (OR hypo-GG)	Not reported.	Measured but not reported.	Recorded at baseline but not reported.	"Major" infections were life-threatening (septicaemia or pneumonia). "Moderate" infections required oral antibiotics and (bronchitis, otitis media, UTIs etc). "Trivial" infections required symptomatic/topical tx.
Chapel et al., 1994 MM	Not defined.	No.	No.	Patients stratified at baseline according to serum Ig >LLN/<LLN: IVIg (n=42), n/n: 10/32 Placebo (n=41), n/n: 15/26	Not reported.	Not reported.	Serious infections: major or moderate. "Major": Life-threatening infections (hospitalisation + IV antibiotics). "Moderate": 2° bacterial infections (oral antibiotics), localised herpes zoster. "Minor" infections: not necessarily requiring antibiotics.
Kobayashi et al., 2014 ALL(34); AML(12); other leukaemia(2); NHL(2); solid tumours(11)	Not defined.	No	Yes (febrile neutropenia)	Serum IgG, mg/dL, median (range): MEPM+IVIG: 673 (236–1344) MEPM: 667.5 (292–2047)	(72h duration per episode)	Patients with febrile neutropenia not responding to 1st line antibiotics.	Febrile neutropenia at entry defined (i) fever, temperature ≥37.5°C for≥1 h or a single temperature >38°C; (ii) ANC <0.5×10^9/L. Tx success: at 120h fever disappearance, clinical improvement, infecting organism eradicated, maintenance of response ≥7d after tx discontinuation. Tx failure: persistent fever/ infecting organism, required modification of antibiotic tx, new infections, infection-related death.
Molica et al., 1996 CLL	serum IgG <600mg/dL	Yes (OR history of infection).	Yes (OR hypo-GG)	IgG level mg/dL(%): <500: 16 (38) >500<650: 13 (30.9) >650: 13 (30.9)	Serum IgG tested in 25/42 patients 2-5 times during tx, but only % increases not	Previous 6-mo. History of infections in 17/42 patients (40.4%)	Infections graded as 'severe or' trivial' (latter including those not requiring antibiotics). 'Severe' divided into major (usually IV antibiotics and hospitalisation needed; e.g.

Study Indication	Definition of hypo-GG	Hypo-GG inclusion criterion?	Infections inclusion criterion?	Baseline IgG values	IgG values during study	Prior infection history	Infections definitions
					g/L values reported.		sepsis, pneumonia). 'Minor' (requiring no IV antibiotics, hospitalisation, e.g. bronchitis, otitis, lower UTIs)
Musto et al., 1995 MM	serum IgG <LLN	Yes (OR history of infection).	Yes (OR hypo-GG)	Not reported	Not reported	Infection risk prior to and during study compared in results.	Infections graded as serious or minor according to criteria in Chapel et al., 1994 (above)
Sullivan et al., 1990	Severe hypo-GG: serum IgG<4g/L IgG (5th %ile is ~6g/L)	No.	No.	Pre-BMT levels recorded but presented as a figure (no values) suggesting pre-BMT values were low but within normal range. IgG d/L only dips below 5th %ile after BMT (as indicated by levels in no IVIg group).	Measured d30, d60, d90 post-BMT, figure only no values reported. (IgG levels for 'No IVIg' group remain under 5th %ile until d90).	Not reported.	Incidence from d0-d100 or until discharge. Systemic infections culture-confirmed, as were local infections unless local site signs were adequate. Infections of URT, oral cavity or herpes simplex were not recorded. Bacteraemia: more than one positive blood culture with the same organism or positive blood culture+fever; Septicaemia: positive blood culture with hypotension, or positive blood culture with local infection both characterised by the same organism. Interstitial pneumonia based on pneumonitis with hypoxia + interstitial infiltrates on x-ray. CMV disease by viral culture or tissue evidence with clinical signs. Chest x-ray weekly until discharge.
Randomised studies – SCIg vs No SCIg							
Vacca et al., 2018 MM	Serum IgG <500mg/dL	Yes	No.	IgG g/L, mean (range): All (N=46): 3.1 (1.3–5.2) SCIg (n=24): 3.2 (1.4–5.7) No SCIg (n=22): 3.2 (1.3–5.7)	Measured monthly. Median IgG trough levels range g/L SCIg: 8.3-9.5 No SCIg: 2.4-5.2	Not reported.	How infections were diagnosed or defined was not stated. Upper and lower respiratory tract infections were not defined. Infections were described variously as major or minor; mild/not serious vs serious; and severe.
Other comparative studies – IVIg vs No IVIg							
Ammann, 2016 CLL, MM	Not stated.	No.	No.	Not reported. *The authors assume patients are hypo-GG, this seems to be based on dispensing for a 'recognised indication' (per (Orange et al.*	Not reported.	Proportion reported with pneumonia, bronchitis, sepsis, UTI, influenza, other infections for prior	History of infections: Infections in 12 months prior to IVIg (influenza, pneumonia, chronic bronchitis, sepsis/septic shock, UTI, other). Extracted per patient records for study (ICD-9-CM codes) but not reported in article.

Study Indication	Definition of hypo-GG	Hypo-GG inclusion criterion?	Infections inclusion criterion?	Baseline IgG values	IgG values during study	Prior infection history	Infections definitions
				2006) and according to FDA labelling) — not clear how/if this was assessed.		12mo.	Hospitalisation due to pneumonia and mortality during tx period compared.
Blombery et al., 2011 MM+HSCT	Combined IgG/A/M <8g/L (excluding paraprotein).	Yes.	No.	All had hypo-GG Median total Ig, g/L (range) IVIg: 3 (0–8) No IVIg: 3 (1–7)	Not available from patient records.	Not reported for majority of patients (215/240 [90%]). History of infections in 25/240 subset (10%) already receiving IVIg as part of ongoing tx.	History of infections: ≥2 previous bacterial infections (period not specified). Infection definitions were based on (Carlisle, Gucalp & Wiernik 1993), included bloodstream infection, pneumonia, urinary tract infection and gastrointestinal infection.
Paxton et al., 2016 CLL (42); MM (18); NHL (27); other (5)	Serum IgG <LLN (Severe hypo-GG serum IgG <4 g/L)	Not for IVIg group; serum IgG <LLN only inclusion for 'No IVIg'.	No.	Mean IgG g/L±sd IVIg: 2.8±1.6 No IVIg: 4.0±1.6 IgG stratification groups, n(%): <4g/L: 56 (61) ≥4g/L: 36 (39)	Not reported.	29 patients had prior history of severe infections (requiring IV antibiotics or hospitalisation);41 had <3 infections in prior 24mo.	No standard definitions. Infections prior to and during study period were per patient records.
Van Winkle et al., 2018 ALL	Policy: IVIg tx at doctor's discretion if serum IgG<LLN Lab LLN varied from 501-757mg/dL	No.	No.	24 of 31 patients tested [68%]) in the IVIg group (n=36) had hypo-GG at baseline.	IgG levels tested an average 7 times (range 2-33) per patient. Mean IgG 474 mg/dL (range 89-785); 31 of 36 IVIg patients tested.	21/36 (58%) patients in the IVIg group had a history of infections. Details compared for both IVIg and No IVIg groups.	Infections reported as bacteraemia, fungaemia and hospitalisations per physician's notes.
Non-comparative studies – IVIg case series							
Besa, 1992 CLL	Serum IgG <700mg/dL	No.	No.	Serum IgG, mean (range): 572 mg/dL (200–1720) *18/23 patients (78%) had hypo-GG.*	Trough levels tested over 150 wks but values not reported.	13/23 patients (57%) had history of infections.	Infection history (3 yr prior to IVIg) compared to infections during 3 yr IVIg tx. Infections: bacterial (sinusitis, cellulitis, pneumonia, sepsis) or viral (zoster).
Brenner, 1996 CLL, MM	serum IgG <700mg/dL	Yes (OR history of infection).	Yes (OR hypo-GG)	Not reported.	Values monitored but data not shown.	CLL: 21 patients had a history of infections. MM: not reported (only 3 evaluable patients).	History of infection: recurrent infections with at least 1 hospitalisation (period not stated). Infections reported as either those requiring hospitalisation; or as 'treated ambulatory'. Infections during study compared to prior

Study Indication	Definition of hypo-GG	Hypo-GG inclusion criterion?	Infections inclusion criterion?	Baseline IgG values	IgG values during study	Prior infection history	Infections definitions
							infections, adjusted to duration equivalent to study period.
Günther & Dreger 2013 CLL, FL and other	Secondary immune deficiency (definition not provided)	Yes	Yes (recurrent serial bacterial infections)	Not reported.	Most had normal IgG trough values (range: 600 – 1800 mg/dL)	All 10 patients had experienced severe bacterial infections within 3 months before IVIg treatment (24 infections total).	Bacterial infections (type, treatment and duration), and non-bacterial infections. No standard definitions.
Jurlander et al., 1994 CLL	Serum IgG level below lower reference limit	Yes	Yes (history of recurrent infections)	Mean: 12.5 micromoll/L	Mean: 28.5 micromol/L	In prior 168 months (total): 78 prior antibiotic prescriptions, 16 prior hospital admissions due to infections, 63 febrile episodes, 6 severe infections	Infections requiring antibiotics, admission, febrile episodes or severe (no standard definition, but included septicaemia, pneumonia and meningitis)
Non-comparative studies – SCIg case series							
Dimou et al. 2018 CLL, others	Serum Ig<LLN	Yes.	Yes (≥2 severe episodes in last 12 months)	Switching from IVIg to SCIg (n=13): Median pre-study trough level 532mg/dL (range 80-982) IVIg naïve (n=18): Median pre-study trough level 403.5 mg/dL (range 102-632)	Measured to permit tx goal trough of >600mg/dL. Values at 3,6,12,24 mo reported.	26/33 patients had a history of severe recurrent infections.	No standard definitions (infections listed in qualifying patients included LRT, URT; renal and soft tissue infections and *Herpes zoste*r reactivation).
Any IgG (IVIg and SCIg) case series							
Benbrahim et al., 2018 MM, CLL, NHL, other (AL, HL)	Serum IgG trough levels <5 g/L	No.	No.	In 195 of 231 patients tested: 134/195 (68.7%) patients had hypo-GG (serum Ig< 5g/L) 61/195 patients had Ig ≥5 g/L Of which, 59 had at least 1 infection within the previous 12 mo, 56 needed antibiotics.	Reported in Benbrahim 2019.	Mean 2.23±1.57 infections in 12 months before study.	Reported in Benbrahim 2019.
Benbrahim et al., 2019	Serum IgG trough levels <5 g/L	No.	No.	138/160 patients (86.3%) had Ig levels tested (median serum	Mean serum IgG increase of 3.4±2.4	Reported for larger group in Benbrahim	Infections were classified according to the World Health Organization (WHO) grading with

Study Indication	Definition of hypo-GG	Hypo-GG inclusion criterion?	Infections inclusion criterion?	Baseline IgG values	IgG values during study	Prior infection history	Infections definitions
MM, CLL, NHL, HL				IgG levels 4.2 g/L). 91 patients were hypo-GG (65.9%) (IgG<5g/L).	g/L from baseline to last visit. Reduction in patients with hypo-GG from 69.2% at baseline to 15.9% at last visit (p=0.14).	2018.	severe infections being WHO grade>2.
Duraisingham et al., 2014 (NHL, others)	Serum IgG <5.5g/L (LLN), with or without low IgA or IgM.	No.	No.	Serum IgG tested for 27 of 39 SID subjects; 21 SID patients (of 26; 80.8%) and 9 'probable SID' patients (of 13; 69.2%) had hypo-GG.	12mo median IgG trough levels (SID): 9.75 g/L	In 12mo preceding IgG-RT; (01/06/12 to 31/05/13) 6 of the 15 HM patients had suffered 1 or more serious infections.	Based on patient records. 'Serious infections' defined as requiring hospitalisation and/or IV antibiotics. 'Non-serious' infections – any mild or moderate infection, with or without antibiotics.
Reiser et al., 2017 CLL(130); NHL(99); MM(43); other(35)	Not defined.	No.	No.	Median IgG level: 5.8g/L (mean 7.2±6.9 g/L).	Measured every 6 mo for 2 years	12mo infection history reported where available.	The subgroup of serious bacterial infections comprised sepsis, osteomyelitis, and pneumonia. Other serious infections comprise e.g. Herpes zoster, otitis media or urinary tract infections. 'General infections' not defined, assumed to be same as those described as 'non-serious' or 'other' infections.
Non-comparative studies – IVIg v SCIg case series							
Sundin et al. 2012 HSCT for 1° or 2° hypo-GG	Plasma IgG <4g/L	Yes, for at least 3 months post-SCT	No.	Not reported (although all patients had to be <4 g/L)	IgG trough levels measured prior to each infusion and after cessation of IgG-RT (values not reported). 64-96% reached IgG ≥4 g/L	Not reported.	Infections reported during IgG-RT (and are compared between SC and IV routes). Clinical infection defined as infectious symptoms requiring medical attention. Infections divided into bacterial, fungal, viral, and unidentified after microbiological testing.
Windegger et al. 2019 Haem. Malig. undefined	Not specified, but would have met NBA criteria from March 2013 to December 2016.	Yes	Yes	Not reported.	Mean serum IgG: IVIg phase: 7.1g/L SCIg phase: 8.4g/L	Not reported.	Number of infections (bacterial, viral and fungal), emergency department visits and hospitalisations from infection collected from medical charts and patient's general practitioner. .

Study Indication	Definition of hypo-GG	Hypo-GG inclusion criterion?	Infections inclusion criterion?	Baseline IgG values	IgG values during study	Prior infection history	Infections definitions
Other (IVIg and SCIg) – dosing studies							
Chapel & Dicato et al., 1994 CLL	Serum IgG level <LLN (IgG ≤6.4g/L)	Yes (OR history of infection)	Yes (OR hypo-GG)	High dose group: 5.1±2.9 (g/L) 11 were ≤6.4; 6 were >6.4 g/L Low dose group: 5.7±5.2 12 were ≤6.4; 6 were >6.4	Not reported.	High dose group: ≥1: 11; none: 5 Low dose group: ≥11; none: 7	Infections were classified as major (usually requiring intravenous antibiotics and hospitalisation); moderate (requiring oral antibiotic therapy) and minor (requiring no antibiotic therapy). Serious infections were both 'major' and 'moderate' combined.
Stump et al., 2017 CLL(74); AL(65); MM(26); NHL(32); HL(7); CML(5)	Serum IgG <400mg/dL	No.	No.	Pre-infusion IgG levels (within 2 weeks prior to each dose, not baseline): tested prior to 133 of 238 infusions (56%) during study; Of which, hypo-GG (<400mg/dL): 47/133 (35%); Of which, post-dose IgG values (within 2 weeks) were only taken after 14 infusions.	Pre-infusion IgG values reported per infusion.	Existing infections reported in 51.2% of patients receiving IBW doses and 33.6% of ABW doses. Note these are pre-infusion not per patient at baseline.	Infections were reported for those patients who received a full dose, were alive at the end of the 30 day observation period and not lost to follow up, based on patient records. Existing infections recorded prior to dosing but not whether the recipient was IgG tx-naïve (or if this was part of ongoing IgG replacement).

AA=aplastic anaemia; AEs=adverse events; AML=acute myeloid leukaemia; BMT=bone marrow transplant CLL=chronic lymphocytic leukaemia; CMV=cytomegalovirus; FL=follicular lymphoma; G-CSF=granulocyte colony stimulating factor (filgrastim); GVHD=graft versus host disease; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HM=haematological malignancy; HR=hazard ratio; HRQoL=health-related quality of life; HSA=human serum albumin; HSCT=haematopoietic stem cell transplant; hypo-GG=hypogammaglobulinaemia; IgA=alpha immunoglobulin; IgG=gamma immunoglobulin; IgM=mu immunoglobulin; IMIg=intramuscular immunoglobulin; IQR=interquartile range; IRB=institutional review board (USA); ITP=idiopathic thrombocytopenic purpura; IVIg=intravenous immunoglobulin; JMML=juvenile myelomonocytic leukaemia) falls into 'other'.; LLN=lower limit of normal (laboratory reference range); MDS=myelodysplastic syndrome; MM=multiple myeloma; NHL=non-Hodgkin lymphoma; NNH=number needed to harm; PAPS=primary antiphospholipid syndrome; QoL=quality of life; RCT=randomised controlled trial; SCIg=subcutaneous immunoglobulin; sd=standard deviation; SID=secondary immunodeficiency; S+T=sulfamethoxazole+ trimethoprim; tx=treatment; TEEs= thromboembolic events; URT=upper respiratory tract; WM=Waldenström macroglobulinaemia.

INFECTIONS

Infections – overview

The way in which infections were defined and reported was variable across all the included studies (see definitions in Table 22). Infections were usually grouped together either by severity or site of infection, but there was no approach common among the studies. Some studies excluded certain types of events – such as neutropenic episodes, localised infections, or infections not requiring IV antibiotics. Infections reporting also varied according to treatment setting; inpatient data were drawn from routine and relatively frequent observations by trained staff and were often supported by microbiological testing and imaging results, whereas outpatient clinics relied on patient diaries or patient recollection for event data. Nevertheless, serious/major/severe infections was either defined similarly across studies (or could be extracted for comparison), as requiring both antibiotics and hospitalisation or being systemic infections or infections of the lower respiratory tract (which would typically require IV antibiotics and hospitalisation).

Studies that provided time periods and events for both arms had the infection incidence rates calculated. The infection incidence rates between groups were then compared using the incidence rate ratios (IRR), which were plotted using Stata/IC 14.1 with the *metan* plug-in. For the meta-analyses of serious infections (both randomised trials and non-randomised studies), the pooled estimates were estimated using a Poisson regression with random intervention effects, as zero events were observed in some study arms.

Infections – randomised studies

Results from the meta-analyses of the randomised studies were presented as forest plots for serious infections (Figure 3) and for non-serious infections reported in the same studies, where available (Figure 4). These plots compared IgG versus No IgG groups. Summary data used to derive these plots are in Appendix F Table 85 (IVIg versus No IVIg) and Table 86 (SCIg versus No SCIg).

The randomised trials had the least risk of bias due to their study design, having either low risk (Chapel et al. 1991; Chapel et al. 1994b; Kobayashi et al. 2014; Sullivan et al. 1990; Vacca et al. 2018) or moderate risk (Boughton et al. 1995; Molica et al. 1996; Musto, Brugiatelli & Carotenuto 1995). Of these studies, the point estimates for major infections, serious infection and septicaemia all favoured the use of IgG (Figure 3). Outcomes including all infections or mild/less serious infections were not always reported and a relationship with IgG treatment was often less obvious.

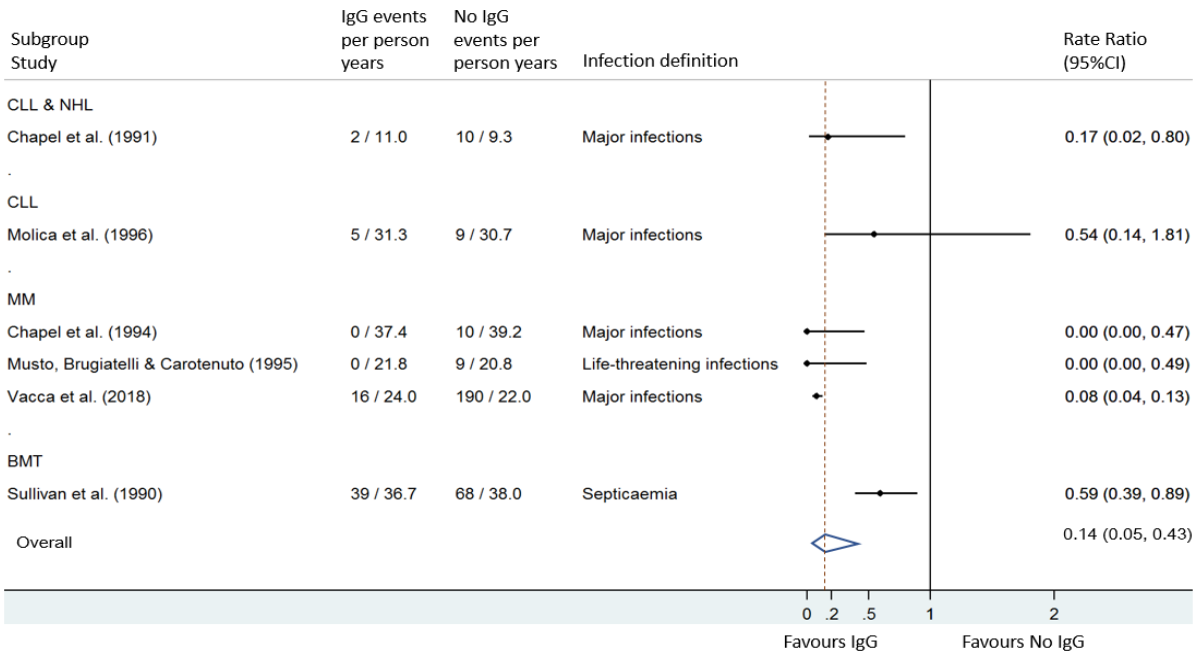


Figure 3 Randomised trials presenting serious infections – IgG vs No IgG groups

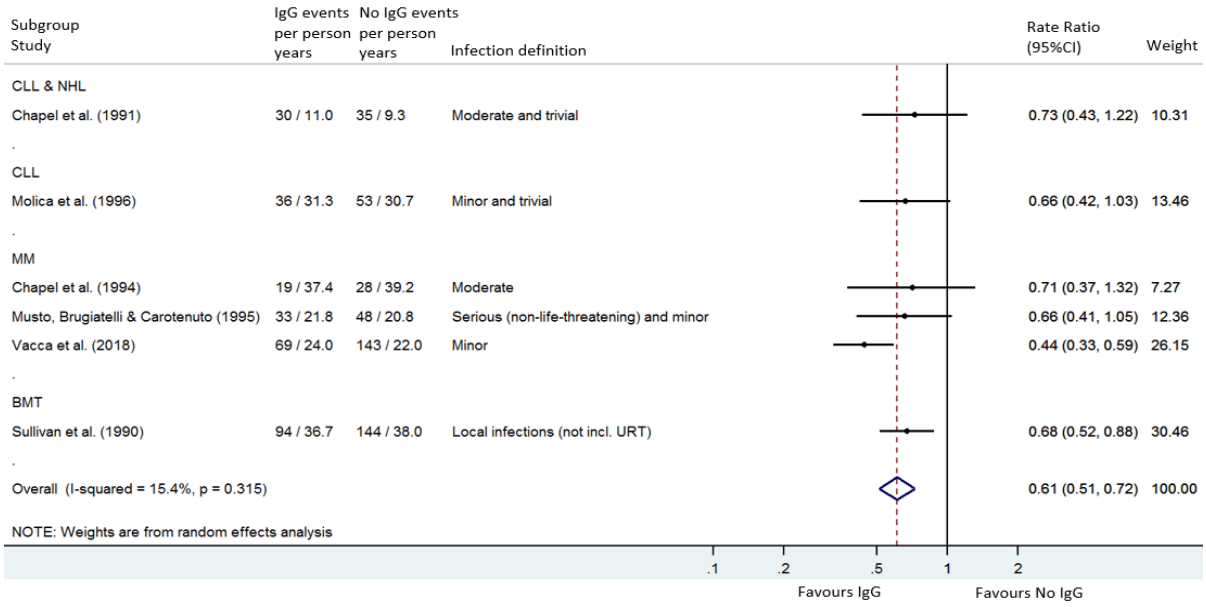


Figure 4 Randomised trials presenting other infections – IgG vs No IgG groups

Two RCTs could not be included that reported infections according to number of episodes (Kobayashi et al. 2014) or reported pooled events according to a semi-quantitative measure (Boughton et al. 1995) thus rates per patient could not be derived.

Infections – non-randomised studies

Forest plots for the non-randomised studies compared before and after IgG treatment (rather than IgG versus No IgG groups as for the RCT data). Plots are in Figure 5 for serious infections and Figure 6 for non-serious infections.

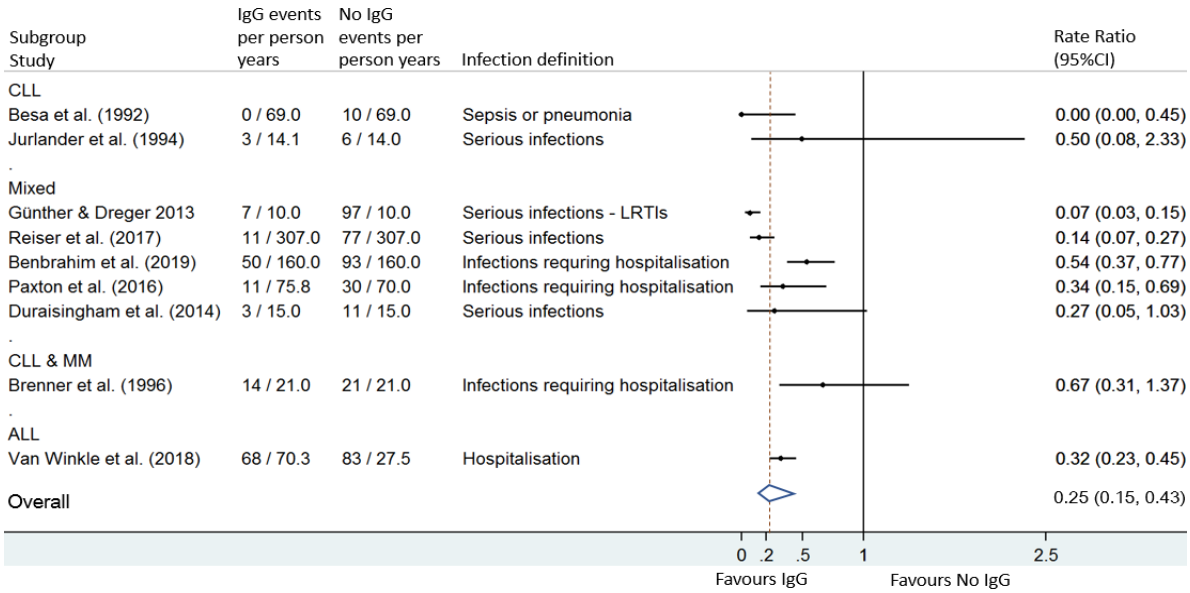


Figure 5 Non-randomised trials presenting serious infections – before and after comparison of IgG

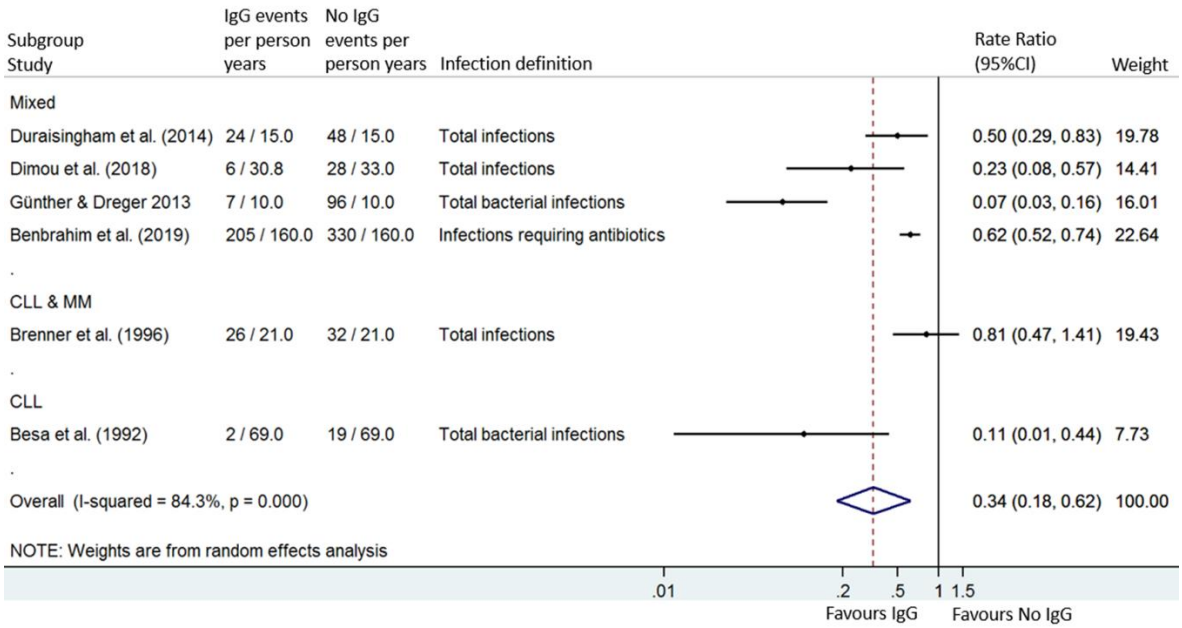


Figure 6 Non-randomised trials presenting total infections – before and after comparison of IgG

Summary data for infections from the non-randomised studies used to derive these plots are in Appendix F as follows:

- Cohort studies: Table 87 (data from a maintenance therapy sub-group (Blombery et al. 2011) in Table 88).
- Case series including before/after time series: summary infections outcomes are in Table 89 (IVIg) and Table 90 (SCIg).
- Case series of patients receiving IVIg and SCIg that reported results without differentiating between route of administration are summarised in Table 91.

Cohort studies were subject to selection bias, i.e. the patients with the highest risk of infections were most likely to receive IgG and this was evident in the difference in baseline incidence of infections (Ammann et al. 2016; Blombery et al. 2011; Paxton, Hawkins & Crispin 2016; Van Winkle et al. 2018), and hence the studies showed misleading results. Data from these studies comparing IgG to No IgG was otherwise considered of limited value. Only the Blombery and Van Winkle studies reported infections as an outcome. Resource use due to infection was reported in the Paxton study and in the US registry study of CLL and MM patients (Ammann et al. 2016). Data from these cohort studies were only included in the forest plots where before/after results were available from the IgG group.

Only patients who met certain criteria regarding infection rates were included in the pooling of results from before and after case series. Therefore, the results may be biased due to regression to the mean. Nevertheless a comparison of before and after IgG treatment was undertaken at the request of the Ig Review Reference Group. The overall / combined value for each meta-analysis has been included with each plot, noting that these values are uncertain due to the differences between the infections outcomes reported for each study.

Tabulated results for infections outcomes for all studies are presented in Appendix F supportive to the forest plots above. These are described further in the following sections according to indication.

Evidence in patients with CLL

Randomised studies – CLL

An RCT in 42 CLL patients in Italy (Molica et al. 1996) reported incidence of infections during the IVIg versus empirical treatment phases of a 24 month crossover study. Although patients were randomised into separate arms and received IVIg or observation according to a 6+12+6 months protocol, the authors pooled events for reporting into 'IVIg' or 'empirical treatment' and did not report which group they were originally randomised to nor how many patients completed the study. It was not clear whether a washout period was employed at crossover. Nevertheless, patients who were in an IVIg phase of the study experienced 35 serious infections (including 5 major) and 6 minor infections versus 51 serious infections (including 9 major) and 11 minor infections for patients in an empirical treatment phase. Ten of the IVIg phase patients remained infection free versus 22 patients

during empirical treatment (p<0.02). These results favoured IVIg, but given the crossover design, the way events were reported, and moderate risk of bias for this study, this study's conclusions should be interpreted with caution.

One randomised study in 42 CLL patients in the United Kingdom (Boughton et al. 1995) could not be included in the meta-analysis (Figure 3) as numbers of infections per group were not reported. Instead, infections were converted into a measure of treatment success (less than 3 infections) or failure (3 or more infections), although the infections threshold was not justified. The authors did not comment on the contribution of serious infections versus any infection to 'success' and 'failure' thus it was possible that a patient with three mild short-lived infections could be considered a failure whereas a patient with two severe refractory infections could be a success.

Patients defined as failures in the Boughton study were switched, either to a higher dose if already on IVIg (7 patients at 5-9 months), or from placebo to IVIg (11 patients at 9-11 months). The article did not describe to which group events were attributed after switching. The authors did however report that serious infections, for example, septicaemia and pneumonia were less frequent in IVIg recipients than placebo patients (21% versus 56%; p=0.02). Also, in the placebo group, ten patients had severe hypogammaglobulinaemia (IgG <3 g/L) and seven of these experienced 80 (65%) of the total infections recorded in the study, noting that this was one of the few studies that required both history of infections and documented hypogammaglobulinaemia in all patients at recruitment. Only four infections coincided with neutropenic episodes. The study favoured use of IVIg in CLL patients, noting it was at moderate risk of bias.

A small RCT in UK patients (N=12, mostly CLL) (Chapel et al. 1991) employed a 24 months crossover protocol which only 5 patients completed, although it did favour IgG. The article was very brief, drawing its substance from discussion of an earlier study (Gale et al. 1988) on which the design of this later study was based.

A supportive RCT that presented a dose comparison of IVIg in 34 CLL patients (Chapel et al. 1994a) reported that the infection rates in the 23 hypogammaglobulinaemic patients (IgG<6.4 g/L) (regardless of dose level) showed that those with previous infections had a slightly higher rate of any infection (0.19 infections/patient-month) than those without prior infections (0.06 infections/patient-month), though the numbers were too small for meaningful analysis.

Non-randomised studies – CLL

Two case series reported infections in relatively large numbers of CLL patients (Reiser et al. 2017)(130 CLL patients out of 307 in total) and (Benbrahim et al. 2019)(54 CLL patients out of 160). These recent studies were conducted in Germany and France, respectively. Both studies also included a mix of patients receiving IVIg and SCIg (Reiser: IVIg=287; SCIg=20; Benbrahim: IVIg n=50, SCIg n=110). The Reiser study was a retrospective analysis of German registry patients and was at

moderate risk of bias with similar selection bias issues as the cohort studies (see overview). The Benbrahim case series had a low risk of bias and was conducted prospectively.

Benbrahim et al. reported incidence of sepsis and of infections of higher than WHO Grade 2 (that is, severe or life-threatening but not including mild or moderate). Both events were reduced on initiation of IgG compared with that during the observation period prior to IgG. However, sepsis events were not included in the meta-analysis as the overall numbers were high compared to other events reported in the same study which was considered likely to be a definition issue.

A retrospective German study reported infections for 307 patients (including 130 CLL patients) receiving either IVIg or SCIg prior to and during IgG treatment (Reiser et al. 2017). Although patients with infections were only reported as a proportion for most infection outcomes, before/after IgG numbers of infection events were reported for serious bacterial infections (77 before versus 11 during 24 months of IgG treatment). A similarly proportionate reduction in outcomes associated with IgG treatment was observed for other infections where only patient proportions were reported.

Several other case series included CLL patients in only small or moderate numbers (Jurlander, Geisler & Hansen 1995)(15 CLL patients), (Besa 1992)(23), (Brenner 1996)(22) and (Dimou et al. 2018)(25). These were each studies in only/mostly CLL patients. Each of these studies showed a reduction in serious infections during IgG treatment compared with a period of observation prior to IgG commencement. In each case, 'serious infections' comprised sepsis and pneumonia (Besa 1992; Brenner 1996), LRTIs (Dimou et al. 2018) or septicaemia, meningitis and pneumonia (Jurlander, Geisler & Hansen 1995). Further details are presented in the summary tables.

Two cohort studies (Paxton, Hawkins & Crispin 2016) and (Ammann et al. 2016) reported resource use due to infectious complications in CLL patients rather than infections incidence – discussed further in the section below. For the Paxton study, this outcome (hospitalisation due to infection) was used in the forest plot in the absence of infections.

A United States dosing study in 79 patients included CLL patients (74 of 209 treatment episodes/infusions) (Stump et al. 2017) but included no control group or baseline values, thus no conclusion could be drawn in terms of infections reported compared with No IgG.

Evidence in patients with MM

A study in 83 MM patients from the UK (Chapel et al. 1994b) recorded serious bacterial infections. The majority of patients in each arm had serum IgG below the lower limit of normal (LLN) (32/42 IVIg patients and 26/41 control patients). The authors reported a lower number of serious bacterial infections in the IVIg arm than the comparator (15 vs 29 respectively; p=0.05), including no cases of septicaemia or pneumonia, compared with 10 such instances in the comparator arm. Incidence of minor infections was not reported although it was noted *"there was no protection against minor infections, which were mainly viral infections of the upper respiratory tract"*. The authors concluded

that IVIg protected against serious infections, serious bacterial infections and recurrent serious infections. The relationship between neutropenia and infections was not evaluated as only 15 patients (of 82 evaluable) had neutropenic episodes during the study.

A small Italian study in 25 MM patients (Musto, Brugiatelli & Carotenuto 1995) featured similar a 6+12+6 month crossover design and pooled reporting of infections as the Molica study in CLL patients above. The study reported 10 serious infections (without any life-threatening septicaemia or pneumonia) for patients in an IVIg phase versus 30 serious infections (including 10 life-threatening septicaemia/pneumonia infections) during observation. Minor infections were unaffected by treatment phases. The same caveats should be applied to these findings as for the Molica study in CLL patients.

One randomised trial of SCIg was included (Vacca et al. 2018), which studied 46 patients with MM. Major infections occurred overwhelmingly in the No SCIg group (190, compared with only 16 in the SCIg group). A similar pattern was observed with upper respiratory tract infections as well as lower respiratory tract infections and minor infections. Days of infections were markedly different in each arm, with 62 days (range 26-87) in SCIg patients versus 135 (88-194) in the control arm ($p<0.01$). These were consistent with results for other outcomes in the study (days of hospitalisation and antibiotics). Serum IgG levels were measured monthly during the study – median values in the SCIg arm were 8.3-9.5 g/L compared with 2.4-5.2 g/L in the control arm patients ($p<0.05$), noting that mean values at enrolment had been consistently low across both arms (3.2 g/L (range 1.4–5.7) versus 3.2 g/L (1.3–5.7), respectively) although infection history had not been required as an entry criterion.

Of the non-randomised trials, several cohort studies and case series described for CLL also included MM patients, and for whom the same observations regarding infections apply as for CLL (Ammann et al. 2016; Benbrahim et al. 2019; Paxton, Hawkins & Crispin 2016; Reiser et al. 2017; Stump et al. 2017).

Evidence in HSCT patients

Only one RCT of HSCT recipients was included, which studied 369 American patients receiving BMT (Sullivan et al. 1990). Although neither hypogammaglobulinaemia nor history of infections were required at entry, serum IgG levels for the both IVIg and control groups were monitored every 30 days during the first 90 days post-transplant – the untreated group showed that patients remained under the 5th percentile without IVIg after BMT. Infections were reported for the first 100 days post-transplant or until discharge of the 12 month protocol. Two patients in the control group received IVIg during the first 100 days after developing recurrent infections. The authors reported an increased risk of septicaemia (relative risk 2.15 ($p=0.0022$)) and local infections (relative risk 1.36

(p=0.029)) but not bacteraemia[10] in patients who received no IVIg compared with IVIg (note that infections were mostly culture confirmed). The authors also concluded that differences in infection rates were unrelated to rates of neutrophil recovery. This was the oldest study in the clinical evidence – patients were recruited between May 1986 and November 1987 and data cut-off was 1 May 1989. Since then, over 30 years have elapsed in which time numerous changes have occurred to standard of care for underlying disease, conditioning/ablation treatments, immunosupression and transplant methodology.

In terms of non-randomised evidence, one Australian cohort study (Blombery et al. 2011) investigated whether a single 'pre-emptive' peri-transplant dose was effective in reducing infections in HSCT recipients (IVIg received any time in a 30 day period peri-transplant) (Blombery et al. 2011). This single dose study was not designed to investigate ongoing replacement therapy and reporting of infections was limited to the 30 day observation period. However, the study included a patient subset who received their single dose as part of NBA-funded IgG maintenance therapy (Table 88). The multi-dose sub-group shows an increased rate of pneumonia and GI infections compared to the single-dose recipients, however the authors noted these numbers were very small and that patients qualifying for replacement therapy likely had a higher baseline risk of infection. No further analysis was presented.

In the Blombery study overall, the infections were reported in the 240 patients enrolled who had hypogammaglobulinaemia at baseline. An additional 19 patients with normal IgG levels were not included in the author's primary analysis but infections were compared in those 19 subjects with those in the No IVIg group (i.e. who had hypogammaglobulinaemia) – there was no different in infections between the two untreated groups (data not shown). This may have been due either to the single dose nature of the study or the presence of a group of patients in this population who do well in spite of their hypogammaglobulinaemia.

The Blombery authors also looked at a range of factors between the IVIg and No IVIg groups to consider whether these predisposed patients to infections (e.g. duration of neutropenia, pre-transplant serum IgG, $CD34^+$ progenitor cell dose, intensity of conditioning), but the patients' history of infections was not considered.

A supportive study comparing IVIg versus SCIg in 58 HSCT patients (including 26 with haematological malignancies) (Sundin et al. 2012) reported infections but included no control group or baseline values, thus no conclusion could be drawn for this evaluation.

[10] Bacteraemia is somewhat less serious than septicaemia, as it involves fewer or less pronounced clinical signs of infection associated with the microbiological finding, and bacteria recovered from blood would typically be fewer.

Evidence in patients with AL

One RCT of 61 children with ALL or AML in Japan explored IVIg in combination with a carpapenem antibiotic meropenem as second-line treatment of febrile neutropenia after first-line antibiotics (Kobayashi et al. 2014). Patients received meropenem with or without IVIg for 72 hours for a given infection episode – the authors reported a range of 1-9 episodes per patient. The study reported no infections data nor episodes per patient – as such this RCT was not included in the meta-analysis. Treatment outcome was reported as 'success' or 'failure' per episode based on eradication or not of febrile neutropenia symptoms measured at 120 h and then maintained for at least a week. There was a trend for patients with serum IgG <500 mg/dL to do better if they received IVIg (81.3% treatment success) than those with MEPM only (62.5% treatment success) (p=0.238). The authors contended that although the difference was not statistically significant in the low IgG patients, this was due to the sample size and that results for this subset could have been significant in a larger study. Otherwise, the authors drew no conclusions about the efficacy of IVIg being mostly concerned with the value of meropenem as an alternative to other second line antibiotics for febrile neutropenia in this setting such as vancomycin.

One cohort study (Van Winkle et al. 2018) in 118 children with ALL found no significant differences in infectious complications (as measured by bacteraemia or infections requiring antibiotics) in the IVIG versus non-IVIG groups. However, the infection rates in the IVIg arm prior to, and then during IVIg administration, shows that patients had considerably higher rates of infections before treatment than the control arm — these infections nonetheless decreased on receipt of IVIg. As neither infection rates nor firm conclusions were available from the Japanese RCT above, this is the key trial for AL.

The United States dosing study in 79 patients described above (Stump et al. 2017) included AL patients (65 of 209 treatment episodes/infusions) but included no control group or baseline values, thus no conclusion could be drawn in terms of infections reported compared with No IgG.

Evidence in patients with NHL

No RCTs were found for patients with NHL (see Table 78 Appendix F). Although one RCT appeared to include NHL patients (Chapel et al. 1991), it was very small with only 12 patients (mostly CLL) and the proportion of NHL patients, though not reported, was likely to be less than 10% at study start (based on numbers from the preceding study on which this was based, (Gale et al. 1988). As such, the three non-randomised studies that report infections for IgG versus No IgG (Benbrahim et al. 2019; Paxton, Hawkins & Crispin 2016; Reiser et al. 2017) represent the key evidence for NHL. The same observations regarding infections in these studies apply to NHL patients as already described for CLL and MM.

Evidence in patients with other haematological malignancies

No studies of any kind were found that included more than a few patients with 'other haematological malignancies' (for example, Hodgkin lymphoma (HL), amyloidosis, Waldenström macroglobulinaemia (WM), heavy chain disease, chronic myeloid leukaemia (CML), MDS and others).

RESOURCE USE OUTCOMES PRESENTED AS INFECTIOUS COMPLICATIONS

Infection-related resource use outcomes such as hospitalisation for infection or antibiotic use were informative outcomes for efficacy and were frequently presented as infectious complications. One RCT (Vacca et al. 2018) and four cohort studies (Ammann et al. 2016; Blombery et al. 2011; Paxton, Hawkins & Crispin 2016; Van Winkle et al. 2018) reported these outcomes (Table 23).

Case series reporting these outcomes are summarised in Table 24 including nine before and after time comparisons (Benbrahim et al. 2019; Brenner 1996; Duraisingham et al. 2014; Günther & Dreger 2013; Jurlander, Geisler & Hansen 1995) and one supportive study (Windegger et al. 2019).

Table 23 Studies presenting resource use – comparative studies (RCTs and cohort studies)

Study, Indication	Outcome	Intervention	Comparator	Comparison
RCTs				
Vacca et al., 2018	**Duration of resource use mean days per patient per year**	**SCIg (n=24)**	**No SCIg (n=22)**	**p-value**
MM	Hospitalisations	8	121	<0.001
	Days of antibiotic treatment	28	217	<0.001
Cohort studies				
Ammann et al., 2016	**Hospitalisation for pneumonia (1-yr cumulative incidence)**	**IgG users (n=2724)**	**Non-users (n=8035)**	
CLL, MM	Propensity matched set	15%	12%	
	Rate hospitalisations/ patient mo	*0.013*	*0.010*	
	Hospitalisation for pneumonia	IgG users (n=2771)	Non-users (n=8313)	
	Randomly matched set	15%	6%	
	Rate hospitalisations/ patient mo	*0.013*	*0.005*	
Blombery et al., 2011	**Duration of resource use median days [range]**	**IVIg (n=130)**	**No IVIg (n=110)**	**p value**
MM+HSCT	IV antimicrobial agents	7 [0–28]	6 [0–33]	p=0.046
	Hospital admission	14 [6–38]	13 [8–48]	p=0.16
Paxton et al., 2016	**Risk of hospitalisation for infection, /patient-years (95% CI)**	**IVIg (n=35)**	**No IVIg (n=57)**	**Relative risk for IVIg pts**
Various*	Prior to study	0.43 (0.29–0.63)	0.08 (0.05–0.13)	5.5 (95% CI 3.0–10)
	Inferred mean # hospitalisations	*15.1*	*4.6*	
	During study	0.14 (0.08–0.23)	(unchanged)	
	Inferred mean # hospitalisations	*4.9*	4.6	
	Rate / patient / month	*0.012*	*0.007*	
	Relative Risk of hospitalisation prior to IVIg	3.1 (1.6–5.9)	—	
	Risk of hospitalisation for infection prior to study, per patient-year (range)	IVIg (n=35)	No IVIg (n=57)	p-value
	IgG <4 g/L	0.51 (0.27–0.90)	0.07 (0. 03–0.13)	p<0.001
	Patients with IgG <4g/L	*27*	*29*	
	Inferred mean # hospitalisations	*13.8*	*2.0*	
	Rate / patient / month	*0.043*	*0.006*	
	IgG ≥4 g/L	0.40 (0.25–0.59)	0.08 (0.04–0.15)	
	Patients with IgG ≥4g/L	*8*	*28*	
	Inferred mean # hospitalisations	*3.2*	*2.2*	
	Crude rate per patient month	*0.033*	*0.007*	
	p-value	p>0.05	p>0.05	
Van Winkle et al., 2018	**Infectious complications during maintenance chemo.±IVIg,**	**IVIg (N=36)**	**No IVIg (N=82)**	**p-value**

	All values mean (SEM)			
ALL	Hospitalisations prior to study (*inferred total events)* Hospitalisations during study (*inferred total events)*	2.3 (0.4) *82.3* 1.9 (0.3) *68.4*	1.9 (0.2) *155.8* 1.7 (0.2) *139.4*	– 0.302
	Days of hospitalisation	11.1 (2.3)	6.7 (0.9)	0.112

*Notes: Ammann (2016) – The study included patients receiving IVIg, SCIg or IMIg but proportions of each were not reported. Paxton et al., 2016 – 'various' haematological malignancies were: CLL (42); MM (18); NHL (27); other (AML+allo-HSCT; amyloidosis; T-cell NHL). ALL=acute lymphoblastic leukaemia; AML=acute myeloid leukaemia; CI=confidence interval; CLL=chronic lymphocytic leukaemia; d=days; HSCT=haematopoietic stem cell transplant; IV=intravenous; IVIg=intravenous immunoglobulin; MM=multiple myeloma; NHL=non-Hodgkin lymphoma; SCIg=subcutaneous immunoglobulin; SEM=standard error of the mean; yr=year.

The one RCT reporting resource use (Vacca et al. 2018) studied patients with MM randomised to receive SCIg or No SCIg. Those in the control group received significantly more days of antibiotics (217 vs 28 days, p<0.001) than those on SCIg, and had more days of hospitalisation (121 vs 8 days, p<0.001). This large effect size was consistent with the difference between groups for other infectious complications described in the Infections outcomes above.

One further RCT, a cross-over study in 42 CLL patients, measured antibiotic use without reporting data (Molica et al. 1996). The authors noted only there was no apparent difference in the mean number of antibiotic prescriptions during the No IVIg phases of the study versus the IVIg therapy phases.

Of the cohort studies, one Australian study (Blombery et al. 2011) investigated a single peri-transplant dose in HSCT recipients, thus it was not representative of current clinical practice as it applies to use IgG within the NBA arrangements. The study found no difference in days of hospital admissions between IVIg and No IVIg groups (p=0.16) and but higher days of IV antimicrobials in IVIg patients compared to No IVIg (p=0.046). This was likely due to higher risk of infection at baseline in the IVIg group. This study is discussed further in the section above on infections, which was the main outcome reported for this study.

A second Australian cohort study (Paxton, Hawkins & Crispin 2016) was considered representative of recent clinical practice for use of IVIg in this population. Hospitalisation for infection was reported as the main outcome, rather than infections themselves. The authors of the article observed that, patients who went on to receive IVIg had a higher rate of hospitalisation for infections at baseline than those who never received IVIg, highlighting the selection bias which was a feature of essentially all the retrospective studies in the clinical evidence. Prior to IVIg, the treated patients had a relative risk of hospitalisation of 3.1 (95% CI 1.6-4.9) compared with after IVIg treatment. In contrast, prior to treatment these same patients had a relative risk of 5.5 (95% CI 3.0-10) compared with the never treated group. Thus the treated group was at higher risk of hospitalisation but this did improve with IVIg treatment, though not to the same level as the never treated patients.

When the groups in the Paxton study were divided by serum IgG levels prior to the study period, never treated patients (regardless of serum IgG levels) had broadly similar rates of hospitalisation as the rates observed in treated patients whose serum IgG was above the 4 g/L threshold. In contrast,

the patients who had serum IgG<4 g/L who also went on to receive IVIg had very high rates of hospitalisation at baseline.

Although the treated and untreated patients had essentially the same risk of hospitalisation during the study, Paxton authors did not conclude a lack of efficacy of IVIg. Instead, the authors considered these results identified a population of hypogammaglobulinaemic patients who were unlikely to develop infections and that this supported withholding IVIg unless the patient had an infection history.

One retrospective cohort study in children in the USA (Van Winkle et al. 2018) was one of the few included studies of patients with ALL. The authors reported incidence and days of hospitalisation as part of infectious complications outcomes, concluding that there was no difference between the IVIg and No IVIg groups. As with the Blombery study, this was likely due to higher risk of infection at baseline in the IVIg group. This study is discussed further in the section above on infections.

A large registry study of CLL and MM patients aimed to evaluate TEE risks associated with IgG (any route of administration) (Ammann et al. 2016). Hospitalisation for pneumonia was the only infection-related parameter reported in the study, though as a covariate rather than an outcome. For the rates of hospitalisation for pneumonia there was essentially no difference between IgG and control groups. The propensity-matched set of patients had corresponding 12 month rates of prior infections (influenza, pneumonia, bronchitis, UTIs, sepsis and others), however there were no data regarding baseline levels of serum IgG and – as with other retrospective studies – the patients that received IgG likely had a higher risk of infection prior to treatment.

Table 24 Studies presenting resource use – non-comparative studies

Study, Indication	Outcome		Comparator (prior IgG)	Intervention (after IgG)	Comparison
Case series					
Benbrahim et al., 2019	**Infectious episodes**		**Baseline Total (N=160) (IVIg n=50, SCIg n=110)**	**Last visit (N=160) (IVIg n=50, SCIg n=110)**	
MM(54), CLL(54), NHL(48), HL(4)	Patients with hypo-GG		69.2%	15.9%	p=0.14
	Incidence of infectious episodes per patient*year		**Prior to study (95% CI)**	**During follow-up (95% CI)**	**p-value**
	Infections requiring antibiotics *total events (12mo)* *rate /patient/month*		2.06 (1.82–2.33) *330* *0.172*	1.28 (0.99–1.66) *205* *0.107*	p<0.0001
	Infections requiring IV antibiotics *total events (12mo)* *rate /patient/month*		0.45 [0.36–0.57] *72* *0.034*	0.27 [0.19–0.39] *43* *0.023*	p=0.09
	Infections requiring hospitalisation *total events (12mo)* *rate /patient/month*		0.58 [0.45–0.73] *93* *0.048*	0.31 [0.22–0.44] *50* *0.026*	p=0.04
Brenner, 1996	**Infections in CLL patients (N=54)**	**Patient history**	**Equivalent to study period (no IVIg)**	**During study period (~12mo)(+IVIg)**	
CLL, MM*	Evaluable patients, N Infections requiring hospitalisation	21 32	21 21	21 14	
Duraisingham	**Prophylactic antibiotics (SID**		**Antibiotics before**	**Antibiotics during**	

et al., 2014	**group N=39; 15 of which HM)**	**IgG (1 yr)**	**IgG (1 yr)**	
Various*	SID patients, n patients (%) Patients with HM+hypo-GG, n patients with event/N patients	27 (69.2%) 12/15	23 (60.0%) 11/15	
Günther & Dreger 2013	**Infections compared before/during IVIg (N=10)**	**Prior to IVIg (3 mo) (N=10)**	**During IVIg (mean tx 51.2±25.4 mo)(N=10)**	
Various*	Courses of antibiotics	n.r.	26	
Jurlander et al., 1994	**Infection-related outcomes (N=15)**	**12 mo prior to study (N=14)**	**12 mo during study (median 14 mo, range 3-20) (n=14)**	**p-value**
CLL	Patient months	168	169	
	Hospital admissions due to infections	16	5	p=0.047
	Antibiotic prescriptions	78	54	p>0.05
[Supportive] Case series				
Windegger et al., 2019	**Infection requiring hospitalisation/total annual (N=13)**	**Initial 12 mo IVIg Mean per patient**	**Subsequent 12 mo SCIg Mean per patient**	
(undefined)	Treatment sought for infection (hospital emergency or GP) LoS per infection without bronchiectasis, mean LoS per infection with bronchiectasis, mean Rate of hospitalisation due to infection	3/24 9/15 3.75 days 0.13	1/30 8/22 2.67 days 0.03	

Notes: Brenner, 1996 studied a population (N=54) of CLL(n=22), MM(n=4) and also ITP and PAPS patients. The CLL and MM patient results are reported separately where possible. For CLL, the total numbers of infections requiring hospitalisation did not correspond with the individual contributing infections but this was not explained by the authors. No further MM data were presented due to small patient numbers. Duraisingham et al., 2014 – only data from n=39 SID patients presented; figures for n=15 haematological malignancy subset in italics extracted from raw data in supplementary spreadsheet, note this includes one patient with MGUS and excludes another with WM. Günther & Dreger 2013 – underlying disease types: CLL(5), FL(2), WM(1), IgA-plasmacytoma (1), MDS(1)]. Sundin et al., 2012 – no observation period for events was reported thus infection rate per patient month could not be derived.
CLL=chronic lymphocytic leukaemia; FL=follicular lymphoma; GP=general practitioner; IgG-RT=immunoglobulin gamma replacement therapy; IVIg=intravenous immunoglobulin; LoS = length of hospital stay; MDS=myelodysplastic syndrome; MM=multiple myeloma; mo=month; n.r.=not reported; n.s.=not statistically significant; n.r.=not reported; SAE=serious adverse event; SID=secondary immunodeficiency; tx=treatment; WM=Waldenström macroglobulinaemia.

The before/after time comparison studies tended to show an improvement in resource use as a measure of infectious complications after IgG compared with before treatment. This was true of two of the older studies in CLL patients (Brenner 1996; Jurlander, Geisler & Hansen 1995), though numbers of patients and/or number of events were relatively small.

A recent French study published in two parts (Benbrahim et al. 2018, 2019) studied 160 patients, mostly with CLL, MM and NHL. The authors showed a consistent difference in antibiotic use, IV antibiotic use and hospitalisations for infection when comparing results before (at baseline) and after IgG therapy (last visit). This was one of the few case studies judged to be at low risk of bias. Although hypogammaglobulinaemia and infection history were not inclusion criteria, mean values at baseline for serum IgG and infection history (see Table 22) suggested the majority of patients had symptomatic hypogammaglobulinaemia at entry.

For three other recent studies, no conclusion could be drawn for IgG versus No IgG:

- A UK study (Duraisingham et al. 2014) reported only antibiotic prophylaxis not in response to infections.
- A very small study of 10 patients (Günther & Dreger 2013) reported on-study numbers of antibiotic prescriptions but no pre-study values.
- A supportive study (Windegger et al. 2019) compared IVIg to SCIg in 13 Australian patients but without an untreated group or values at baseline.

SURVIVAL AND/OR MORTALITY

A total of four studies reported survival or mortality in patients who received IgG (Table 25).

Table 25 Studies presenting survival and mortality

Study, Indication	Outcome	Intervention	Comparator	Comparison
Sullivan et al., 1990	**Survival**	**IVIg (n=184)**	**No IVIg (n=185)**	**p-value**
BMT	Survivors at follow-up	66	69	
	Median duration of follow-up, yr, since randomisation	1.9	2.0	
	Actuarial survival, % after 2 years	33±4	35±4	p=0.79
	Cumulative incidence of non-relapse mortality			
	Patients <20 yo			
	Patients ≥20 yo	36%	48%	p=0.083
	• Patients ≥20 yo, who received HLA-identical BMT	30% (n=88)	46% (n=89)	p=0.023
Blombery et al., 2011	**Survival post-HSCT**	**IVIg (n=130)**	**No IVIg (n=110)**	**p-value**
MM+HSCT	Median survival post-HSCT, mo [range]	45.0 [0.3–104.7]	44.8 [0.6–118.4]	p=0.75
Ammann 2016	**All cause mortality**	**IgG users (n=2724)**	**Non-users (n=8035)**	
CLL, MM	Propensity matched set (1-yr cumulative incidence)	26%	26%	
	All cause mortality	IgG users (n=2771)	Non-users (n=8313)	
	Randomly matched set (1-yr cumulative incidence)	26%	14%	
Reiser et al., 2017	**Average follow-up – overall (N=307)**	**20.5 months**	**N/A**	
CLL(130); NHL(99); MM(43); other(35)	• CLL	21.4 months		
	• MM	21.6 months		
	• Indolent lymphoma	22.3 months		
	• Other conditions (incl. other NHL)	19.9 months		
	Mortality rate – overall	9.3%	N/A	
	• CLL	12.6%		
	• MM	14.0%		
	• Indolent lymphoma	6.5%		

	• Other conditions (incl. other NHL)	1.8%	
	Mean survival from enrolment (no differences [p=0.104] between malignancies)	23 months	N/A

Notes: Ammann (2016) – The study included patients receiving IVIg, SCIg or IMIg but proportions of each were not reported;
BMT=bone marrow transplant; CLL=chronic lymphocytic leukaemia; HLA=human leukocyte antigen; HSCT=haematopoietic stem cell transplant; IVIg=intravenous immunoglobulin; MM=multiple myeloma; mo=months; NHL=non-Hodgkin lymphoma; yr=year.

The highest level of evidence available was a single American RCT from 1990 (Sullivan et al. 1990). The authors reported that survival at two years did not significantly differ between those who received IVIg and those who did not. In subgroup analyses, they reported that there was a higher rate of non-relapse mortality in patients older than 20 years old, who received HLA-identical bone marrow transplantation, in those who received IVIg (30%) than those did not receive IVIg (48%; p=0.023). Given that these results represent patients who received treatment in the late 1980s, it is uncertain whether this remains relevant to patients receiving present day standard of care for their underlying disease.

The US registry study in over 10,000 CLL and MM patients (Ammann et al. 2016) found that after balancing the IgG and control groups for TEE risk factors, there was no difference in all-cause mortality between the two, removing the otherwise much higher rate of mortality from the IgG group in the unbalanced set (randomly matched) (noting a maximum of only 12 months follow-up). Likewise, one Australian cohort study (Blombery et al. 2011) reported no significant difference (median survival post-HSCT of approximately 45 months in both arms). A retrospective case series in Germany (Reiser et al. 2017) did not have a control group, so no comparison could be made.

Authors of several studies commented that survival analysis was not possible due to short study duration or follow-up duration (Chapel et al. 1994b; Molica et al. 1996; Vacca et al. 2018). For example, the mean survival from enrolment of 23 months reported in the Reiser study above suggests several years at a minimum would be needed for a meaningful assessment of survival associated with IgG use.

TRANSPLANT-RELATED OUTCOMES

One RCT from the US (Sullivan et al. 1990) and one supportive study from Sweden (Sundin et al. 2012) reported transplant-related outcomes in HSCT recipients.

Table 26 Transplant-related outcomes – Sullivan et al., 1990 (IVIg vs No IVIg)

Study, Indication	Outcome	Intervention	Comparator	Comparison
Sullivan et al., 1990	**Grade of acute GVHD**	**IVIg (n=184)**	**No IVIg (n=185)**	**p-value**
BMT	Total allo-BMT recipients	166	159	
	Grade of acute GVHD; n/N patients (%)			

	• Grade 0 (none) • Grade I (mild) • Grade II (moderate) • Grade III (severe) • Grade IV (life-threatening)	79/166 (48%) 17/166 (10%) 36/166 (22%) 29/166 (17%) 5/166 (3%)	60/159 (38%) 16/159 (10%) 38/159 (24%) 32/159 (20%) 13/159 (8%)	
	Relative risk, Grades II-IV GVHD	—	—	1.63 (0.0056)
	Acute GVHD, Grade II-IV, cumulative incidence Patients ≥20 yo	34% (n=108)	51% (n=110)	p=0.0051
	Interstitial Pneumonia CMV seropositive patients, all (n=308) Patients with interstitial pneumonia Types of pneumonia • CMV • Idiopathic • Clinical (not culture confirmed) • Parainfluenza virus Interstitial pneumonia, cumulative incidence Relative risk of interstitial pneumonia (p-value) • CMV+ patients <20 years old • CMV+ patients ≥20 years old	IVIg, CMV+ (n=154) 19 16 1 2 0 13% — n=65 patients 8 patients (12%) n=119 patients 11 patients (9%)	No IVIg, CMV+ (n=154) 34 23 4 6 1 22% — n=57 patients 7 patients (12%) n=128 patients 27 patients (21%)	 p=0.021 1.70 (p=0.064) n.s. p=0.0032

Sullivan et al., 1990 – all CMV seropositive patients received prophylactic acyclovir from –d5 to d30 post-BMT. No CMV seronegative patients developed interstitial pneumonia, noting that these patients all received BMT from CMV- donors.
BMT=bone marrow transplant; CMV=cytomegalovirus; GVHD=graft versus host disease; IVIg=intravenous immunoglobulin

In the Sullivan study (Table 26), patients who received IVIg were significant less likely to have a grade II to IV GVHD (RR=1.63, p=0.0056). Interstitial pneumonia (a risk of CMV reactivation) was evaluated only in CMV seropositive patients in the same study as a transplant-related outcome. Patients who were randomised to receive IVIg were significantly less likely to develop interstitial pneumonia than those who did not receive IVIg (cumulative incidence 13% vs 22%, p=0.021).

It was however considered that management of HSCT transplants and GVHD risk in current clinical practice has changed radically compared with when this study was conducted in the late 1980s (new immunosuppressants and conditioning regimens, changes in HLA typing, use of mobilised stem cells) thus in the absence of other high quality studies reporting this outcome it was not clear whether this result for GVHD risk could be replicated in a similarly designed study in a modern population.

The Swedish study (Sundin et al. 2012) reported GVHD in terms of acute, chronic and graft rejection in 46 HSCT recipients receiving either IVIg or SCIg (Table 27). The authors concluded that IVIg recipients had a higher incidence than SCIg of acute GVHD but concluded that this was not significant (p-value not presented). Given the observational nature of the study, the difference in results may have been due to selection bias. The absence of a No IgG control group precludes any conclusion for the main purpose of this evaluation.

Table 27 Transplant-related outcomes – Sundin et al., 2012 (IVIg vs SCIg)

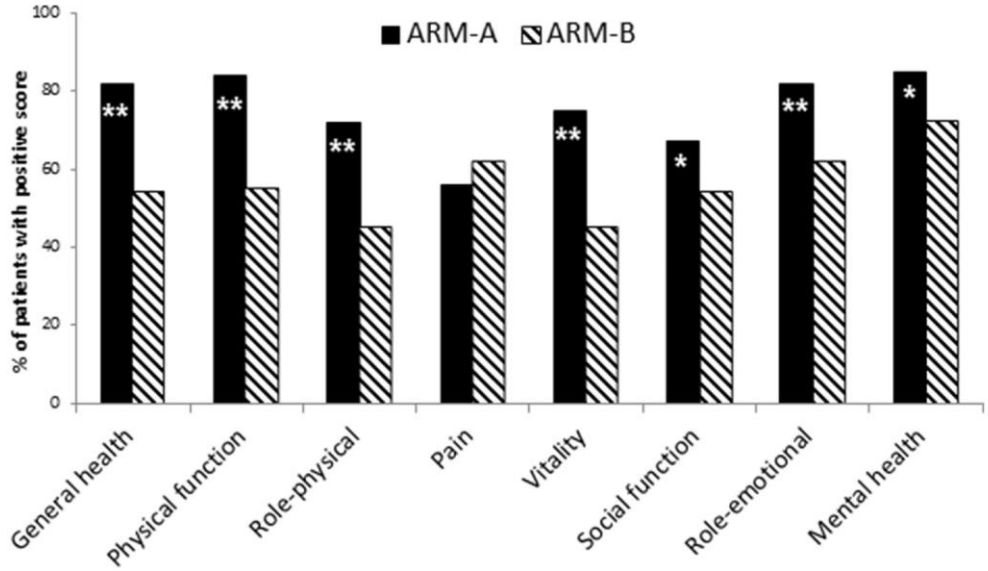
Study, Indication	Outcome	Intervention	Comparator	Comparison
Sundin et al., 2012	**GVHD, n (%)**	**IVIg (N=46) n=24 haem. malignancy**	**SCIg (N=12) n=2 haem. malignancy**	
HSCT	Acute GvHD	30 (65.2%)	5 (41.7%)	
	Chronic GvHD	9 (19.6%)	1 (8.3%)	
	Rejection	1 (2.2%)	1 (8.3%)	

GVHD=graft versus host disease; IVIg=intravenous immunoglobulin; SCIg=subcutaneous immunoglobulin

QUALITY OF LIFE

Three studies administered QoL questionnaires (Reiser et al. 2017; Vacca et al. 2018; Windegger et al. 2019) and a fourth interviewed patients and families regarding acceptance of SCIg (Sundin et al. 2012).

Figure 7 Quality of Life (SF-36) – Vacca et al., 2018



Arm A: patients receiving SCIg; Arm B: 'No SCIg' controls (Vacca et al. 2018). Asterisks indicate p-values *<0.05; **<0.01
Note: this figure will need to be redacted prior to making this document publicly accessible.

One RCT (Vacca et al. 2018) used the SF-36 questionnaire to assess health-related quality of life in patients randomised to receive SCIg or no SCIg (Figure 7). SCIg patients scored better than the untreated control patients by all measures except pain.

A study in Germany in 307 haematological malignancy patients receiving either IVIg or SCIg (Reiser et al. 2017) also used both EQ-5D and SF-36 tools to assess QoL. Patients commencing on IgG improved slightly during follow-up across all domains except psychological health. QoL values for patients entering the study on IgG maintenance did not change during follow-up.

An Australian study (Windegger et al. 2019) surveyed 84 patients to ask whether SCIg was a cost-effective option for patients with secondary immunodeficiency disease compared to IVIg using the Assessment of Quality of Life (AQoL)-6D questionnaire (Table 28). The target population was patients with acquired hypogammaglobulinaemia secondary to malignancy or associated treatment – patients were surveyed who were receiving either IVIg or SCIg or picking up SCIg product from one of two different clinics in Queensland, to determine the utilities associated with different health states. The presence of infection and bronchiectasis (lung disease which allows mucus to pool in the damaged airways) reduced quality of life in these patients compared to no infection or bronchiectasis. In terms of cumulative QALYs, SCIg was dominant (3.51 QALY) compared to IVIg (3.07 QALY), given that costs for SCIg were lower (not shown)

Table 28 Utility weights based on AQOL-6D survey

Study Indication	Risk of bias	Population	Health state	Utility score (95%CI)
Windegger et al. (2019) (undefined)	Moderate/ high	84 patients with acquired hypogammaglobulinaemia secondary to haematological malignancy (192 responses)	No infection	0.71 (0.67, 0.75)
			With infection	0.70 (0.63, 0.76)
			With bronchiectasis no infection	0.64 0.55, 0.72)
			With bronchiectasis with infection	0.63 (0.56, 0.70)

A Swedish study (Sundin et al. 2012) interviewed 10 SCIg and 22 IVIg paediatric HSCT recipients and their families about acceptability of the IgG treatment the child was receiving. All families interviewed were positive about IgG treatment regardless of route of administration. The authors noted that four families of IVIg recipients who had indicated acceptance of IVIg still wanted to switch or wanted their child to switch to SCIg based on the reduced burden of clinic visits or difficulties with venous access for IVIg. Two SCIg families had anxiety about administering injections to their own child at home and chose to come to the clinic for infusions but this did not appear to affect acceptability of SCIg.

QoL data from a further study (Chapel et al. 1994b) have been reported separately in a symposium presentation[11], but these data do not appear to have been published in the peer-reviewed literature.

B.7. EXTENDED ASSESSMENT OF HARMS

IgG has a long history of use for treatment of immunodeficiency dating back to the 1950s or earlier. IVIg has been used to manage hypogammaglobulinaemia infection risk in haematological

[11] Lee ML, Couter SG, Chapel HM. Quality of life and cost effectiveness issues in chronic lymphocytic leukaemia: a reevaluation. *Symposium on drugs, drug companies and quality of life issues*, New York, 1993.

malignancies since the late 1980s or so. In the European Union, the authorised product information for authorised products must include core text prescribed for both IVIg and SCIg presentations[12], reflecting the extent of safety information available for these products across these patient populations. The current approved Product Information for IgG products registered in Australia contain a corresponding extent of safety information, however the wording varies between products. Hence the EMA's core text specifically relating to IgG safety profile (below) can be considered representative of IgG products registered in Australia.

Adverse reactions caused by human normal immunoglobulins (in decreasing frequency) encompass:

- *chills, headache, dizziness, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and moderate low back pain*
- *reversible haemolytic reactions; especially in those patients with blood groups A, B, and AB and (rarely) haemolytic anaemia requiring transfusion*
- *(rarely) a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration*
- *(rarely) transient cutaneous reactions (including cutaneous lupus erythematosus - frequency unknown)*
- *(very rarely) thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism, deep vein thromboses*
- *cases of reversible aseptic meningitis*
- *cases of increased serum creatinine level and/or occurrence of acute renal failure*
- *cases of Transfusion Related Acute Lung Injury (TRALI)*

In 2011, the EMA undertook a review of at least two immunoglobulin products (Octagam[13]; Vivaglobin[14]) which were associated with reports of increased TEEs and which led to a worldwide withdrawal of Octagam from the market. The EMA concluded that these events were due to residual impurities (clotting factors in the case of Octagam) which had caused the spike in events. Octagam remains authorised in both the EU, Australia and elsewhere following improvements to the manufacturing process to control for these impurities. The potential TEE risk is now highlighted in product information as described above. In the USA, TEE risks were added as a black box safety warning to IgG products. Relevant to this, a US registry study included in this evaluation (Ammann et al. 2016) further investigated TEE risks associated with any IgG use in more than 10,000 matched subjects with CLL or MM.

[12] Core summary of product characterisitcs for human normal immunoglobulin for intravenous administration
[13] European Medicines Agency: Octagam
[14] European Medicines Agency: Vivaglobin

B.8. INTERPRETATION OF THE CLINICAL EVIDENCE

The overall evidence shows that, in patients with hypogammaglobulinaemia secondary to any haematological malignancy, IgG replacement will significantly reduce the number of infections compared with 'No IgG'. Studies were less likely to support this conclusion if they enrolled a high proportion of patients without documented risk factors (hypogammaglobulinaemia and a history of infections). Infections incidence appeared to be as variable between indications such as CLL or MM as they were within a single indication due to differences in disease severity, concomitant medications and other factors.

The effectiveness of IgG in reducing infections incidence was confirmed in meta-analyses of randomised trials, as well as meta-analyses of before-and-after case series (within patient comparisons of infection rates before receiving IgG and while on IgG). The limitations of the evidence mean that the risk ratios reported in these meta-analyses are highly uncertain.

The studies included in the report were low level evidence consisting primarily of case series with a small number of randomised studies (several of which did not adequately report the primary efficacy outcome, infections). An assessment of the quality of evidence for each outcome using GRADE is in Table 29. The quality of evidence was low for efficacy (as measured by infections) and also low for safety (though not for TEE risk which had high quality evidence).

Clinical evidence for IgG safety was limited to infusion reactions, with the exception of a registry study reporting TEE risk which showed a transient increase in TEE events following IgG initiation. It was considered that the safety profile described in approved Product Information (using the EMA core text as an example) provides a better and more comprehensive assessment of IgG safety for this population.

This evaluation could not address:

- Confirmation of a clinically active dose or frequency of dosing. Most studies included explored doses between 200 and 500 mg/kg. Variability in patient characteristics and disease status, and the effect this had on infections, precluded any assessment of dose-response.

- Definition of adequate treatment response: a qualitative reduction in infections rate was usually taken as evidence of a response. Timeframes for assessment were highly variable.

- Criteria for discontinuation. An initial patient response in terms of infections seemed to be adequate reason for ongoing IgG replacement which often lasted for some months or years. The majority of the included studies did not describe criteria for treatment continuation or cessation – for those that did, it was typically the reasoning of the treating physician was reported. There was no prospective set of discontinuation criteria offered by any of the included studies.

- Frequency of serum IgG monitoring as a basis for response assessment or a decision to discontinue. Several studies monitored serum IgG levels, some as frequently as monthly or every 3 months. Others tested patients based on availability as representative of the whole cohort.

Regarding the 'other haematological malignancies' category, use of IgG replacement in these patients is based on the principle that a history of infections and presence of hypogammaglobulinaemia is sufficient to warrant treatment. This is the basis of the current funding of IgG for this category of patients in Australia, but it still remains an assumption. On the other hand, the evidence reviewed does not suggest that response to IgG replacement therapy is any more variable in patients with the less-studied/infrequent malignancies compared with CLL and MM. A large registry study with adequate patients having 'other' conditions would be needed to address this.

On the basis of the benefits and harms reported in the evidence base (summarised above), it is suggested that, relative to No IgG replacement with antibiotics as required, the use of IgG products with antibiotics as required has **inferior safety** and **superior effectiveness**.

Table 29 Balance of clinical benefits and harms of IgG with antibiotics as required, relative to No IgG with antibiotics as required (GRADE assessment)

Outcomes (units) Follow-up	Participants (studies)	Quality of evidence (GRADE)	Relative effect	Comments
Safety	K=13 studies; N=1,342 (2 RCTs reported AEs for both IgG and No IgG; N=125)	⊕⊕⊙⊙ Low quality	IgG has worse safety than No IgG	Safety data were limited and sometimes absent for the included studies, focusing on infusion-related events only (key RCTs (Boughton et al. 1995; Chapel et al. 1994b)). No evidence was available for longer-term outcomes other than TEE risk. Adverse events reported were nevertheless consistent with the established safety profile for IgG products (discussed in Extended Assessment of Harms).
TEE risk (arterial or venous)	1 registry study N=10,759	⊕⊕⊕⊕ High quality	% Risk difference (95% CI), 1 yr IgG tx: 1.0 (-0.2, 2.7)	Only 1 included study, but very large, recent registry study. Control and intervention groups were balanced for cardiovascular risk. Selection bias which limits use of this study for infections is unlikely to affect cardiovascular safety (the main endpoint of this study) – high confidence in risk of TEE due to IgG.
Infections	K=20 studies, N=1,930 (15 in meta-analyses: 6 RCTs, 2 cohort, 7 case series; N=1,536)	⊕⊕⊙⊙ Low quality	Rate ratio (95% CI) 0.14 (0.05, 0.43) for reduction of serious infections with IgG compared to No IgG	The quality of evidence was poor overall and infections were both reported and defined in widely variable ways. Moderate confidence that IgG reduces serious infections in patients based on a meta-analysis, but effective dose range could not be identified with any confidence and evidence was absent or limited for some of the conditions such as HSCTs, AL and 'Other haematological malignancies'.
Transplant-related events	1 RCT (N=369) 1 supportive study (N=58)	⊕⊙⊙⊙ Very low quality	No conclusion drawn.	Only two studies investigated transplant-related outcomes. One study from 1990 may not be replicable with current standard of care for HSCTs and management of GVHD risk. A second supportive study could not be used.
Mortality	4 included studies (1 RCT, 1 cohort study, 1 registry and 1 retrospective case series) N=11,674	⊕⊙⊙⊙ Very low quality	No conclusion drawn.	Insufficient duration of follow-up and variability between patient disease stage and other clinical factors precluded any meaningful assessment.
QoL	1 RCT (N=46) 1 case series with small amount of before and after data (N=307)	⊕⊕⊙⊙ Low quality	IgG marginally improves QoL compared to No IgG	Only 2 of the 4 studies reported QoL for IgG versus no IgG.

[a] 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.

SECTION C TRANSLATION ISSUES

C.1. OVERVIEW

The model presented in Section D is a cost-utility analysis, where Ig therapy is associated with an effective reduction in infection rates, but that is traded off against a reduced safety profile. Ig therapy is already in use in Australia and four applicability issues are considered:

1. How do the patient demographics and settings in the clinical evidence compare to those that currently receive Ig therapy for acquired hypogammaglobulinaemia?

2. How were antibiotics used in the absence of Ig in the clinical evidence, and is this reflective of what would happen in the absence of Ig in the contemporary setting?

3. How do the doses used in the clinical evidence compare to those currently dispensed in the Australian population that receives Ig for acquired hypogammaglobulinaemia?

4. What was the duration of Ig treatment in the clinical evidence, and how does this compare to use in the current Australian population?

Extrapolation issues considered are:

1. What is the expected duration of the treatment effect of Ig?

2. What is the natural history of recurrent infections in patients with acquired hypogammaglobulinemia?

Finally, one transformation issue is presented:

1. How to transform the outcomes of the clinical evidence into a common patient-relevant outcome?

C.2. APPLICABILITY TRANSLATION ISSUES

C.2.1. PATIENT DEMOGRAPHICS AND SETTINGS

The aim of this translation study is to determine how the patient demographics and settings in the clinical evidence compare to those of patients that currently receive Ig therapy for acquired hypogammaglobulinaemia in Australia. As per the Version 3 criteria, Ig is indicated for acquired hypogammaglobulinaemia secondary to haematological malignancies (including acute leukaemia, CLL, MM, NHL and others), or post-HSCT. BloodSTAR data are used to inform the average ages and

weights of patients in Australia who currently receive Ig for this indication. These demographics will be compared to those of the patients enrolled in the primary clinical evidence used to inform the economic analysis.

The demographics of patients in Australia who currently receive Ig for acquired hypogammaglobulinaemia are presented in Table 30. As the primary evidence that will inform the economic analysis will be the randomised studies identified in Section B (Chapel et al. 1991; Chapel et al. 1994b; Molica et al. 1996; Musto, Brugiatelli & Carotenuto 1995; Sullivan et al. 1990; Vacca et al. 2018) (though noting that sensitivity analyses based on the before/after non-randomised studies will also be presented), this table presents a comparison of the demographics to those in the randomised studies.

Table 30 A comparison of the demographics of the Australian population that receives Ig for acquired hypogammaglobulinaemia to those in the clinical evidence

	Average patient age		Average patient weight	
	BloodSTAR data [a]	Section B studies	BloodSTAR data [a]	Section B studies
CLL	72.5	Chapel et al. (1991): NR Molica et al. (1996): 64 ± 11.5	77.3	Chapel et al. (1991): NR Molica et al. (1996): NR
MM	70.2	Chapel et al. (1994b): 66 Musto, Brugiatelli & Carotenuto (1995): NR Vacca et al. (2018): 71	77.8	Chapel et al. (1994b): NR Musto, Brugiatelli & Carotenuto (1995): NR Vacca et al. (2018): NR
NHL	68.3	Chapel et al. (1991): NR	76.3	Chapel et al. (1991): NR
Other HM	54.7	-	67.1	-
Post-HSCT	42.0	Sullivan et al. (1990): NR	63.6	Sullivan et al. (1990): NR
Overall	66.5	-	75.0	-

CLL = chronic lymphocytic leukaemia; HM = haematological malignancy; HSCT = hematopoietic stem cell transplantation; Ig = immunoglobulin; MM = multiple myeloma; NHL = non-Hodgkin lymphoma.
[a] Based on Version 2 data collected for the whole financial year, 2017-18 from the 'HTA Data April2019.xlsx' workbook provided by the NBA.

Patient demographics in the studies were generally not well reported (Table 30). Mean ages were only reported in three of the six studies (Chapel et al. 1994b; Molica et al. 1996; Vacca et al. 2018), while mean weights were not reported in any of the randomised studies. While MM patients were generally consistent with the average ages of patients in Australia who currently receive Ig for acquired hypogammaglobulinaemia, CLL patients in the clinical evidence may have been slightly younger. Similar trends with respect to average ages were observed in the before/after non-randomised evidence identified in Section B (see Table 80 and Table 81, Appendix D). One non-randomised study reported patient weights (Günther & Dreger 2013) in a mixed, though predominantly CLL, population of 77 kg (which is consistent with the CLL patients in BloodSTAR).

The randomised studies were all conducted in either the UK (Chapel et al. 1991; Chapel et al. 1994b), Italy (Molica et al. 1996; Musto, Brugiatelli & Carotenuto 1995; Vacca et al. 2018) or the US (Sullivan et al. 1990). However, only one of the studies had been conducted in the previous 20 years (Vacca et al. 2018). One non-randomised study, Paxton, Hawkins & Crispin (2016), was conducted in Australia, and another in the UK (Duraisingham et al. 2014). Others were conducted in the US, Europe and Israel. More of the non-randomised studies were conducted in the contemporary setting (Benbrahim et al. 2019; Dimou et al. 2018; Duraisingham et al. 2014; Günther & Dreger 2013; Paxton, Hawkins & Crispin 2016; Reiser et al. 2017; Van Winkle et al. 2018). Contemporary studies, which were predominantly non-randomised, tended to enrol patients with mixed haematological malignancies.

It is unclear what impact these differences would have, if any, on baseline infection rates and the relative treatment effect of Ig. It is conceivable that changes in contemporary practice could decrease the absolute numbers of infections with or without Ig, which would likely increase the ICER. The implications of this on the relative treatment effect of Ig are unknown, however the treatment effect was observed to be reasonably consistent in the older and newer studies (both randomised and non-randomised before/after studies). Therefore the more recent Australian data from a mixed haematological malignancy population (Paxton, Hawkins & Crispin 2016) will be used to approximate the baseline infection rate in the absence of Ig, and the pooled risk reductions estimated in Section B will be applied to the baseline infection rate in order to model the treatment effect of Ig.

C.2.2. ANTIBIOTIC USE IN THE ABSENCE OF IG

The aim of this translation study is to determine how antibiotics were used in the absence of Ig in the clinical evidence, and whether this is reflective of what would happen in the absence of Ig in the contemporary setting. Antibiotic use in the 'No Ig' arms of the randomised evidence will be reviewed and compared to what would happen in Australian clinical practice in the absence of Ig.

Prophylactic antibiotic use was generally not allowed in the randomised evidence presented in Section B (Chapel et al. 1994b; Molica et al. 1996; Musto, Brugiatelli & Carotenuto 1995; Vacca et al. 2018). One study did not report whether antibiotic use was allowed (Chapel et al. 1991), and the study in patients undergoing HSCT (Sullivan et al. 1990) required prophylactic co-trimoxazole for the first 120 days post-transplant in both trial arms.

One of the non-randomised studies (Duraisingham et al. 2014) reported that prior to Ig initiation 12 of 15 (80%) patients with hypogammaglobulinaemia secondary to a haematological malignancy were on prophylactic antibiotics, whereas after the initiation of Ig replacement this reduced to 10 (67%) patients. A substantial decrease in the number of serious and non-serious infections was observed after Ig initiation (Table 31). It is noted though that this study was conducted in the UK where

guidelines require a trial of prophylactic antibiotics before considering Ig replacement, and that this is not a requirement in Australia (Wong et al. 2019).

Table 31 Analysis of prophylactic antibiotic use and infection outcomes from Duraisingham et al. (2014)

	Before Ig	After Ig
Proportion of patients on prophylactic antibiotics in HM subset	12/15 (80%)	10/15 (67%)
No. serious infections in HM subset	11	3
Serious infection rate	0.9	0.2
No. non-serious infections in HM subset	37	21
Non-serious infection rate	3.1	1.4

HM = haematological malignancy; Ig = immunoglobulin.
Source: Duraisingham et al. (2014), supplemental data

It is unclear what would occur in Australian clinical practice in the absence of Ig. A survey of Australian clinicians experienced in the care of patients with acquired hypogammaglobulinaemia indicated that only 3% of clinicians would routinely trial prophylactic antibiotics before initiating Ig replacement therapy, with a further 17% indicating that they would trial prophylactic antibiotics in certain situations (Wong et al. 2019). However this study was conducted in the setting where Ig is available, and rates of antibiotic prophylaxis may differ in the setting where Ig is not available, which may have implications for the relative treatment effect of Ig.

While the results from the Duraisingham et al. (2014) study are supportive of a benefit of similar magnitude for Ig irrespective of whether prophylactic antibiotics are used in the comparator, due to the inherent biases associated with the small patient numbers and study design, this is not conclusive. An Australian RCT comparing antibiotic prophylaxis to Ig in acquired hypogammaglobulinaemia (Australian New Zealand Clinical Trials Registry no. ACTRN12616001723471) is currently ongoing and aims to address this question.

In the absence of alternative evidence to i) suggest that rates of antibiotic prophylaxis would increase in the absence of Ig (given that randomised trials, including one contemporary trial, did not allow antibiotic prophylaxis; or where allowed, use was equal irrespective of Ig use); and ii) that this increase in antibiotic use would affect the relative treatment effect of Ig (given that this comparison is currently being explored and the one non-randomised study identified showed a consistent effect despite prophylactic antibiotic use), the economic analysis will assume no increase in prophylactic antibiotic use relative to that in the Ig arm of the model – and so the relative treatment effect observed in the randomised studies is assumed to apply to the current setting. However a scenario analysis based on the results from the Duraisingham et al. (2014) study, including the cost of prophylactic antibiotics and observed treatment effect, will be presented.

C.2.3. DOSE OF IG

The third translation study presented aims to determine how the doses used in the clinical evidence compare to those currently dispensed in the Australian population that receives Ig for acquired hypogammaglobulinaemia. BloodSTAR data are used to inform the average dose in current practice, and will be compared to the doses reported in the clinical evidence.

The Version 3 criteria suggest doses of 0.4 g/kg every 4 weeks or more frequently to achieve targeted IgG trough levels. However it is also specified that the lowest dose possible that achieves the appropriate clinical outcome should be used. A comparison of the average doses dispensed per episode of treatment as reported in the BloodSTAR data to the doses used in the clinical evidence are presented in Table 32.

Table 32 A comparison of the doses dispensed in the Australian population that receives Ig for acquired hypogammaglobulinaemia to that used in the clinical evidence

	Ig dose	
	BloodSTAR data [a]	**Section B studies**
CLL	0.37 g/kg	Chapel et al. (1991): 0.4 g/kg q3w Molica et al. (1996): 0.3 g/kg q4w
MM	0.37 g/kg	Chapel et al. (1994b): 0.4 g/kg q4w Musto, Brugiatelli & Carotenuto (1995): 0.3 g/kg q4w Vacca et al. (2018) (SCIg): 4 weekly infusions to give a total dose of 0.4–0.8 g/kg/month
NHL	0.36 g/kg	-
Other HM	0.38 g/kg	-
Post-HSCT	0.37 g/kg	Sullivan et al. (1990): 0.5 g/kg/week for first three months, then monthly
Weighted average	0.37 g/kg	-

CLL = chronic lymphocytic leukaemia; HM = haematological malignancy; HSCT = hematopoietic stem cell transplantation; Ig = immunoglobulin; MM = multiple myeloma; NHL = non-Hodgkin lymphoma.

[a] Based on Version 2 data collected for the whole financial year, 2017-18 from the 'HTA Data April2019.xlsx' workbook provided by the NBA.

The doses used in the randomised evidence varied from 0.3 g/kg to 0.8 g/kg every three to four weeks, which was similar to the average doses observed in the BloodSTAR data (0.36−0.38 g/kg). The non-randomised before/after studies were also generally consistent with these doses and frequencies (see Table 80 and Table 81, Appendix D). Despite variations in the doses used in each of the studies, the relative treatment effect of Ig was observed to be reasonably consistent (see Section B.6). Given the experience in use with Ig in current practice, it will be assumed that current dosing is appropriate to achieve the clinical outcome of preventing infections, and so the economic analysis will use actual doses from the BloodSTAR data under the assumption that this has no effect on the relative treatment effect of Ig as observed in the trials. This is further supported by the similar doses used in the studies compared to current practice and that consistency was observed in the

treatment effect across the included studies, in spite of variations in dose. A sensitivity analysis is presented assuming the recommended dose of 0.4 g/kg every 4 weeks.

C.2.4. DURATION OF IG TREATMENT

The final applicability translation issue aims to determine what the duration of Ig treatment was in the clinical evidence, and how this compares to use in the current Australian population. Duration in the clinical evidence will be reviewed and compared against evidence to suggest what treatment durations are in current practice.

The randomised evidence most commonly reported an Ig treatment duration of 12 months. This was generally fixed and not conditional on an assessment of treatment response. As a few of the studies had a randomised cross-over design (Chapel et al. 1991; Molica et al. 1996; Musto, Brugiatelli & Carotenuto 1995), patients in these studies may have been considered at-risk of infections for two years, rather than just the one year while on Ig. The most recent of the studies, Vacca et al. (2018), specified no maximum treatment duration (or reasons for cessation of Ig other than side effects), and the average was observed to be 18 months.

The non-randomised studies included in the clinical evidence reported varied treatment durations. Of the data presented in Australian patients with mixed haematological malignancies, Paxton, Hawkins & Crispin (2016) reported that patients received Ig for a median of 26 months (range: 3−79), and the cohort of patients described in Windegger et al. (2019) had received at least 12 months of IVIg prior to switching to 12 months of SCIg treatment. Treatment durations in other non-randomised studies are summarised below:

- The small Greek study (Dimou et al. 2018) (n=13 mixed haematological malignancies) included patients who had been on IVIg for an average of 26.2 months prior to switching to SCIg.

- A small German study (Günther & Dreger 2013) (n=10 mixed haematological malignancies) reported that patients received treatment on average for 4.5 years.

- Jurlander et al. (1995) (n=15 CLL) reported that Danish patients received an average of 12 months of treatment.

- A Swedish study (Sundin et al. 2012) (n=26 post-HSCT) reported a median treatment duration of 9 months (range 6−20 months).

- Finally, a French study conducted by Benbrahim et al. (2019) (n=160 mixed haematological malignancies) reported a mean exposure to Ig of 8.4 months, though the follow-up period was a maximum of 12 months.

Thus the clinical evidence are highly variable with respect to the duration of Ig treatment, and may have limited applicability to the current Australian population that initiates Ig replacement therapy for acquired hypogammaglobulinaemia (as treatment duration across the population that initiates therapy is likely to follow some distribution with a long tail, and that some of these studies may be focussed on those with longer treatment durations, such as Windegger et al. 2019 which required 12 months on IVIg prior to switching to SCIg).

The Version 3 criteria do not specify a maximum treatment duration for patients with acquired hypogammaglobulinaemia in Australia. Rather treatment is indicated if there is a demonstrated clinical benefit, and cessation should be considered at least after each 12 months of treatment. BloodSTAR data were not available to inform the average treatment durations of patients who currently receive Ig for acquired hypogammaglobulinaemia. The survey of Australian clinicians (Wong et al. 2019) indicated quite variable results with regards to the duration of Ig treatment: 21% indicated that they would continue Ig until an AE, 24% indicated a fixed duration (mostly 6 or 12 months – 11% and 8% respectively), 15% indicated they would cease treatment when normal trough levels were achieved and the patient was infection-free, and 34% indicated that decisions were made on a case-by-case basis.

The ongoing clinical trial conducted in Australia (ACTRN12616001723471) that compares prophylactic antibiotics to Ig in CLL, MM and NHL allows treatment for 12 months, or until the treating physician determines that the patient should come off the treatment.

As patients enrolled in Paxton, Hawkins & Crispin (2016) were not required to have received Ig for a minimum period of time, the treatment duration observed, 26 months, is considered to be most applicable to the current setting and will be assumed in the base case economic analysis. This is also not too dissimilar to the duration at-risk of infections in three of the randomised studies (i.e. those with the cross over design) (Chapel et al. 1991; Molica et al. 1996; Musto, Brugiatelli & Carotenuto 1995).

C.3. EXTRAPOLATION TRANSLATION ISSUES

C.3.1. WHAT IS THE DURATION OF THE TREATMENT EFFECT OF IG IN PATIENTS WITH ACQUIRED HYPOGAMMAGLOBULINAEMIA?

The economic model in Section D will assume that while on Ig therapy, patients are at risk of infections, however after treatment cessation, it will be assumed that no new infections are modelled – in either model arm – after such time.

As described in Section C.2.4 above, treatment durations in the randomised trials were generally fixed and not conditional on an assessment of treatment response. The Version 3 criteria do not specify a maximum treatment duration for patients with acquired hypogammaglobulinaemia in Australia, rather treatment is indicated if there is a demonstrated clinical benefit. As Section C.2.4 concluded that an average treatment duration of 26 months would be most applicable it is assumed this also represents the duration of clinical benefit or direct treatment effect of Ig, whereby a different risk of infection is modelled across the Ig treatment and no treatment arms of the model.

Since this is beyond the duration of the randomised trial evidence presented in Section B (up to 18 months) this constitutes an extrapolation of treatment administration and benefit beyond the evidenciary time horizons (8−14 months). As there is no evidence to support an ongoing direct treatment effect once Ig treatment is ceased, it is appropriate for transition rates between all 'off-treatment' health states to be the same for each arm of the model.

Therefore it is only the difference in health state allocation at the end of Ig treatment that results in long-term differences in overall survival and quality of life differences between the study arms.The long term transition probabilities, in the absence of other evidence, assume an ongoing constant per cycle risk, except for disease-adjusted age-specific mortality; these are fully detailed in Section D.4.1.

C.3.2. WHAT IS THE NATURAL HISTORY OF RECURRENT INFECTIONS IN PATIENTS WITH ACQUIRED HYPOGAMMAGLOBULINAEMIA?

As described in Section C.3.1, while patients are on Ig treatment they are assumed to be at risk of infections, however once Ig treatment has ceased, no new infections are modelled. An extrapolation translation issue is presented to determine whether there are longterm sequelae related to recurrent infections.

There is very little published information regarding the long term consequences of recurrent infections in patients with acquired hypogammaglobulinaemia. One narrative review (Brown, Baxendale & Floto 2011) was identified which described the association of secondary immune deficiencies with bronchiectasis. In haematological malignancies:

> "*case reports or case series data have described bronchiectasis complicating chemotherapy, acute and chronic leukaemias, myeloma and lymphomas (Kearney, Kershaw & Stevenson 1977; Knowles, Stanhope & Green 1980; Li et al. 2005; Okada et al. 2004). In particular, due to the combination of prolonged survival and the high frequency of secondary hypogammaglobulinaemia, multiple myeloma and chronic lymphocytic leukaemia (CLL) seem to be relatively commonly associated with bronchiectasis, although the exact incidence has not been reported (Knowles, Stanhope & Green 1980). CLL and myeloma patients with proven bronchiectasis and hypogammaglobulinaemia should be assessed for IVIG therapy.*

Bronchiectasis has also been reported to develop in association with more acute haematological malignancies, perhaps as a consequence of severe lung infections and/or due to the affects of leukaemia or chemotherapy on host immunity (Kearney, Kershaw & Stevenson 1977). However, there are no precise data on the incidence and rate of progression of bronchiectasis in patients with haematological malignancies." (Brown, Baxendale & Floto 2011, p185)

In post-HSCT:

"Haematopoietic stem cell transplantation (HSCT) is associated with an increased incidence of respiratory infections and potentially prolonged defects in cellular and humoral immunity in survivors (Parkman 2008). These factors could predispose to bronchiectasis (Morehead 1997) and, in the authors' experience, serial CT scans after allograft HSCT can demonstrate rapidly developing bronchiectasis over a period of weeks to months. In addition, up to 10% of HSCT allograft recipients will develop bronchiolitis obliterans (the main pulmonary manifestation of graft versus host disease) which precedes the appearance of diffuse bronchiectasis in ~40% of cases (Gunn et al. 2008; Tanawuttiwat & Harindhanavudhi 2009). Hence, although there are no precise prevalence data on bronchiectasis post-HSCT, it is probably a relatively common complication, especially in allograft recipients. Similarly, patients who develop bronchiolitis obliterans after lung transplantation may also have CT evidence of bronchiectasis (de Jong et al. 2006), and there are case reports of bronchiectasis developing after transplantation of other solid organs (Pijnenburg et al. 2004), presumably because of damage caused by intercurrent pneumonias and/or impaired pulmonary immunity due to prolonged immunosuppressive therapy." (Brown, Baxendale & Floto 2011, p185)

While these data cannot enable an estimate of the incidence of bronchiectasis in acquired hypogammaglobulinaemia, they support the premise that reducing recurrent infections due to the use of Ig may reduce the development of bronchiectasis. Furthermore, modelling the development of bronchiectasis is consistent with a recent Australian economic evaluation that compared SCIg to IVIg in this population (Windegger et al. 2019) (see also Section D.3). As described in Section D.3, the model structure will include health states associated with bronchiectasis in the base case analysis, however the inclusion of these health states are tested in a sensitivity analysis.

C.4. TRANSFORMATION ISSUES

C.4.1. TRANSFORMATION OF OUTCOMES INTO A COMMON, PATIENT-RELEVANT OUTCOME

A transformation pre-modelling study is conducted which aims to transform both the benefits (i.e. a reduction in infections) and any harms associated with Ig treatment into a common measure to

allow these opposing effects to be traded-off in the economic evaluation. Quality-adjusted life years (QALYs) are considered to be an appropriate measure for transformation.

A review of the economic literature was conducted (see Section D.3) and two relevant cost-utility analyses were identified (Weeks, Tierney & Weinstein 1991; Windegger et al. 2019). The utility weights used in these studies are reported in Table 33.

Table 33 Utility weights used in the relevant economic literature

Health state	Value
Windegger et al. (2019)	**Utility weight (95% CI)**
Utility of infection-free	0.71 (0.67, 0.75)
Utility of infection	0.70 (0.63, 0.76)
Utility of Bronchiectasis	0.64 (0.55, 0.72)
Utility of Bronchiectasis with infection	0.63 (0.56, 0.70)
Utility of Bronchiectasis with chronic *P. aeruginosa* infection	0.63 (0.56, 0.70)
Weeks, Tierney & Weinstein (1991)	**Utility weight (range)**
Utility of infection-free	0.87 (0.50, 0.999)
Utility of trivial infection[a]	0.86 (0.50, 0.999)
Utility of moderate infection[b]	0.81 (0.50, 0.99)
Utility of major infection[c]	0.46 (0.2, 0.90)
IVIg infusion	0.66 (0.20, 0.99)

[a] Infections such as folliculitis or a paronychia
[b] Infections such as bronchitis or otitis, requiring oral antibiotic therapy
[c] Life-threatening infections, such as pneumonia or septicaemia, requiring parenteral anitbiotics, hospitalisation or both.
Source: Table 2, Windegger et al. (2019) and Table 2, Weeks, Tierney & Weinstein (1991)

The utilities reported in Windegger et al. (2019) were derived from a sample of 84 patients, and included patients who had only received one treatment mode (i.e. IVIg or SCIg), or who had not received 12 months of IVIg prior to switching to SCIg. Utilities were measured using the AQoL-6D instrument, whereas the utilities in Weeks, Tierney & Weinstein (1991) were derived from 10 oncologists experienced with the care of CLL.

The utility weights as reported in Windegger et al. (2019) will be preferentially used, as these were derived from an Australian population using a multi attribute utility instrument, rather than being based on clinicians' assessment. Utilities were also reported for the selected health states used in the model (see Section D.3). However the disutility reported for the infection health state (a decrement of 0.01 relative to infection-free) seems small and on face-value may underestimate the disutility associated with infections, particularly severe infections. Further, as Ig also changes the distribution of infection severity, and reduces those infections that are most severe, the utilities modelled need to be able to capture this difference between the model arms. Therefore the model applies the decrements (relative to infection-free) in Weeks, Tierney & Weinstein (1991) for infection severity to the distribution of infection severity (see Section D.4.1), to determine a revised weighted disutility of infection.

A utility decrement is also applied in the model to account for reduced quality-of-life associated with infusions. This has been derived from the difference in utility between infection-free and IVIg infusions as reported by Weeks, Tierney & Weinstein (1991) to determine a daily disutility associated with infusions. Over the course of a year, 13 infusion days have been estimated, leading to an estimated annual disutility of 0.0075 associated with IVIg infusions every four weeks. As the source data for baseline infection-free utility were based on patients on treatment, this disutility is implicit within the data, and so will be added to the infection-free utility in the No Ig arm of the model. A sensitivity analysis will be presented where this disutility is excluded.

AEs in the clinical evidence associated with Ig were generally infusion-related. While AEs related to infusion were frequent, these were generally mild and manageable with adjustments to infusion. Moderate AEs tended to be less frequent and were manageable with dose adjustment, cessation or corticosteroids. None of the included studies reported any AEs greater than Grade 3 severity, nor were there any deaths or anaphylaxis due to Ig. On this basis, no quality-of-life adjustments have been made with respect to AEs related to IVIg infusion.

The utility weights used in the model are presented in Table 34.

Table 34 Utility weights used in the economic evaluation

	Ig	No Ig	Source
Utility infection-free	0.7073	0.7073	Windegger et al. (2019)
Disutility per infusion day	0.0006 [a]		Weeks, Tierney & Weinstein (1991)
No. infusion days per year	13 [b]		
Annual disutility due to infusions	0.0075		
Utility in infection-free, including IV infusions	0.7073	0.7148 [c]	
Distribution of infection severity			Section D.4.1
− Serious infections, utility decrement 0.41	19.1%	29.0%	Weeks, Tierney & Weinstein (1991)
− Non-serious infections, utility decrement 0.06	80.9%	71.0%	Weeks, Tierney & Weinstein (1991)
Weighted utility decrement of infections	0.1268	0.1616	
Utility with infection	0.5805	0.5532	Infection-free utility minus the weighted utility decrement of infections
Utility of bronchiectasis	0.6392	0.6392	Windegger et al. (2019)
Distribution of infection severity with bronchiectasis [d]			
− Serious infections, utility decrement 0.41	12.5%	12.5%	Weeks, Tierney & Weinstein (1991)
− Non-serious infections, utility decrement 0.06	87.5%	87.5%	Weeks, Tierney & Weinstein (1991)
Weighted utility decrement of infections	0.1038	0.1038	
Utility of bronchiectasis with infection	0.5355	0.5355	Bronchiectasis utility minus the weighted utility decrement of infections
Utility of Bronchiectasis with chronic *Pseudomonas aeruginosa* infection	0.5355	0.5355	As for Bronchiectasis with infection

Ig = immunoglobulin; IV = intravenous.

[a] (0.87 – 0.66)/365.25

[b] weeks per year divided by infusion frequency (i.e. 52/4)

[c] As source of baseline health state data were from patients on treatment, the disutility due to infusions has been assumed to be incorporated in the utility weight

[d] In the absence of data to suggest a difference between model arms, the proportion of serious infections with bronchiectasis is assumed to be the same across both model arms and has been based on the proportion assumed in Windegger et al. (2019).

C.5. RELATIONSHIP OF EACH PRE-MODELLING STUDY TO THE ECONOMIC EVALUATION

A summary of the pre-modelling studies and their relationship to the model conducted in Section D is presented in Table 35.

Table 35 Summary of results of pre-modelling studies and their uses in the economic evaluation

Section	Pre-modelling study	Results used in Section D	Cross-reference
Applicability	Patient demographics	Patient demographics in the included studies were generally not well reported. A comparison of the available information to the current population that receives Ig for acquired hypogammaglobulinaemia in Australia observed that CLL patients may be older than those studied. Further the majority of studies were conducted in the 1990s. However the treatment effect of Ig seemed relatively consistent across included studies (Section B.6). Contemporary Australian data will be used to inform baseline infection rates, and the pooled estimates for the treatment effect of Ig from randomised studies will be used in the base case analysis. These inputs will be tested in the sensitivity analyses.	Section D.2
	Antibiotic use in the absence of Ig	In the absence of alternative evidence to i) suggest that rates of antibiotic prophylaxis would increase in the absence of Ig; and ii) that this increase in antibiotic use would decrease the relative treatment effect of Ig, the economic analysis will assume no increase in prophylactic antibiotic use relative to that in the Ig arm of the model – and so the relative treatment effect observed in the randomised studies is assumed to apply to the current setting.	Section D.3
	Dose of Ig	The doses in the clinical evidence are consistent with doses used in current practice. Given the experience with Ig in the current setting, doses are assumed as per the real world data under the assumption that this has no effect on the relative treatment effect of Ig as observed in the trials. This is supported by the similarities in doses used in the studies compared to current practice and that consistency was observed in the treatment effect across the included studies, in spite of variations in dose.	Section D.2 and D.4
	Duration of Ig treatment	Duration of Ig treatment in the included studies was variable. As patients in the Australian Paxton, Hawkins & Crispin (2016) study were not required to have received Ig for a minimum period of time, the treatment duration observed, 26 months, is considered to be most applicable to the current setting and will be assumed in the base case analysis. The economic model in Section D will assume that while on Ig therapy, patients are at risk of infections, however after treatment cessation, it will be assumed that their risk of infections decreases to normal levels (and so no new infections are modelled after such time).	Section D.2

Section	Pre-modelling study	Results used in Section D	Cross-reference
Extrapolation	Duration of treatment effect	Based on the continuing access criteria it is assumed that the direct treatment effect of Ig (reduced infection rate and severity) is maintained for the duration of treatment. No direct treatment effect occurs after this time, but there is a residual difference in survival and quality of life associated with the difference in the proportions of patients in the various health states at the end of the treatment period, between the treatment arms.	Section D.4.1
	Natural history of recurrent infections	There is very little published information regarding the long term consequences of recurrent infections in patients with acquired hypogammaglobulinaemia. One narrative review (Brown, Baxendale & Floto 2011) was identified which described the association of secondary immune deficiencies with bronchiectasis. This study reported that patients with haematological malignancies (particularly MM and CLL) or post-HSCT were relatively commonly associated with bronchiectasis. This is consistent with a recent Australian economic evaluation in this population which modelled the development of bronchiectasis. Therefore, the model structure will include health states associated with bronchiectasis in the base case analysis, however the inclusion of these health states are tested in a sensitivity analysis.	Section D.3
Transformation	Utilities	Utility weights were sourced from the published literature. Utilities reported in a relevant Australian population using the AQoL-6D instrument will be preferentially used in the model presented in Section D. The utilities related to infections were based on an alternative source as the Australian data do not allow for differences in infection severity to be quantified. A disutility is applied per IV infusion, however no disutilities have been assumed due to infusion-related AEs (which were generally mild and manageable).	Section D.4.3

AE = adverse events; AQoL-6D = Assessment of Quality of Life, six dimension; CLL = chronic lymphocytic leukaemia; Ig = immunoglobulin; MM = multiple myeloma; post-HSCT = post- haemopoietic stem cell transplantation.

SECTION D ECONOMIC EVALUATION

D.1. OVERVIEW

The clinical evaluation suggested that in patients with acquired hypogammaglobulinaemia secondary to haematological malignancies, relative to no Ig, Ig has inferior safety and superior effectiveness based on the evidence profile given in Table 29. Table 94, Appendix G, presents 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 present. On this basis, a modelled cost-utility analysis will be presented.

The majority of higher quality evidence was identified in CLL and MM. Use in other haematological malignancies has been based on the principle that a history of infections and presence of hypogammaglobulinaemia is sufficient to warrant treatment. While no evidence was presented to support this use, the conclusion from Section B indicates that the evidence reviewed does not suggest that response to Ig is any more variable in patients with less-studied malignancies compared with CLL and MM.

One economic analysis will be presented across the acquired hypogammaglobulinaemia indications. Given the heterogeneity within each indication, the studies presented in the clinical evidence are likely to be as applicable across the broader acquired hypogammaglobulinaemia indication as they are within each indication (see Section B.8). To further support this approach, contemporary clinical and economic modelling studies generally included patients with mixed haematological malignancies (see also Section D.3). As the purpose of Ig in acquired hypogammaglobulinaemia is to reduce the risk of infection and as the treatment effect of Ig was observed to be consistent across indications with respect to this outcome, this is considered to be a reasonable approach. Scenario analyses are presented determining the cost-effectiveness per indication assuming the best estimates available.

D.2. POPULATIONS AND SETTINGS

Under the Version 3 criteria, Ig is indicated for acquired hypogammaglobulinaemia secondary to haematological malignancies (including acute leukaemia, CLL, MM, NHL and others), or post-HSCT. A comparison of the demographics of the patients in Australia who currently receive Ig across these indications to those in the randomised evidence was presented in Section C.2.1. Patient demographics were generally not well reported. CLL patients in the randomised clinical studies included were on average younger than those receiving Ig in the BloodSTAR database. Further, the majority of the randomised evidence was published in the 1990s. However the treatment effect of Ig seemed relatively consistent across included studies. Contemporary Australian data will be used to

inform baseline infection rates, and the pooled estimates for the treatment effect of Ig from the randomised studies will be used in the base case analysis.

As described in Section C.2.3, doses of Ig in the clinical evidence (0.3 g/kg to 0.8 g/kg) were generally consistent with those used in current Australian practice (0.36−0.38 g/kg). Given that currently there is substantial experience with Ig use, it will be assumed that current dosing is appropriate to achieve the clinical outcome of preventing infections, and so the economic analysis will use actual doses from the BloodSTAR data under the assumption that this has no effect on infection rates as observed in the trials. This is consistent with the Version 3 criteria which state that the aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for the patient.

The majority of randomised studies allowed Ig treatment for a fixed period of time, rather than continuation based on an assessment of treatment response (as per the Version 3 criteria). BloodSTAR data were not available to inform the average treatment duration of patients who currently receive Ig for acquired hypogammaglobulinaemia. The translation study presented in Section C.2.4 concluded that as most patients would be managed on a case-by-case nature, the model will assume an average treatment duration of 26 months, based on Paxton, Hawkins & Crispin (2016). This was the only study conducted in the Australian setting where patients were not required to have received Ig for a minimum period of time, and so is considered to be most applicable to the current setting.

It is unclear what would occur in Australian clinical practice in the absence of Ig, given that it is currently available for acquired hypogammaglobulinaemia and is considered to be the standard of care: a recent survey of Australian clinicians experienced in the care of patients with acquired hypogammaglobulinaemia observed that 93% of clinicians surveyed use IVIg to prevent infections in this population, and 19% use SCIg. Pneumococcal vaccination and prophylactic antibiotics were used by 63% and 21% of clinicians respectively (Wong et al. 2019). As described in Section C.2.2, prophylactic antibiotics were either not allowed in the absence of Ig; or where allowed, use was equal irrespective of Ig use. One small (n = 15) non-randomised before/after study conducted in the UK (Duraisingham et al. 2014) reported a decrease in the use of prophylactic antibiotics after initiation of Ig therapy (from 80% to 67%), with similar relative reductions in infection rates as the studies in which prophylactic antibiotic use was not allowed. This translation study concluded that while the results from the Duraisingham et al. (2014) study are supportive of a benefit of similar magnitude for Ig irrespective of whether prophylactic antibiotics are used in the comparator, due to the inherent biases associated with the small patient numbers and study design, this is not conclusive. The economic analysis therefore assumes no increase in prophylactic antibiotic use relative to that in the Ig arm of the model – and so infection rates reported in the randomised studies apply to the current setting. A scenario analysis based on the results of this study is presented.

D.3. STRUCTURE AND RATIONALE OF THE ECONOMIC EVALUATION

A summary of the key characteristics of the economic evaluation is given in Table 36.

Table 36 Summary of the economic evaluation

Perspective	Australian healthcare
Comparator	No Ig
Type of economic evaluation	Cost-utility and cost-effectiveness analyses
Sources of evidence	Systematic review presented in Section B
Time horizon	10 years
Outcomes	QALYs Infections avoided
Methods used to generate results	Markov model
Health states	Infection-free Infection Bronchiectasis Bronchiectasis, with infection Bronchiectasis, with chronic *Pseudomonas aeruginosa* infection Dead
Cycle length	1 week
Discount rate	5%
Software packages used	Microsoft Excel and TreeAge Pro

Ig = immunoglobulin; QALY = quality-adjusted life year.

LITERATURE REVIEW

A search of the literature was conducted to identify published cost-effectiveness analyses of Ig in acquired hypogammaglobinaemia secondary to haematological malignancies. The terms and databases searched are presented in Table 95, Appendix G. The search retrieved 292 unique studies, of which one was identified that explored the cost-effectiveness of Ig use in CLL (Weeks, Tierney & Weinstein 1991).

Weeks, Tierney & Weinstein (1991)

Weeks, Tierney & Weinstein (1991) published a cost-utility analysis, using a decision-analytic model based on the results of the randomised trial in CLL patients conducted by Gale et al. (1988). The model compared Ig therapy (at 0.4 g/kg of IVIg every three weeks) for one year to no Ig therapy, with no prophylactic antibiotic use allowed. A lifetime time horizon was modelled, where a median life expectancy of 4.2 years was assumed. Gale et al. (1988) reported that Ig use led to a reduction in the number of bacterial infections, but no survival benefit. Assumptions regarding rates of infection subsequent to Ig treatment cessation were not reported. Utilities were derived from 10 oncologists experienced with the care of CLL, and costs (in 1989 USD) related to Ig acquisition, preparation, administration and related to treating infections were included. The resulting ICER was observed to be $6 million per additional QALY gained (incremental cost of $13,984, for incremental QALY gain of

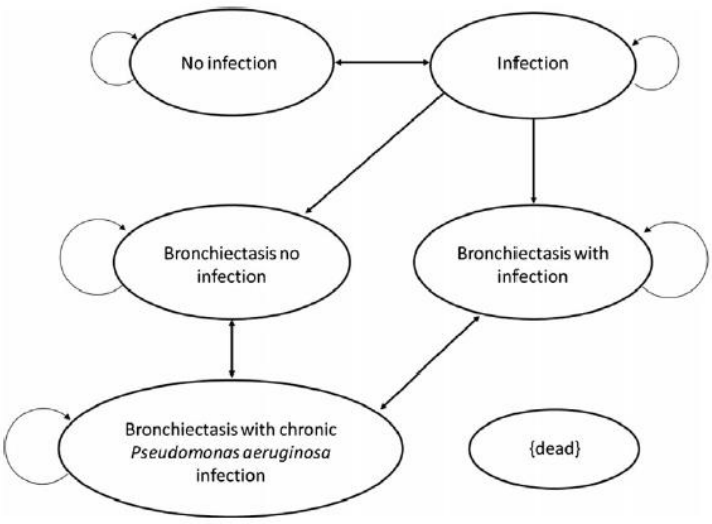
0.0023). The base case analysis did not include disutility due to Ig infusion – Ig treatment was observed to be dominated (i.e. more costly and less effective) if this inconvenience was included.

Windegger et al. (2019)

The search additionally identified a recently published cost-utility analysis conducted in the Australian setting that compared SCIg to IVIg in acquired hypogammaglobulinaemia secondary to malignancy or associated treatment (Windegger et al. 2019). While this study could not be used to answer the question of the cost-effectiveness of Ig relative to no Ig in population of interest, this study could be used to inform the model structure, and, given how recent and relevant the data are to the population of interest, other inputs, such as transition probabilities, costs and utility weights.

The structure of the model and transition probability matrix are replicated below in Figure 8 and Table 37, respectively. A six-health state Markov model was used, which included health states for infection and the development of bronchiectasis and chronic *P. aeruginosa* infection. The model had a 10-year time horizon, with weekly cycles to account for weekly administrations of SCIg. Patients were assumed to remain on Ig treatment until death. The clinical data used to inform the transition probabilities and costs were derived from a cohort of Australian patients (n = 13) who had received at least one year of IVIg followed by one year of SCIg, with limited baseline information provided. No patients died or developed bronchiectasis or *P. aeruginosa* infections during the two year observation period, however four patients had bronchiectasis at the beginning of the observation period. Transition probabilities that could not be informed by the clinical data were supplemented by the published literature. For each health state of interest, utility weights, using the AQoL-6D instrument, were derived from a wider cohort of patients (n = 84), which additionally included those who had only experienced one form of treatment, or who switched to SCIg prior to having 12 months of IVIg.

Figure 8 State transition model used in Windegger et al. (2019)



Source: Fig 1, Windegger et al. (2019).

Table 37 Transition probability matrix used in Windegger et al. (2019)

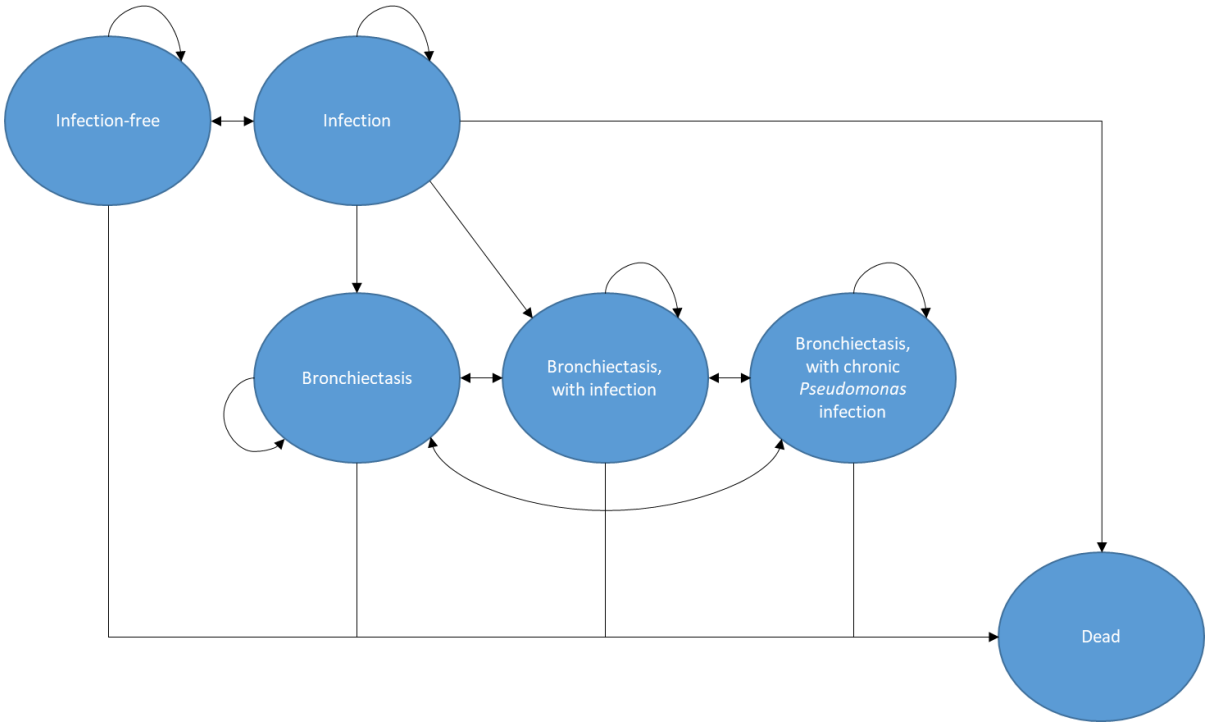
Health states	(1)	(2)	(3)	(4)	(5)	(6) Dead
IVIg						
(1) No infection	0.947	0.053				0.00034
(2) Infection	0.592	0.313	0.063	0.031		0.00142
(3) Bronchiectasis with no infection			0.917	0.05	0.03	0.00311
(4) Bronchiectasis with infection			0.3	0.664	0.033	0.00311
(5) *Pseudomonas aeruginosa* infection			0.182	0.091	0.718	0.00916
SCIg						
(1) No infection	0.956	0.044				0.00034
(2) Infection	0.463	0.486	0.024	0.024		0.00142
(3) Bronchiectasis with no infection			0.924	0.054	0.019	0.00311
(4) Bronchiectasis with infection			0.433	0.5	0.064	0.00311
(5) *Pseudomonas aeruginosa* infection			0.182	0.091	0.718	0.00916

1 = No infection; 2 = Infection; 3 = Bronchiectasis with no infection; 4 = Bronchiectasis with infection; 5 = Bronchiectasis with chronic *Pseudomonas aeruginosa* infection; 6 = dead.
IVIg = intravenous immunoglobulin; SCIg = subcutaneous Ig.
Source: Table A1, Windegger et al. (2019)

STRUCTURE OF THE ECONOMIC EVALUATION

As the studies identified in the search of the economic literature could not answer the question of the cost-effectiveness of Ig relative to no Ig in the contemporary Australian setting, an economic evaluation is presented. As Windegger et al. (2019) provides a model structure that captures the natural history of infections in acquired hypogammaglobulinaemia (see Section C.3.2) in an Australian population, a Markov model with a similar model structure will be used. The six health states modelled include: infection-free, infection, bronchiectasis, bronchiectasis with infection, bronchiectasis with chronic *P. aeruginosa* infection, and dead. The Markov model structure with allowable transitions between health states is depicted in Figure 9. A sensitivity analysis is presented exploring the effect of reducing the number of health states in the model (such as excluding progression to bronchiectasis, which would reflect a similar approach as used in Weeks, Tierney & Weinstein 1991) (see Section D.6).

Figure 9 Markov model structure



Patients with acquired hypogammaglobulinaemia with a history of infections enter the model in the infection-free health state. The model compares scenarios where Ig is available, to that where it is not available. As described in Section C.2.2 and Section D.2, in the model arm where Ig is not available, no prophylactic antibiotic use is assumed. The risk of developing an infection varies depending on whether Ig is available and as such has been informed by the clinical evidence presented in Section B (see also Section D.4).

While subsequent transitions were predominantly based on those reported in Windegger et al. (2019), some were adjusted according to infection severity, and so varied by model arm (see Section D.4.1). As transitions in this study were reported for weekly cycles, a cycle length of one week has also been assumed up to the model time horizon of 10 years (also as per Windegger et al. 2019). The duration of the time horizon is tested in sensitivity analyses (see Section D.6).

D.4. INPUTS TO THE ECONOMIC EVALUATION

D.4.1. TRANSITION PROBABILITIES

Infection rates

Baseline infection rate (i.e. rate with no Ig)

As described in Section C.2.1, infection rates in the absence of Ig modelled will be based on that reported in Paxton, Hawkins & Crispin (2016). This study reported that prior to initiation of Ig therapy, patients experienced 0.43 serious infections per year. However this study did not report the number of non-serious infections experienced. As Ig has been shown to reduce both serious and non-serious infections (see Section B.6), an estimate of the rate of non-serious infections is required.

All of the randomised studies except Chapel et al. (1994b) reported the number of serious and non-serious infections. Only two of the non-randomised studies reported this information (Brenner 1996; Duraisingham et al. 2014). In the study arm where no Ig was used (or before Ig was used in the non-randomised evidence), non-serious infections were observed to occur from half as often to up to six-times more likely (Table 38). The weighted average was estimated to be 2.45. Thus in the base case analysis, the rate of non-serious infections is estimated to be 1.05[15]. Sensitivity analyses are presented to explore the uncertainty associated with this assumption (see Section D.6).

Table 38 Incidence of non-serious to serious infections

Study [N patients]	Number of infections	Ratio of non-serious to serious infections
Chapel et al. (1991) [N = 12]	10 serious, 35 non-serious	3.5 times
Molica et al. (1996) [N = 42]	9 serious, 53 non-serious	5.9 times
Musto, Brugiatelli & Carotenuto (1995) [N = 25]	9 serious, 48 non-serious	5.3 times
Vacca et al. (2018) [N = 46]	190 serious, 143 non-serious	0.75 times
Sullivan et al. (1990) [N = 382]	68 serious, 144 non-serious	2.1 times
Duraisingham et al. (2014) [N = 15]	11 serious, 37 non-serious	3.4 times
Brenner et al. (1996) [N = 21]	21 serious, 11 non-serious	0.5 times

The baseline rate of infection will assume to apply for the duration of Ig treatment, 26 months (see Section C.2.4). While it is possible that, in the absence of Ig, patients would be at risk of infections for a longer duration of time, no evidence was identified to enable this to be quantified. However it is noted that this is may be a conservative approach. Conversely, if patients are being treated with Ig for longer than they are at risk of infections, the ICER may be underestimated.

[15] 0.43 × 2.45

Infection rate with Ig

To estimate the rate of serious and non-serious infections with Ig, the IRRs estimated in Section B.6 are applied to the baseline rates of infection. The base case analysis will assume the IRRs estimated from the pooled randomised studies, with a sensitivity analysis presented using the IRRs based on the non-randomised studies (see Section D.6).

Table 39 Relative treatment effect of Ig

	IRR for serious infections (95% CI)	IRR for non-serious infections (95% CI)
Pooled randomised studies	0.15 (0.05, 0.43)	0.61 (0.51, 0.72)
Pooled non-randomised studies	0.25 (0.15, 0.43)	0.46 (0.29, 0.74)

Ig = immunoglobulin; IRR = incidence rate ratio.

Applying these IRRs to the baseline rates of infection described above, the annual rate of serious and non-serious infections with Ig is estimated to be 0.06[16] and 0.64[17], respectively.

Duration of infection

The probability of infection resolution is estimated to vary by model arm, as recovery from an infection is likely to vary depending on the severity of the infection. The average duration of infection is estimated in Table 40.

Table 40 Average duration of infection by model arm

	Ig	No Ig
Proportion of serious infections	0.06/0.70 (8.9%)	0.43/1.48 (29.0%)
Average duration of non-serious infections	1 cycle	1 cycle
Average duration of serious infections	2 cycles	2 cycles
Average duration of infections	1.1 cycles	1.3 cycles

Ig = immunoglobulin.

A gamma distribution was then fitted to these data to estimate the per-cycle probability of infection resolution (Table 41). A gamma distribution was chosen as it is constrained from zero to positive infinity.

Table 41 Per cycle probability of infection resolution in patients who had not died or developed bronchiectasis

	Proportion resolved [a]		Per cycle probability of resolution [b]	
	Ig	No Ig	Ig	No Ig
Cycle 1	0.5938	0.5097	59.4%	51.0%

[16] 0.43 × 0.15

[17] 1.05 × 0.61

	Proportion resolved [a]		Per cycle probability of resolution [b]	
	Ig	No Ig	Ig	No Ig
Cycle 2	0.8444	0.7948	61.7%	58.2%
Cycle 3	0.9412	0.9176	62.2%	59.9%
Cycle 4	0.9779	0.9676	62.4%	60.7%
Cycle 5	0.9917	0.9874	62.6%	61.2%
Cycle 6	0.9969	0.9952	62.7%	61.5%
Cycle 7	0.9989	0.9981	62.8%	61.7%
Cycle 8	0.9996	0.9993	62.8%	61.9%
Cycle 9	0.9998	0.9997	62.9%	62.1%
Cycle 10	0.9999	0.9999	62.9%	62.2%
Cycle 11	1.0000	1.0000	62.9%	62.3%

[a] Gamma distributions assuming the alpha parameter is equal to the average duration of infection, estimated in Table 40 above, and that the beta parameter equals 1.
[b] Calculated as the proportion resolved at t minus the proportion resolved at t−1, divided by 1 minus the proportion resolved at t−1, e.g. in cycle 2 in the Ig model arm, (0.84 – 0.59)/(1 − 0.59).
Ig = immunoglobulin.

In Section D.6, a sensitivity analysis is presented using the transition probability from the IVIg arm of Windegger et al. (2019) for both model arms (59.2%), however this is considered to underestimate the cost-effectiveness of Ig as infections tended to be less severe. Different per-cycle probabilities of infection resolution are considered to be more reasonable.

Transitions from the infection health state

Aside from infection resolution, other transitions from the infection health state include those to the bronchiectasis, bronchiectasis with infection and dead health states. As the per-cycle probabilities of resolution vary according to time in the health state (Table 41), these other transitions have been adjusted to maintain the same relative proportions per cycle (see Table 37). The relative weight of these other transitions were assumed as per Windegger et al. (2019): 76.6% for remaining in the infection state, 15.4% transitioning to the bronchiectasis health state, 7.6% to bronchiectasis with infection health state and 0.3% to dead.

Table 42 Remaining transition probabilities from the infection health state

	Ig				No Ig			
	I_I (76.6%)	I_B (15.4%)	I_BI (7.6%)	I_D (0.3%)	I_I (76.6%)	I_B (15.4%)	I_BI (7.6%)	I_D (0.3%)
Cycle 1	31.1%	6.3%	3.1%	0.1%	37.6%	7.6%	3.7%	0.2%
Cycle 2	29.4%	5.9%	2.9%	0.1%	32.1%	6.5%	3.2%	0.1%
Cycle 3	29.0%	5.8%	2.9%	0.1%	30.8%	6.2%	3.0%	0.1%
Cycle 4	28.8%	5.8%	2.9%	0.1%	30.1%	6.1%	3.0%	0.1%
Cycle 5	28.7%	5.8%	2.8%	0.1%	29.8%	6.0%	2.9%	0.1%
Cycle 6	28.6%	5.8%	2.8%	0.1%	29.5%	5.9%	2.9%	0.1%
Cycle 7	28.5%	5.7%	2.8%	0.1%	29.3%	5.9%	2.9%	0.1%
Cycle 8	28.5%	5.7%	2.8%	0.1%	29.2%	5.9%	2.9%	0.1%

	Ig				No Ig			
	I_I (76.6%)	I_B (15.4%)	I_BI (7.6%)	I_D (0.3%)	I_I (76.6%)	I_B (15.4%)	I_BI (7.6%)	I_D (0.3%)
Cycle 9	28.5%	5.7%	2.8%	0.1%	29.1%	5.9%	2.9%	0.1%
Cycle 10	28.4%	5.7%	2.8%	0.1%	29.0%	5.8%	2.9%	0.1%
Cycle 11	28.4%	5.7%	2.8%	0.1%	28.9%	5.8%	2.9%	0.1%

Note: Transitions were calculated by applying the relative proportion by 1 minus the per cycle probability of resolution reported in Table 41.
I_B = transition from infection to bronchiectasis health state; I_BI = transition from infection to bronchiectasis with infection health state; I_D = transition from infection to dead health state; Ig = immunoglobulin; I_I = proportion remaining in the infection health state.

A sensitivity analysis is presented assuming no adjustment to the Windegger et al. (2019) transition probabilities, and so the same transitions would apply in both model arms (Section D.6).

Transition probabilities related to bronchiectasis

Developing infections in bronchiectasis

Patients in the bronchiectasis health state are at-risk of developing infections, including chronic *P. aeruginosa* infections. The transition probabilities reported in Windegger et al. (2019) for patients on IVIg treatment are assumed to apply to the model arm where Ig is available (as the majority of current use is by IV). However Ig treatment is assumed to continue to reduce the risk of such infections in patients with bronchiectasis. Though not well reported, some studies in Section B did include patients with bronchiectasis (e.g. 4/15 patients in Duraisingham et al. 2014 had bronchiectasis). In the absence of evidence to suggest that Ig would have a different treatment effect in patients with bronchiectasis, the IRRs presented in Table 39 are applied to adjust the transition probabilities reported in Windegger et al. (2019) to the model arm where no Ig is available. Assuming that 12.5% of infections with bronchiectasis are serious (as per Windegger et al. 2019), the weighted risk reduction using the IRRs estimated from the meta-analyses presented in Section B is 0.552. The adjusted transitions are presented in Table 43.

Table 43 Adjusted transition probabilities of developing infections in bronchiectasis

	pB_BI	pB_P
Probability reported in Windegger et al. (2019) (applicable to Ig model arm)	5.0%	3.0%
Ig rate	2.667	1.584
No Ig rate (i.e. Ig rate / weighted IRR, 0.552)	4.832	2.869
No Ig adjusted transition probability	8.9%	5.4%

Ig = immunoglobulin; pB_BI = probability of transitioning from the bronchiectasis to the bronchiectasis with infection health state; IRR = incidence rate ratio; pB_P = probability of transitioning from the bronchiectasis to the bronchiectasis with chronic *P. aeruginosa* infection health state.

A sensitivity analysis will be presented assuming no adjustment to the Windegger et al. (2019) transition probabilities, and so the same transitions would apply in both model arms (Section D.6).

Other transitions between non-dead health states

Transitions within the bronchiectasis health state with infection and with chronic *P. aeruginosa* infection health states are assumed as per Windegger et al. (2019), and so have been assumed to be the same across model arms.

Mortality

The sources of data to model increased risk of death in each of the health state are consistent with those applied in Windegger et al. (2019).In the infection-free health state, an increased mortality risk of 2.55 times that of the general Australian population has been applied. This was based on the increased risk of mortality in CLL patients, relative to the general Australian population, reported in Royle et al. (2011). Visentin et al. (2015) did report that patients with a history of major infections had a 2.34 increased risk of death, however as increased mortality with infection health states has been modelled separately, this has not been included in the base case analysis as it may double-count mortality risk due to infections. The inclusion of this additional risk in the infection-free health state has been tested in a sensitivity analysis.

In the bronchiectasis health state, a 2.20 increased risk of death has been applied to the mortality rates estimated for the infection-free health state, based on the increased risk reported in Quint et al. (2016). With infections, a 4.18 increase in the risk of death has been assumed, which has been estimated from Windegger et al. (2019), derived from the relative increase in death in the infection health state compared to the infection-free health state. The basis for this increased risk of death was not clear, and will be tested in sensitivity analyses.

An increased risk of death with chronic *P. aeruginosa* infection will be assumed based on Finch et al. (2015), which reported increased odds of death with *P. aeruginosa* infection, relative to bronchiectasis without *P. aeruginosa* infection of 2.95. Using this OR and assuming a 12% mortality at five years, the RR is estimated to be 2.39.

Summary matrix of transition probabilities

A summary of the transition probabilities used in the model is depicted in Table 44.

Table 44 Transition probability matrix

From/To	IF	I	B	BI	P	Dead
Ig						
IF	#	1.3% [a]				varies [b]
I	Cycle 1: 59.4% … Cycle 11: 62.9%	#	Cycle 1: 6.3% … Cycle 11: 5.7%	Cycle 1: 3.1% … Cycle 11: 2.8%		Cycle 1: 0.1% … Cycle 11: 0.1%
B			#	5.0%	3.0%	varies [b]
BI			30.0%	#	3.3%	varies [b]
P			18.2%	9.1%	#	varies [b]
No Ig						
IF	#	2.8% [a]				varies [b]
I	Cycle 1: 51.0% … Cycle 11: 62.3%	#	Cycle 1: 7.6% … Cycle 11: 5.8%	Cycle 1: 3.7% … Cycle 11: 2.9%		Cycle 1: 0.2% … Cycle 11: 0.1%
B			#	8.9%	5.4%	varies [b]
BI			30.0%	#	3.3%	varies [b]
P			18.2%	9.1%	#	varies [b]

Note: shaded cells depict transitions that are not allowed.
B = bronchiectasis health state; BI = bronchiectasis with infection health state; I = infection health state; IF =infection-free health state; Ig = immunoglobulin; P = Bronchiectasis with chronic *Pseudomonas aeruginosa* infection health state # = the proportion that remain in that health state after considering all other allowable transitions.
[a] risk of infection is modelled only for the duration that patients would have received Ig therapy
[b] Transition probabilities vary by age

D.4.2. RESOURCE USE

Cost of Ig

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) (see also Table 96, Appendix G). Analyses will be presented assuming:

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

These costs were also provided by the Applicant and were derived from the 2017/18 National Report on the issue and use of Ig in Australia (NBA 2019b). While there are slight variations between the

prices per gram used in the model to that published on the NBA website (e.g. domestic IVIg has a current published price per gram of $58.23 as of July 1 2019), as all costs (including that of plasma fractionation) could be sourced from the same year, for consistency the prices retrospectively estimated from the NBA report are used. A sensitivity analysis will be presented using the current published price of domestic IVIg.

As dosing for Ig is weight based, an average patient weight of 75 kg has been assumed (based on Table 30, Section C.2.1) and the average dose assumed is 0.37 g/kg (as per Section C.2.3). The estimated Ig cost per IVIg infusion is therefore estimated to be $1,671. The dose frequency modelled is assumed to be every four weeks and so the average cost per cycle of Ig is $417.81.

Other costs associated with Ig treatment include the cost of consumables (including syringes, needles, cannula, infusion lines and alcohol wipes) and ward costs (including the use of a treatment chair and nursing supervision during Ig infusion). Per infusion, the costs of consumables have been estimated to be $21.41 and the administration costs, $232.01. These have been derived from the weekly costs reported in Windegger et al. (2019), in which IV infusions were performed monthly.[18] The total per-cycle costs related to Ig treatment and administration are presented in Table 45.

Table 45 Cost per cycle of Ig

	Cost	Source
Cost of Ig	$417.81	Calculated [a]
Consumables	$5.35	Windegger et al. (2019) [b]
Administration costs	$58.00	Windegger et al. (2019) [b]
Total cost of Ig per week	**$476.29**	

Ig = immunoglobulin.

[a] Calculated assuming patient is 75.0kg and receives a 0.37 g/kg dose every 4 weeks, at a cost of $60.41 per gram.

[b] Costs reported in Windegger et al. (2019) have been adjusted for infusion frequency, as this study reported monthly infusions, compared to the base case analysis, which assumes infusions every four weeks.

These costs are assumed to apply for up to 26 months based on the median treatment duration reported in Paxton, Hawkins & Crispin (2016) (see Section C.2.4 for further information), whilst patients are in the infection-free or infection health states. However if patients develop

[18] This costing approach varies from the approach used in MSAC Application 1566, where a published Australian source could not be identified for IVIg in the context of myasthenia gravis. Given the dose of IVIg used preoperatively and for maintenance in myasthenia gravis is substantially higher than in acquired hypogammaglobulinaemia (up to 1 g/kg compared to 0.4 g/kg), it is expected to incur significantly longer chair and nursing supervision times and therefore the estimated administration cost in that Application was $461, based on Service 10.13 using the National Weighted Activity Unit calculator. Despite the different approach, administration costs appear reasonably consistent given expected differences with administration times.

bronchiectasis while on Ig therapy, as transition probabilities have been adjusted to account for Ig use (see Section D.4.1), the cost of Ig will continue to apply. This approach is somewhat different to Windegger et al. (2019) which assumed continued Ig use through the 10 year time horizon, in all health states including infection-free. A sensitivity analysis is presented excluding the cost of Ig from the bronchiectasis health states, and as such, assuming no benefit of Ig with regards to preventing infections in the bronchiectasis health state.

Ongoing disease management costs

Other costs associated with the management of patients with acquired hypogammaglobulinaemia who are at-risk of infections are reported in Table 46. These costs are assumed to apply equally to both model arms. Costs included two haematologist visits per year and a test to monitor IgG trough levels. These costs have been based on the relevant MBS item numbers (MBS items 110 and 71068, respectively) and are assumed to apply while patients are considered to be at-risk of infections (i.e. up to 26 months in the infection-free health state and ongoing if bronchiectasis had developed).

The cost of professional attendances were slightly lower than modelled in Windegger et al. (2019) ($6.84), while pathology test costs were substantially lower than in the published analysis, $6.00, which may have assumed more frequent monitoring of IgG trough levels and also included costs to screen for infections. As infection screening tests have been included in the cost of treating infections, and no guidelines were identified that supported routine infection screening, these costs have not been included in the disease management costs. A sensitivity analysis will be presented using the costs from Windegger et al. (2019).

Table 46 Ongoing disease management costs included in the model

	Cost	Source
Haematologist consult fee (two per year)	$5.98	MBS item 110
Monitoring of serum IgG trough levels	$0.28	MBS item 71068
Cost per week	**$6.26**	

Ig = immunoglobulin

Costs associated with treating infections

The clinical studies included in Section B reported infections by severity – serious infections which generally required hospitalisation, and non-serious infections, which did not require hospitalisation. The cost of treating a serious infection in Windegger et al. (2019) was $6,927. During the Assessment process, the Ig Review Group considered that this cost was likely an underestimate of the cost and resource use associated with treating the various types of serious infections that patients were vulnerable to.

Weeks, Tierney & Weinstein (1991) reported resource utilisation by infection severity. Major infections required hospitalisation and a follow-up outpatient attendance. Thus the cost of treating a serious infection was estimated to be $12,775, based on the weighted average of treating a range of infection types of major complexity (see Table 47). The total cost of treating a serious infection, including a follow-up outpatient attendance, was estimated to be $12,852 (Table 48). Alternate costs will be tested in sensitivity analyses.

Table 47 Average cost to treat a serious infection

		Separations		
DRG	**DRG Description**	**No.**	**weight**	**Total cost**
T60A	Septicaemia, Major Complexity	8,218	13.8%	$25,381
R01A	Lymphoma and Leukaemia W Major GIs, Major Complexity	455	0.8%	$52,961
I64A	Osteomyelitis, Major Complexity	2,126	3.6%	$18,269
I67A	Septic Arthritis, Major Complexity	709	1.2%	$15,261
E62A	Respiratory Infections and Inflammations, Major Complexity	48,076	80.7%	$9,961
Weighted				**$12,775**

Source: National Hospital Cost Data Collection, Cost Weights for AR-DRG Version 9.0, Round 21 (2016-17) Public Sector - Estimated National (IHPA 2019).

In Weeks, Tierney & Weinstein (1991), moderate infections required two outpatient attendances, a 10-day treatment course of antibiotics and a range of tests including urinalysis, urine, blood and sputum culture, complete blood count and a chest x-ray, while trivial infections required one outpatient attendance. Outpatient attendances by GPs were assumed for moderate and trivial infections (as per Windegger et al. 2019). Using the applicable MBS and PBS items, the cost of treating a non-serious infection was estimated to be $184 (Table 48) and assumed that approximately two-thirds of non-serious infections were of moderate severity, based on Weeks, Tierney & Weinstein (1991). This was similar to the cost modelled in Windegger et al. (2019) ($160). The alternate costs will be tested in a sensitivity analysis.

Table 48 Estimated cost of treating infections, by infection severity

	Cost	**Source**
Serious infections		
- Hospitalisation	$12,775	Weighted average cost of T60A, R01A, I64A, I67A and E62A AR-DRGs (IHPA 2019) – see also Table 47.
- Follow-up outpatient attendance	$76.65	MBS item 116
Total cost of treating serious infections	$12,852	
Non-serious moderate infections		
- Two outpatient attendances	$76.40	MBS item 23
- Urinalysis	$4.55	MBS item 73805
- Urine culture	$20.55	MBS item 69333
- Blood culture	$30.75	MBS item 69354
- Sputum culture	$33.75	MBS item 69318
- Complete blood count	$16.95	MBS item 65070

	Cost	Source
- Chest x-ray	$47.15	MBS item 58503
- 10-day antibiotic course	$26.72	PBS item 2951H
Total cost of treating moderate infections	$412.67	
Cost of treating trivial infections	$38.20	MBS item 23
Weighted cost of treating non-serious infections	$183.95	Based on weighting of infections as reported in Weeks, Tierney & Weinstein (1991) (67% moderate)

As infection severity varies with or without Ig so too will the overall cost of treating infections. Infection severity by model arm has previously been described in Section D.4.1, thus the overall cost of treating infections with Ig is estimated to be $1,313 and without Ig, $3,861 (Table 49). This cost is applied on the transition from the infection-free to infection health state.

Table 49 Average cost of treating infections by model arm

	Ig	No Ig	Source
Proportion of serious infections	8.9%	29.0%	Table 40
Cost to treat a serious infection	$12,852.05	$12,852.05	Table 48
Proportion of non-serious infections	91.1%	71.0%	
Cost to treat a non-serious infection	$183.95	$183.95	Table 48
Average cost per infection	**$1,313.44**	**$3,861.10**	

Ig = immunoglobulin

Costs associated with bronchiectasis

Costs associated with the management of bronchiectasis are reported in Table 50, and were based on those reported in Windegger et al. (2019). These include additional attendances, respiratory function tests and imaging. Disease management costs for patients at-risk of infections have also been included in the cost per cycle of this health state.

Table 50 Cost associated with the management of bronchiectasis

	Cost	Source
Respiratory consult fee	$8.95	Windegger et al. (2019)
Respiratory function test (including ward costs)	$18.07	Windegger et al. (2019)
Imaging tests	$5.63	Windegger et al. (2019)
Disease management costs	$6.26	Table 46
Cost per week of treating bronchiectasis	**$38.91**	

Infections with bronchiectasis

The resource utilisation of treating infections with bronchiectasis has been estimated using a similar approach as for infections without bronchiectasis, and assumes the cost of hospitalisation (based on

the weighted relevant AR-DRG costs) and a follow-up outpatient attendance. The estimated cost per serious infection is estimated to be $9,143. This is lightly lower than the cost modelled in Windegger et al. (2019), $9,580, and the alternate cost will be tested in a sensitivity analysis. No difference in resource utilisation, and so cost, has been assumed for the treatment of non-serious infections.

The model presented will assume that the cost of treating infections in the bronchiectasis health state will be the same irrespective of model arm and that the proportion of serious infections is as reported in Windegger et al. (2019) (i.e. 12.5%). Thus the average cost of treating an infection with bronchiectasis is estimated to be $1,360. This is applied on the transition between the bronchiectasis and the bronchiectasis with infection health states.

Table 51 Average cost of treating infections by model arm

Cost associated with treating infections	Cost	Source
Proportion of serious infections	12.5%	Windegger et al. (2019)
Cost to treat a serious infection		
- Hospitalisation	$9,066	Average weighted cost per E77A and B AR-DRG (IHPA 2019)
- Follow-up outpatient attendance	$77	MBS item 116
Total cost	$9,143	
Cost to treat a non-serious infection	$183.95	Table 48
Average cost per infection with bronchiectasis	**$1,303.83**	

Costs associated with chronic P. aeruginosa infection

The model presented in Windegger et al. (2019) did not quantify resource use with the chronic *P. aeruginosa* infection health state and assumed the same cost as for the bronchiectasis with infection. Blanchette et al. (2017) compared resource utilisation in a US population in patients with non-cystic fibrosis bronchiectasis 12-months before and after a diagnosis of *P. aeruginosa* infection. This study observed a significant increase in the number of hospitalisations (from 3.45 to 7.44), ER attendances (from 0.53 to 0.98) and outpatient physician attendances (from 16.33 to 27.11) in the year after *P. aeruginosa* diagnosis. Assuming annual resource utilisation as per this study and applying local costs, the estimated cost per cycle is estimated to be $1,322 (Table 52). This is slightly lower than the cost modelled in Windegger et al. (2019) for this health state when the cost of Ig is excluded ($1,370). This alternate cost will be tested in a sensitivity analysis.

Table 52 Cost per cycle in the chronic *P. aeruginosa* infection health state

	Annual resource use and cost	Source
Hospital admissions	7.44	Blanchette et al. (2017)
Cost per admission	$9,066	Average weighted cost per E77A and B AR-DRG (IHPA 2019)
Cost of hospital admissions with chronic *P. aeruginosa* infection	$67,454	

	Annual resource use and cost	Source
ED visits	0.98	Blanchette et al. (2017)
Cost per ED visit	$533	Average cost per non-admitted ED presentation (IHPA 2019)
Cost of ED visits with chronic *P. aeruginosa* infection	$522	
Increase in annual outpatient physician attendances	166%	Blanchette et al. (2017)
Annual cost of physician attendances with bronchiectasis	$465	Annual cost of respiratory consultant (based on Table 50)
Cost of physician visits with chronic *P. aeruginosa* infection	$773	
Total annual cost	$68,749	
Total cost per week	**$1,322**	

ED = emergency department; NHCDC = Nation Hospital Cost Data Collection.

Summary of health state costs

The weekly cost per cycle in each model health state are summarised in Table 53.

Table 53 Health state costs per cycle

	Ig	No Ig
Infection-free	$487.43	$6.26
Infection (applied only on transition to health state)	$1,313.44	$3,861.10
Bronchiectasis	$520.08	$38.91
Bronchiectasis with infection (applied only on transition to health state)	$1,303.83	$1,303.83
Bronchiectasis with chronic *P. aeruginosa* infection	$1,842.16	$1,361.00

Ig = immunoglobulin.

D.4.3. UTILITY WEIGHTS

A premodelling study was presented in Section C.4.1 to identify relevant utility weights for use in the economic model. A summary of the utility weights used is presented in Table 54.

Table 54 Utility weights used in the economic evaluation

	Ig	No Ig
Utility in infection-free, including IV infusions	0.7073	0.7148
Utility with infection	0.5805	0.5532
Utility of bronchiectasis	0.6392	0.6392
Utility of bronchiectasis with infection	0.5355	0.5355
Utility of Bronchiectasis with chronic *Pseudomonas aeruginosa* infection	0.5355	0.5355

Ig = immunoglobulin; IV = intravenous.

D.5. RESULTS OF THE ECONOMIC EVALUATION

D.5.1. STEPPED ECONOMIC EVALUATION

A stepped economic evaluation will be presented. A summary of each of the steps is presented below:

- Step 1: Trial-based analysis. This step will apply the dose, dose frequency, relative infection rates, trial time horizon and Ig treatment duration from the Chapel et al. (1994b) trial. This study was selected on the basis that, of the randomised studies, this study had the most patient years of data and used a dose that was most consistent with those recommended in the Version 3 criteria.

- Step 2: Trial-based analysis, extrapolated. The second step of the model will continue to apply the trial doses, dose frequency and relative infection rates as reported in the Chapel et al. (1994b) trial. However the time horizon is extrapolated to 10 years and the model allows for the development of bronchiectasis. Ig treatment duration is estimated based on Paxton, Hawkins & Crispin (2016).

- Step 3: Modelled base case analysis. The final step of the analysis models the benefit of Ig relative to no Ig based on the pooled IRRs estimated in Section B.6, assuming baseline infection rates from Paxton, Hawkins & Crispin (2016). The dose of Ig modelled is that of the weighted average dose estimated from 2017/18 BloodSTAR data, with a dose frequency of every four weeks assumed.

The results of the stepped analysis is presented in Table 55.

Table 55 Results of the stepped economic analysis

	Inc. cost	Inc. QALYs	ICER
Step 1 – Trial-based analysis. Applies the dose (0.4 g/kg), dose frequency (q4w), infection rates, time horizon (1 year) and Ig treatment duration (1 year) as per the Chapel et al. (1994b) study.[a]	$22,734	–0.0035	Dominated [b]
Step 2 – Trial-based, extrapolated analysis Applies the dose, dose frequency and infection rates from the Chapel et al. (1994b) study, with the model time horizon extrapolated to 10 years, with the development of bronchiectasis to be modelled. Ig treatment duration is based on Paxton, Hawkins & Crispin (2016) (26 months).	$66,922	0.2556	$261,789
Step 3 – Modelled economic evaluation Applies the pooled IRRs estimated in Section B.6 to the best available source of baseline infection rates in Australia (based on Paxton, Hawkins & Crispin 2016), while assuming the weighted average dose from BloodSTAR data (0.37 g/kg).	**$41,011**	**0.4109**	**$99,803**

ICER = incremental cost-effectiveness ratio; Ig = immunoglobulin; IRR = incidence rate ratio; QALY = quality-adjusted life years.

[a] This study was chosen on the basis that, of the randomised studies, this study had the most patient years of data and used a dose that was most consistent with those recommended in the Version 3 criteria.

[b] Ig is more costly and less effective than the comparator.

In Step 1 of the analysis the ICER of Ig is observed to be dominated, with a net reduction in QALYs resulting from the inclusion of a disutility per IV infusion. In Step 2, the time horizon is extrapolated to 10 years and allows for the development of bronchiectasis which leads to a substantial improvement in the ICER. Further improvements in the ICER are observed when the best estimates of baseline infection rates, Ig treatment effect and dose are included in the modelling.

D.5.2. MODELLED BASE CASE ANALYSIS

Disaggregated costs and outcomes

The costs and outcomes disaggregated for the base case analysis are presented in Table 56 and Table 57.

Table 56 Disaggregated costs

	Ig	No Ig	Incremental cost
Ig	$66,565	$0	$66,565
Antibiotic prophylaxis	$0	$0	$0
Disease management	$596	$519	$77
Infections	$1,659	$8,668	–$7,009
Bronchiectasis	$1,680	$3,528	–$1,848
Infections in bronchiectasis	$2,136	$6,713	–$4,577
Bronchiectasis with chronic *P. aeruginosa*	$5,638	$17,835	–$12,197
Total cost	**$78,273**	**$37,262**	**$41,011**

Ig = immunoglobulin.

The cost of Ig was the main driver of the incremental cost, with offsets related to a reduction in the number of infections and costs associated with managing chronic *P. aeruginosa* infections.

Table 57 Disaggregated LYs and QALYs

	Ig	No Ig	Increment
Life-years gained			
Infection-free LYs	5.8997	4.5297	1.3700
Infection LYs	0.0349	0.0668	–0.0319
Bronchiectasis LYs	0.6303	1.1162	–0.4859
Bronchiectasis with infection LYs	0.1177	0.3676	–0.2500
Bronchiectasis with chronic *P. aeruginosa* LYs	0.0820	0.2594	–0.1774
Total LYs	**6.7646**	**6.3398**	**0.4248**
QALYs gained			
Infection-free QALYs	4.2035	3.2377	0.9658
Infection QALYs	0.0215	0.0369	–0.0154
Bronchiectasis QALYs	0.4029	0.7135	–0.3106
Bronchiectasis with infection QALYs	0.0630	0.1969	–0.1338
Bronchiectasis with chronic *P. aeruginosa* QALYs	0.0439	0.1389	–0.0950

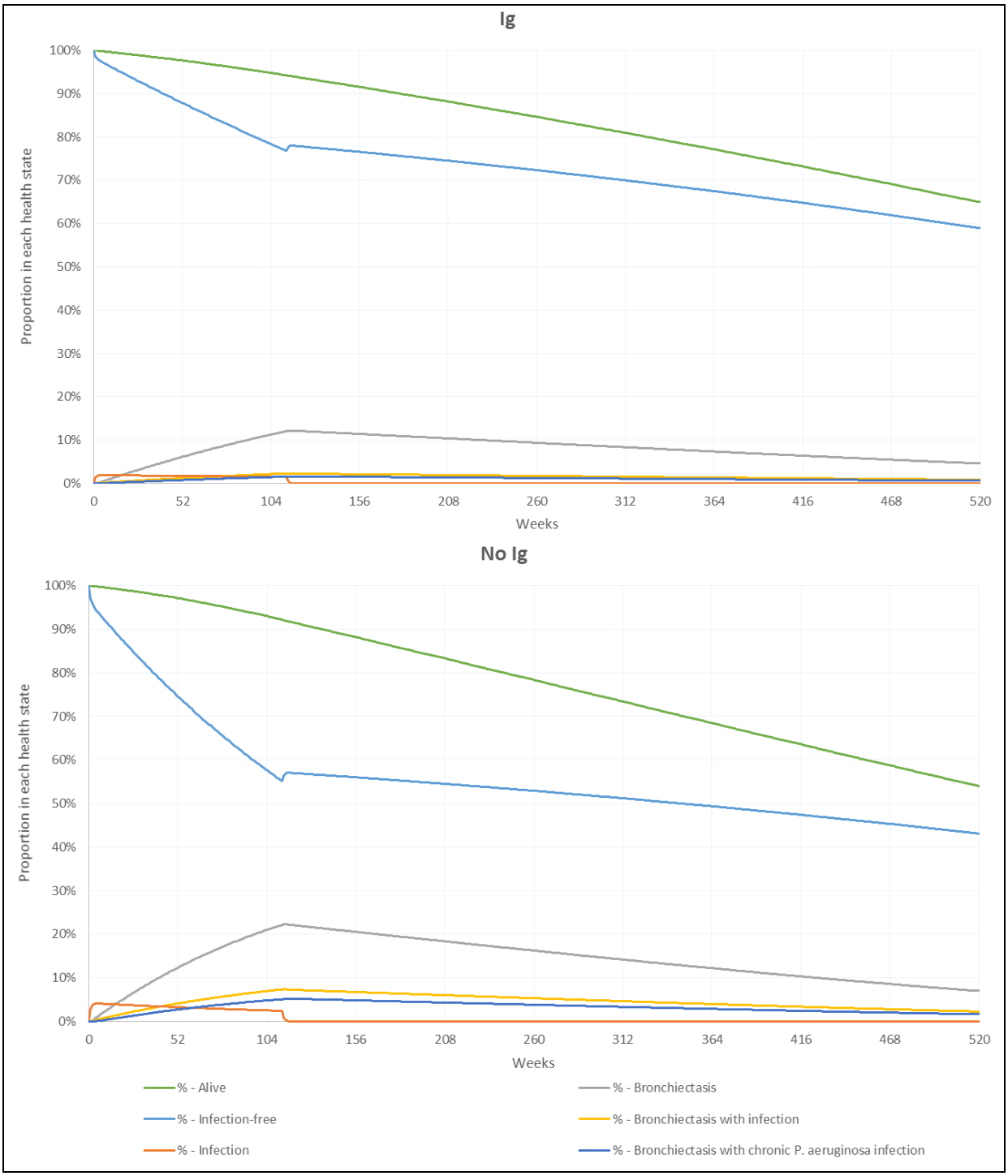
	Ig	No Ig	Increment
Total QALYs	**4.7349**	**4.3239**	**0.4109**
Number of infections			
No. infections, without bronchiectasis	1.26	2.24	–0.98
No. infections, with bronchiectasis	1.64	5.15	–3.51
Number of infections	**2.90**	**7.39**	**–4.49**
Development of chronic *P. aeruginosa*	1.18	3.75	–2.56

Ig = immunoglobulin; LY = life years; QALY = quality-adjusted life years.

The incremental QALYs were primarily accrued in the infection-free health state. As Ig was associated with fewer infections of lower severity, less time was spent in the infection health state with Ig and patients had a lower risk of developing bronchiectasis and subsequent health states.

Markov traces depicting health state membership over time are presented in Figure 10.

Figure 10 Markov model traces



Ig = immunoglobulin.

Incremental cost-effectiveness

The ICERs per additional QALYs gained and per infection avoided are presented in Table 58.

Table 58 Incremental cost-effectiveness ratios

	Ig	No Ig	Increment
Total cost	$78,273	$37,262	$41,011
Total QALYs	4.7349	4.3239	0.4109
ICER per additional QALY gained			**$99,803**
Number of infections	2.90	7.39	–4.49
ICER per infection avoided			**$9,128**

ICER = incremental cost-effectiveness ratio; Ig = immunoglobulin; QALY = quality-adjusted life years.

D.6. SENSITIVITY ANALYSES

D.6.1. COST PER GRAM OF IG

Sensitivity analyses (Table 59) are presented applying differing assumptions regarding the cost of Ig modelled.

Table 59 Scenario analyses regarding the cost of Ig

	Inc. cost	Inc. QALYs	ICER
Base case analysis ($60.41)	**$41,011**	**0.4109**	**$99,803**
High cost of Ig ($140.18)	$117,335	0.4109	$285,543
Low cost of Ig ($44.94)	$26,209	0.4109	$63,782
Weighted average cost of Ig ($94.51)	$73,634	0.4109	$179,195

ICER = incremental cost-effectiveness ratio; Ig = immunoglobulin; QALY = quality-adjusted life years.

D.6.2. SCENARIO BASED ON THE STUDY WHICH INCLUDED ANTIBIOTIC PROPHYLAXIS

As described in Section C.2.2, it is uncertain whether rates of antibiotic prophylaxis would increase in the absence of Ig (given that randomised trials, including one contemporary trial, did not allow antibiotic prophylaxis in the absence of Ig). In the case that rates did increase in the absence of Ig, it is uncertain what effect this would have on the relative treatment effect of Ig, given that this comparison is currently being explored. One non-randomised study was identified that did observe a decrease in prophylactic antibiotic use after Ig initiation (Duraisingham et al. 2014), and so scenario analyses are presented based on the results of this study (Table 60).

Table 60 Scenario analyses based on the study which included antibiotic prophylaxis

	Inc. cost	Inc. QALYs	ICER
Base case analysis	**$41,011**	**0.4109**	**$99,803**
Duraisingham et al. (2014) (trial based dose, 0.53 g/kg)	$82,843	0.5315	$155,864
Duraisingham et al. (2014) (base case dose, 0.37 g/kg)	$51,221	0.5315	$96,369

ICER = incremental cost-effectiveness ratio; Ig = immunoglobulin; QALY = quality-adjusted life years.

A substantial increase in the ICER is observed relative to the base case analysis. This is predominantly driven by a higher dose of Ig used (0.53 g/kg). When the dose is decreased to the weighted average (0.37 g/kg), a moderate reduction in the ICER relative to the base case analysis is observed (Table 60).

D.6.3. SCENARIOS BASED ON THE BEST ESTIMATES OF ANALYSIS FOR SPECIFIC INDICATIONS

Scenario analyses are presented using the best estimates of model inputs specific to each indication (Table 61). Disaggregated events (i.e. infections and development of chronic *P. aeruginosa* infections) are also depicted in Table 62. Given that there was not data to inform all model inputs specifically by indication, these are indicative results only, and should be interpreted with caution. No studies were available to enable an estimate for the 'other haematological malignancies' indication.

Table 61 Scenario analyses estimating indicative cost-effectiveness per indication

	Cost			LYs			QALYs			ICER /QALY (Low – High cost)
	Ig	No Ig	Inc.	Ig	No Ig	Inc.	Ig	No Ig	Inc.	
Base case analysis Assumes the average patient demographics (age: 66, weight: 75.0 kg) and dose (0.37 g/kg) from BloodSTAR data for acquired hypogammaglobulinaemia patients overall. The treatment effect of Ig is based on the pooled IRRs (IRR_S = 0.146, IRR_{NS} = 0.61).	**$78,273**	**$37,262**	**$41,011**	**6.76**	**6.34**	**0.42**	**4.73**	**4.32**	**0.41**	**$99,803** ($63,782 − $285,543)
CLL Assumes the average patient demographics (age: 72, weight: 77.3 kg) and dose (0.37 g/kg) from BloodSTAR data for this indication. Baseline infection rates and mortality rates are unchanged from the base case analysis and the treatment effect of Ig is based on the pooled IRRs for CLL (IRR_S = 0.38, IRR_{NS} = 0.69).	$81,220	$28,345	$52,875	5.91	5.52	0.39	4.12	3.79	0.33	$161,491 ($115,562 − $398,319)
MM Assumes the average patient demographics (age: 70, weight: 77.8 kg) and dose (0.37 g/kg) from BloodSTAR data for this indication. Baseline infection rates are unchanged from the base case analysis however a 100% increase in the infection-free mortality rate has been assumed[a]. The treatment effect of Ig is based on the pooled IRRs for MM (IRR_S = 0.08, IRR_{NS} = 0.55).	$62,096	$24,391	$37,705	5.33	4.69	0.65	3.76	3.23	0.52	$71,951 ($48,060 − $195,142)
NHL Assumes the average patient demographics (age: 68, weight: 76.3 kg) and dose (0.36 g/kg) from BloodSTAR data for this indication. Baseline infection rates and mortality rates[b] are unchanged from the base case analysis and the treatment effect of Ig is based on the Duraisingham et al. (2014) study[c] (IRR_S = 0.27, IRR_{NS} = 0.57).	$78,786	$35,295	$43,491	6.53	6.08	0.45	4.57	4.16	0.41	$106,290 ($70,579 − $290,434)

	Cost			LYs			QALYs			ICER /QALY (Low – High cost)
	Ig	No Ig	Inc.	Ig	No Ig	Inc.	Ig	No Ig	Inc.	
AL Assumes the average patient demographics (age: 37, weight: 57.1 kg) and dose (0.37 g/kg) from BloodSTAR data for this indication. Baseline infection rates and mortality rates[d] are unchanged from the base case analysis and the treatment effect of Ig is based on the Van Winkle et al. (2018) study (IRR_S = 0.32, IRR_{NS} = 0.11).	$64,623	$82,737	–$18,113	7.79	7.64	0.15	5.48	5.08	0.40	Dominant[e] (Dominant − $98,879)
Post-HSCT Assumes the average patient demographics (age: 42, weight: 63.6 kg) and dose (0.37 g/kg) from BloodSTAR data for this indication. Baseline infection rates and mortality rates[f] are unchanged from the base case analysis and the treatment effect of Ig is based on the Sullivan et al. (1990) study (IRR_S = 0.59, IRR_{NS} = 0.68).	$104,842	$46,594	$58,249	7.68	7.62	0.06	5.29	5.16	0.13	$442,863 ($314,180 − $1,106,408)

AL = acute leukemia; CLL = chronic lymphocytic lymphoma; HSCT = haemopoietic stem cell transplantation; ICER = incremental cost-effectiveness ratio; Ig = immunoglobulin; IRR_{NS} = incidence rate ratio for non-serious infections; IRR_S = incidence rate ratio for serious infections; MM = multiple myeloma; NHL = non-Hodgkin's lymphoma; QALY = quality-adjusted life years.

[a] higher mortality rate has been assumed as Cancer Australia statistics indicate that five-year survival at MM diagnosis was approximately 49%, compared to five-year survival at diagnosis in CLL of 77%. The ICER is not sensitive to this change – assuming the same mortality risk as in the base case analysis increases the ICER slightly to $73,306.

[b] No change in the mortality rate has been assumed relative to the CLL mortality rate used in the base case analysis as five-year survival estimates at diagnosis were similar between NHL (72%) and CLL (77%).

[c] While the Duraisingham et al. (2014) study included patients with mixed haematological malignancies, these were predominantly NHL.

[d] No change in the mortality rate has been assumed relative to the CLL mortality rate used in the base case analysis as it is unclear what proportion of patients with AL and acquired hypogammaglobulinaemia have AML or ALL, which are associated with different five-year survival estimates at diagnosis (25% and 90%, respectively). One average, it is assumed that it would be approximately similar to CLL patients.

[e] Ig is less costly and more effective than no treatment.

[f] No change in the mortality rate has been assumed relative to the CLL mortality rate used in the base case analysis as no data could be identified to inform what the difference would be.

Table 62 Disaggregated events estimated for each of the per-indication analyses

	No. infections - no bronchiectasis			No. infections - with bronchiectasis			Development of chronic *P. aeruginosa*		
	Ig	No Ig	Inc.	Ig	No Ig	Inc.	Ig	No Ig	Inc.
Base case analysis	**1.26**	**2.24**	**–0.98**	**1.64**	**5.15**	**–3.51**	**1.18**	**3.75**	**–2.56**
CLL	1.50	2.21	–0.71	1.68	3.51	–1.84	1.21	2.55	–1.34
MM	1.07	2.16	–1.09	0.79	2.91	–2.12	0.57	2.11	–1.55
NHL	1.26	2.24	–0.97	1.66	4.81	–3.15	1.20	3.50	–2.30
AL	0.49	2.28	–1.80	1.38	13.75	–12.36	1.00	10.48	–9.48
Post-HSCT	1.65	2.28	–0.63	3.56	6.70	–3.14	2.58	4.87	–2.29

AL = acute leukemia; CLL = chronic lymphocytic lymphoma; HSCT = haemopoietic stem cell transplantation; Ig = immunoglobulin; MM = multiple myeloma; NHL = non-Hodgkin's lymphoma.

In AL, Ig is observed to be both less costly and more effective (i.e. the ICER is dominant). This appears to be due to an assumed younger patient age, and therefore lower background mortality risk. AL patients therefore spend more time alive in the bronchiectasis health states which are associated with a higher cost. Further, the study in which this analysis was based on reported a substantial reduction in non-serious infections (and so preventing bronchiectasis with Ig). A substantial increase is observed in the ICER for post-HSCT. This is driven by higher IRRs modelled.

D.6.4. UNIVARIATE SENSITIVITY ANALYSES

All other sensitivity analyses conducted around areas of uncertainty in the model are presented in Table 97, Appendix G. Key sensitivity analyses (i.e. those which changed the ICER by more than 10%) are presented in Table 63, below.

Table 63 Key sensitivity analyses

	Inc. cost	Inc. QALYs	ICER	% change
Base case analysis	**$41,011**	**0.4109**	**$99,803**	**-**
Baseline annual infection rates (base case: Paxton, Hawkins & Crispin 2016, serious 0.43, non-serious 1.05)				
Molica et al. (1996): serious 0.29, non-serious 1.73	$50,160	0.3819	$131,328	32%
Chapel et al. (1994): serious 0.26, non-serious 1.75	$51,346	0.3653	$140,555	41%
Sullivan et al. (1990): serious 1.79, non-serious 3.79	$48,062	0.7121	$67,493	–32%
IRR of Ig treatment effect (base case: serious, 0.15; non-serious 0.61)				
Serious infections, 0.43	$52,526	0.3139	$167,315	68%
Non-serious infections, 0.72	$46,236	0.3523	$131,233	31%
Duration of Ig treatment (base case: 2.2 years)				
5 years	$84,261	0.5430	$155,168	55%
10 years	$125,097	0.5457	$229,233	130%
Exclude development of bronchiectasis	$41,213	0.0141	$2,927,525	2833%
Time horizon (base case: 10 years)				
2.2 years (as per Ig treatment duration)	$38,869	0.0322	$1,208,343	1111%
5 years	$39,552	0.1509	$262,086	163%
Transition probabilities (base case: adjusted)				
Transitions from infection health state, unadjusted	$45,309	0.3087	$146,792	47%
Transitions from infection and bronchiectasis, unadjusted	$29,927	0.2335	$128,154	28%
Cost of hospitalisation of serious infections (base case: $12,775)				
$52,961, based on AR-DRG R01A	$19,349	0.4109	$47,088	–53%

ICER = incremental cost-effectiveness ratio; Ig = immunoglobulin; IRR = incidence rate ratio; QALY = quality-adjusted life year.

The model is highly sensitive to the inclusion of the bronchiectasis health states. When these health states are excluded, the ICER significantly increases to $3 million per additional QALY gained. This result is consistent with that observed in Weeks, Tierney & Weinstein (1991), which also did not

model the development of bronchiectasis. The inclusion of these health states had been justified based on the model structure used in a contemporary economic evaluation (Windegger et al. 2019).

The model is also sensitive to the selection of the time horizon, the treatment effect of Ig, baseline infection rates and whether transition probabilities from Windegger et al. (2019) have been adjusted for the comparison to no Ig.

SECTION E FINANCIAL IMPLICATIONS

A market-based approach has been used to estimate the financial implications of Ig in acquired hypogammaglobulinaemia, based on current utilisation of Ig products in patients with acquired hypogammaglobulinaemia. As data available on utilisation were only available for use under the Version 2 Criteria, the impact of transitioning to the Version 3 Criteria were not able to be captured in the analysis. There is uncertainty as to whether trends observed in the past would continue.

It is also acknowledged that rapid technological development is occurring in this therapeutic area and this may also change clinical demand and Ig use in the future. For example, demand may increase if patients using new therapies (such as monoclonal antibodies, CAR-T cell therapy and BTK inhibitors) live longer with suppressed immune systems.

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

The primary sources of data used in the estimates of the financial impact of Ig in acquired hypogammaglobulinaemia are:

- NBA (2019a) National reports on the issue and use of immunoglobulin (Ig), which report the number of patients and Ig use, by indication, from 2011-12 to 2015-16.
- The 'HTA Data April2019.xlsx' workbook provided by the NBA - which reports use, by indication, for the full financial year 2017-18 and for the 2018-19 partial year to December 31, 2018 (and so reports some use under the Version 3 criteria).

The full year data available from these sources are summarised in Table 64 and Table 65.

Table 64 Number of patients who received Ig by indication, 2011-12 to 2017-18

	2011-12	2012-13	2013-14	2014-15	2015-16	2016-17	2017-18
CLL	1,060	1,080	1,179	1,283	1,380	-	1,632
MM	901	971	1,012	1,100	1,177	-	1,458
NHL	-	940	1,060	1,208	1,308	-	1,651
Post HSCT	-	-	-	307	345	-	443
Other HM	-	510	448	428	574	-	625

CLL = chronic lymphocytic lymphoma; HM = haematological malignancies; HSCT = haemopoietic stem cell transplantation; Ig = immunoglobulin; MM = multiple myeloma; NHL = non-Hodgkin's lymphoma.
Source: NBA (2019a) National Reports on the issue and use of immunoglobulin (Ig), 2012-13, 2013-14, 20114-15 and 2015-16 and the 'HTA Data April2019.xlsx' workbook provided by the NBA.

Table 65 Ig grams issued by indication, 2011-12 to 2017-18

	2011-12	2012-13	2013-14	2014-15	2015-16	2016-17	2017-18
CLL	-	253,763	280,076	315,205	350,066		435,193
MM	-	208,997	229,303	255,962	275,685		354,158
NHL	-	218,655	245,436	287,900	332,148		422,919
Post HSCT	-	-	-	42,738	48,266		72,141
Other HM	-	83,571	80,807	80,969	94,004		117,613

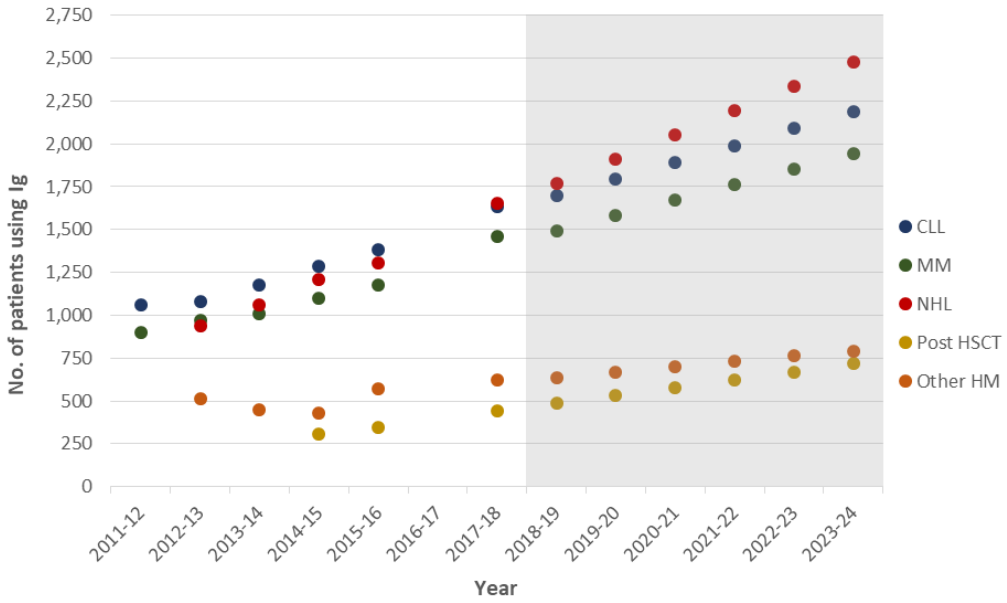
CLL = chronic lymphocytic lymphoma; HM = haematological malignancies; HSCT = haemopoietic stem cell transplantation; Ig = immunoglobulin; MM = multiple myeloma; NHL = non-Hodgkin's lymphoma.
Source: NBA (2019a) National Reports on the issue and use of immunoglobulin (Ig), 2012-13, 2013-14, 20114-15 and 2015-16 and the 'HTA Data April2019.xlsx' workbook provided by the NBA.

E.2. USE AND COST OF IG FOR ACQUIRED HYPOGAMMAGLOBULINAEMIA

ESTIMATED NUMBER OF PATIENTS WHO RECEIVE IG

Patient numbers were projected using linear extrapolations fitted to the observed data presented in Table 64 (Figure 11). The projected estimated patient numbers for each indication are presented in Table 66.

Figure 11 Patient number projections



CLL = chronic lymphocytic lymphoma; HM = haematological malignancies; HSCT = haemopoietic stem cell transplantation; Ig = immunoglobulin; MM = multiple myeloma; NHL = non-Hodgkin's lymphoma.
Note: Grey portion denotes estimates that have been projected.
Source: 'Estimated patient numbers' worksheet in '1565 Financials.xlsx' workbook.

Prior to the Version 3 criteria, patients with acute leukaemia were counted under the 'Other relevant haematological malignancies' indication. Thus to project patient numbers with acute leukaemia, the partial 2018-19 Version 3 data have been used. During the observation period, 68 patients with acute leukaemia received Ig, while 86 patients received Ig for other haematological

malignancies. Therefore patients with acute leukaemia are estimated to account for 44.2% of other haematological malignancies.

Table 66 Number of patients projected to receive Ig by indication, 2019-20 to 2023-24

	2019-20	2020-21	2021-22	2022-23	2023-24
CLL	1,794	1,892	1,990	2,089	2,187
MM	1,583	1,673	1,763	1,853	1,943
NHL	1,910	2,051	2,193	2,334	2,475
Post HSCT	533	579	625	670	716
Other HM (Version 2)	667	699	730	762	793
Acute leukaemia (44.2%)	295	309	322	336	350
Other HM (Version 3)	373	390	408	425	443
Total	**6,488**	**6,894**	**7,301**	**7,707**	**8,114**

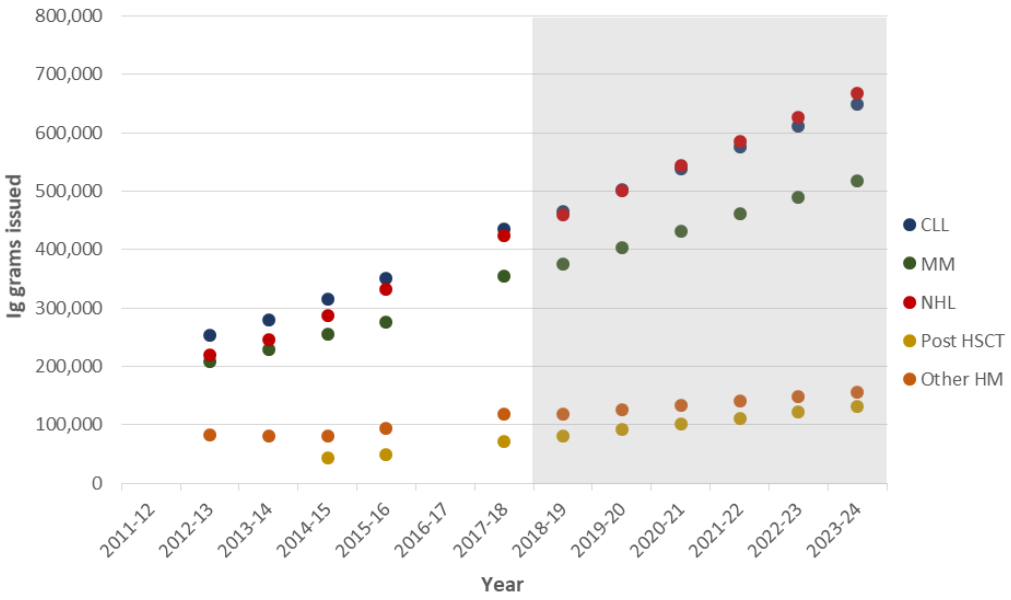
CLL = chronic lymphocytic lymphoma; HM = haematological malignancies; HSCT = haemopoietic stem cell transplantation; Ig = immunoglobulin; MM = multiple myeloma; NHL = non-Hodgkin's lymphoma.
Source: 'Estimated patient numbers' worksheet in '1565 Financials.xlsx' workbook.

ESTIMATED USE AND COST PER PATIENT WHO RECEIVES IG

Average grams per patient per year

A similar approach is used to estimate Ig use over the projected period, as patient weights and dose may change over time. The projected estimated grams for each indication are presented in Table 67.

Figure 12 Ig use projections



CLL = chronic lymphocytic lymphoma; HM = haematological malignancies; HSCT = haemopoietic stem cell transplantation; Ig = immunoglobulin; MM = multiple myeloma; NHL = non-Hodgkin's lymphoma.
Note: Grey portion denotes estimates that have been projected.
Source: 'Estimated grams issued' worksheet in '1565 Financials.xlsx' workbook.

The proportion of Ig use attributable to acute leukaemia was also estimated using a similar approach, with 6,700 grams issued during the observed period under the Version 3 criteria for acute leukaemia, compared to 13,407 for other haematological malignancies. Thus the proportion attributable to acute leukaemia was estimated to be 33.3%.

Table 67 Number of Ig grams issued by indication, 2019-20 to 2023-24

	2019-20	2020-21	2021-22	2022-23	2023-24
CLL	502,376	538,942	575,508	612,074	648,640
MM	403,000	431,787	460,574	489,361	518,148
NHL	501,437	543,109	584,781	626,453	668,125
Post HSCT	91,434	101,543	111,652	121,761	131,870
Other HM (Version 2)	126,258	133,522	140,786	148,049	155,313
Acute leukaemia (33.3%)	42,073	44,494	46,914	49,335	51,755
Other HM (Version 3)	84,185	89,028	93,871	98,714	103,558
Total	**1,624,506**	**1,748,903**	**1,873,301**	**1,997,698**	**2,122,096**

CLL = chronic lymphocytic lymphoma; HM = haematological malignancies; HSCT = haemopoietic stem cell transplantation; Ig = immunoglobulin; MM = multiple myeloma; NHL = non-Hodgkin's lymphoma.
Source: 'Estimated grams issued' worksheet in '1565 Financials.xlsx' workbook.

Using the projected number of grams issued and the projected patient numbers, the average number of grams of Ig issued per patient is estimated to increase over the projected period (Table 68).

Table 68 Average Ig use (g) per patient per year

	2017-18 [observed]	2019-20	2020-21	2021-22	2022-23	2023-24
CLL	267	280	285	289	293	297
MM	243	255	258	261	264	267
NHL	256	262	265	267	268	270
Post HSCT	163	172	175	179	182	184
Acute leukaemia	133	143	144	146	147	148
Other HM	232	226	228	230	232	234

CLL = chronic lymphocytic lymphoma; HM = haematological malignancies; HSCT = haemopoietic stem cell transplantation; Ig = immunoglobulin; MM = multiple myeloma; NHL = non-Hodgkin's lymphoma.
Source: 'Section E tables' worksheet in '1565 Financials.xlsx' workbook.

Average cost per gram of Ig

The base case financial estimates will assume the cost per gram of Ig of $60.41 (see Section D.4.2). As per Section D, sensitivity analyses will be conducted assuming:

i) The highest cost of Ig (i.e. domestic Ig including plasma, $140.18)

ii) The lowest cost of Ig (i.e. imported IVIg, $44.94)

iii) Average cost of Ig, weighted across all indications, $94.51

Prices per gram are assumed to remain constant over the projected period.

Estimated cost of Ig

Projected costs across the acquired hypogammaglobulinaemia indications are presented in Table 69.

Table 69 Cost of Ig for acquired hypogammaglobulinaemia, 2019-20 to 2023-24

	2019-20	2020-21	2021-22	2022-23	2023-24
Cost per gram of Ig	$60.41				
No. CLL patients	1,794	1,892	1,990	2,089	2,187
Ig grams issued for CLL	502,376	538,942	575,508	612,074	648,640
Cost of Ig for CLL	$30,348,534	$32,557,486	$34,766,438	$36,975,390	$39,184,342
No. MM patients	1,583	1,673	1,763	1,853	1,943
Ig grams issued for MM	403,000	431,787	460,574	489,361	518,148
Cost of Ig for MM	$24,345,230	$26,084,253	$27,823,275	$29,562,298	$31,301,321
No. NHL patients	1,910	2,051	2,193	2,334	2,475
Ig grams issued for NHL	501,437	543,109	584,781	626,453	668,125
Cost of Ig for NHL	$30,291,809	$32,809,215	$35,326,620	$37,844,026	$40,361,431
No. post-HSCT patients	533	579	625	670	716
Ig grams issued for post-HSCT	91,434	101,543	111,652	121,761	131,870
Cost of Ig for post-HSCT	$5,523,545	$6,134,230	$6,744,915	$7,355,600	$7,966,284
No. AL patients	295	309	322	336	350
Ig grams issued for AL	42,073	44,494	46,914	49,335	51,755
Cost of Ig for AL	$2,541,652	$2,687,872	$2,834,093	$2,980,313	$3,126,533
No. other HM patients	373	390	408	425	443
Ig grams issued for other HM	84,185	89,028	93,871	98,714	103,558
Cost of Ig for other HM	$5,085,618	$5,378,192	$5,670,765	$5,963,339	$6,255,913
Total number of patients	**6,488**	**6,894**	**7,301**	**7,707**	**8,114**
Total number of Ig grams issued	**1,624,506**	**1,748,903**	**1,873,301**	**1,997,698**	**2,122,096**
Total cost of Ig	**$98,136,389**	**$105,651,248**	**$113,166,107**	**$120,680,966**	**$128,195,825**
Proportion Commonwealth funded	63.0%				
Cost of Ig to the Commonwealth	$61,825,925	$66,560,286	$71,294,647	$76,029,008	$80,763,370
Cost of Ig to the States	$36,310,464	$39,090,962	$41,871,460	$44,651,957	$47,432,455

CLL = chronic lymphocytic lymphoma; HM = haematological malignancies; HSCT = haemopoietic stem cell transplantation; Ig = immunoglobulin; MM = multiple myeloma; NHL = non-Hodgkin's lymphoma.

[a] Under the National Blood Agreement, products are funded 63% by the Commonwealth and 37% by the states and territories.

E.3. CHANGES IN USE AND COST OF OTHER MEDICAL SERVICES

Additional costs due to Ig administration

The majority of patients who currently receive Ig for acquired hypogammaglobulinaemia do so by intravenous infusion. The average number of treatment episodes per year has been derived from data provided by the NBA (Table 70). These have been used to approximate the average number of IV infusions per year to estimate the additional cost associated with Ig administration.

Table 70 Average number of treatment episodes per year

	Average number of treatment episodes per year
CLL	10.0
MM	9.1
NHL	10.1
Post HSCT	7.6
Acute leukaemia	7.1
Other HM	8.4

CLL = chronic lymphocytic lymphoma; HM = haematological malignancies; HSCT = haemopoietic stem cell transplantation; Ig = immunoglobulin; MM = multiple myeloma; NHL = non-Hodgkin's lymphoma.
Source: 'Ig use' worksheet in '1565 Financials.xlsx' workbook.

The total number of administrations per year are estimated within each indication by multiplying the number of patients per year by the average number of treatment episodes per patient. The estimated cost per infusion is $253.42, as per Section D.4.2. The estimated additional costs due to administration increase from $15.4 million in 2019-20 to $19.3 million in 2023-24. Administration costs are all assumed to be incurred by the States.

Table 71 Additional costs due to Ig administration

	2019-20	2020-21	2021-22	2022-23	2023-24
Number of infusions per year	60,876	64,694	68,513	72,331	76,149
Cost per administration	$253.42				
Cost associated with Ig due to infusion administration	**$15,427,172**	**$16,394,813**	**$17,362,453**	**$18,330,093**	**$19,297,734**

Ig = immunoglobulin.

Changes in costs associated with Ig due to a reduction in infections

It is unclear whether in the absence of Ig, use of prophylactic antibiotics would increase (see Section C.2.2), and so no direct cost offsets have been assumed. However the clinical evidence did support that Ig would lead to a reduction in antibiotic use and hospitalisations, due to a reduction in infections. While these are indirect cost offsets, these have been quantified in Table 72 and an estimate of the net financial implications to different government budgets is presented. As per Section D.4.2, each serious infection is associated with one hospitalisation (assumed to be

attributable to State budgets) and one follow-up outpatient attendance (attributable to the Commonwealth), while non-serious infections were associated with outpatient attendance(s), and depending on the severity of infection, oral antibiotics and pathology and imaging tests (all assumed to be attributable to the Commonwealth).

Table 72 Cost offsets associated with Ig use due to a reduction in infections

	2019-20	2020-21	2021-22	2022-23	2023-24
Change in the number of serious infections per patient per year	–0.37				
Total change in serious infections	–2,382	–2,532	–2,681	–2,830	–2,980
Cost of hospitalisation for serious infection	$7,349				
Cost of follow-up outpatient attendance for serious infection	$77				
Change in hospitalisation costs due to reduction in serious infections	–$17,508,780	–$18,606,202	–$19,703,623	–$20,801,045	–$21,898,466
Change in outpatient attendance costs due to reduction in serious infections	–$182,608	–$194,053	–$205,499	–$216,944	–$228,390
Change in the number of non-serious infections per patient per year	–0.41				
Total change in non-serious infections	–2,660	–2,827	–2,994	–3,160	–3,327
Cost per non-serious infection (attributable to the MBS or PBS)	$184				
Change in costs due to reduction in non-serious infections	–$489,328	–$519,998	–$550,668	–$581,339	–$612,009
Total cost offsets due to a reduction in the number of infections	**–$18,180,716**	**–$19,320,253**	**–$20,459,790**	**–$21,599,328**	**–$22,738,865**
Offsets attributable to the Commonwealth	–$671,936	–$714,051	–$756,167	–$798,283	–$840,399
Offsets attributable to the States	–$17,508,780	–$18,606,202	–$19,703,623	–$20,801,045	–$21,898,466

Ig = immunoglobulin.

E.4. FINANCIAL IMPLICATIONS FOR GOVERNMENT HEALTH BUDGETS

The net financial implications for government budgets associated with the funding of Ig for acquired hypogammaglobulinaemia are presented in Table 73. However, there is uncertainty associated with the estimated cost offsets as these are indirect in nature and rely on assumptions regarding the treatment effect of Ig.

Table 73 Net financial implications to government associated with Ig for acquired hypogammaglobulinaemia

	2019-20	2020-21	2021-22	2022-23	2023-24
Total cost of Ig	$98,136,389	$105,651,248	$113,166,107	$120,680,966	$128,195,825
Cost of Ig to the Commonwealth	$61,825,925	$66,560,286	$71,294,647	$76,029,008	$80,763,370
Cost of Ig to the States	$36,310,464	$39,090,962	$41,871,460	$44,651,957	$47,432,455
Cost of Ig administration to the States	$15,427,172	$16,394,813	$17,362,453	$18,330,093	$19,297,734
Total cost offsets due to a reduction in the number of infections	–$18,180,716	–$19,320,253	–$20,459,790	–$21,599,328	–$22,738,865
Offsets to the Commonwealth	–$671,936	–$714,051	–$756,167	–$798,283	–$840,399
Offsets to the States	–$17,508,780	–$18,606,202	–$19,703,623	–$20,801,045	–$21,898,466
Net cost	**$95,382,845**	**$102,725,807**	**$110,068,769**	**$117,411,732**	**$124,754,694**
Net cost to the Commonwealth	$61,153,989	$65,846,235	$70,538,480	$75,230,725	$79,922,971
Net cost to States	$34,228,856	$36,879,572	$39,530,289	$42,181,006	$44,831,723

Ig = immunoglobulin.

E.5. IDENTIFICATION, ESTIMATION AND REDUCTION OF UNCERTAINTY

Sensitivity analyses exploring uncertainty in the assumptions used to determine the financial implications are presented in Table 74.

Table 74 Sensitivity analyses around the financial implication estimates

	2019-20	2020-21	2021-22	2022-23	2023-24
Base financial implications	**$95,382,845**	**$102,725,807**	**$110,068,769**	**$117,411,732**	**$124,754,694**
Cost of Ig (base case: $60.41 per gram)					
High cost of Ig, $140.18	$224,969,664	$242,235,823	$259,501,981	$276,768,140	$294,034,299
Low cost of Ig, $44.94	$70,251,742	$75,670,273	$81,088,805	$86,507,336	$91,925,867
Weighted average of Ig across all indications, $94.51	$150,773,057	$162,357,562	$173,942,066	$185,526,570	$197,111,075
Weighted average across the acquired hypogammaglobulinemia indication, $129.66 [a]	**$207,881,199**	**$223,838,797**	**$239,796,396**	**$255,753,994**	**$271,711,592**
Current published price, $58.23	$91,841,423	$98,913,198	$105,984,973	$113,056,749	$120,128,524
Change in infections per patient per year (base case: −0.37 serious, −0.41 non-serious)					
Using lower bounds of the 95% CIs: −0.41 serious, −0.52 non-serious	$93,268,649	$100,479,097	$107,689,545	$114,899,992	$122,110,440
Using the upper bounds of the 95% CIs: −0.25 serious, −0.29 non-serious	$101,404,179	$109,124,549	$116,844,918	$124,565,288	$132,285,657
Using the pooled IRRs based on the non-randomised studies: −0.32 serious, −0.57 non-serious	$97,349,097	$104,815,300	$112,281,504	$119,747,708	$127,213,911
Growth rate of Ig use (base case: average 7.2%)					
5%	$90,624,094	$95,121,079	$99,851,508	$104,827,053	$110,059,971

	2019-20	2020-21	2021-22	2022-23	2023-24
Base financial implications	**$95,382,845**	**$102,725,807**	**$110,068,769**	**$117,411,732**	**$124,754,694**
6%	$92,411,185	$97,949,172	$103,829,752	$110,073,480	$116,702,146
8%	$96,036,185	$103,767,467	$112,131,003	$121,177,373	$130,961,205

[a] For estimation of the average weighted price per gram within the acquired hypogammaglobulinemia see Table 98, Appendix H.
Ig = immunoglobulin; IRR = incidence rate ratios.

Appendix A Clinical Experts and Assessment Group

ASSESSMENT GROUP

Adelaide Health Technology Assessment

Name	Position
Allison Wyndham	Senior research officer
Arlene Vogan	Health economist
Skye Newton	Team leader
Camille Schubert	Team leader - Health economics

Noted conflicts of interest

There were no conflicts of interest.

APPENDIX B SEARCH STRATEGIES

IgG replacement therapy has been in use since the 1940s for primary immunodeficiencies, mostly as IM injections. IV presentations were developed in the late 1970s and early 80s at the same time as use of IgG in other indications began to be explored. Authorisation of commercial IVIg products for secondary immunodeficiencies did not occur until 1990 or so at which time consensus was reached that IgG could be used in certain haematological malignancies (Eibl 2008).

The literature search terms were kept broad to capture the range of terminology used for 'immunoglobulin' and 'hypogammaglobulinaemia' as well as the range of malignancies relevant to this evaluation. It was not possible to narrow the search string to exclude studies of patients with malignancy having immunoglobulin investigations but no IVIg given, or studies in patients with solid tumours or those with primary immunodeficiencies. Hence there were a very large number of results from initial searches. There is a body of experimental literature from the 1980s investigating IVIg in patients with haematological malignancies, however the search strategy for this evaluation only included results from 1990 onwards in order to keep the number of search results manageable and the low likelihood of relevant trials conducted prior to 1990. Results from Embase were further limited using the 'evidence-based medicine' function to focus results with the highest level of evidence. The search relied on pearling of the included and 'near miss' excluded studies, especially systematic reviews, to identify results not returned by the search strings.

BIBLIOGRAPHIC DATABASES

Electronic database	Time period searched
Embase	From 1990 onwards
Medline	From 1990 onwards
The Cochrane Library (CDSR, Central, DARE, HTA, HEED)	From 1990 onwards

The bibliographic databases above were searched for relevant studies using the representative search string in Table 75. During the process of the review, it was apparent that studies with patients who have received bone marrow transplantation (BMT, as opposed to HSCT with mobilised stem cells collected by apheresis) may not have been identified with the search terms used. An additional search was therefore performed (Table 76).

IgG product brand names were included in both search strings but results indicated that these identified only a small number of results – they are included here for completeness.

As well as the terms in the search strings, pre-specified criteria for excluding studies included: no studies published prior to 1990, no grey literature, no non-peer reviewed articles, no non-English language articles, no conference abstracts or conference presentations.

Culling against PICO criteria could not be done against the title and abstract in some cases, thus many of the search results were downloaded and read in part particularly to determine whether the population and intervention were appropriate (articles read in part were not included in the PRISMA flowchart in Figure 2).

Table 75 Search terms for IgG replacement in patients with hypogammaglobulinaemia due to haematological malignancies (Pubmed)

Element	Pubmed search terms
Population	(Hypogammaglobulinemia OR Hypogammaglobulinaemia OR hypogamma* OR "low immunoglobulin" OR "immunoglobulin deficiency" [mh]) AND (leukaemia* OR leukemia* OR "Leukemia, Lymphoid"[mh] OR "Leukemia, Mast-Cell"[mh] OR "Leukemia, Myeloid"[mh] OR "Leukemia, plasma cell"[mh] OR "Leukemia, Radiation-Induced"[mh] OR "Multiple myeloma"[mh] OR "multiple myeloma" OR "Lymphoma"[mh] OR lymphoma OR lymphoproliferative OR "non-hodgkin" OR ((B-cell OR haematological OR hematological) AND (malignancy OR malignancies OR neoplasm[mh]) OR "Hematologic Neoplasms"[mh]) OR "Hematopoietic Stem Cell Transplantation"[mh] OR HSCT OR (("stem cell" OR "progenitor cell") AND (transplantation OR transplant OR transplants)))
Intervention	AND ("Immunoglobulin G"[mh] OR immunoglob* OR "immune globulin" immunoglobulin OR "gamma globulin" OR gammaglobulin OR IVIg OR SCIg OR IgG OR Ig OR Intragam OR Privigen OR Hizentra OR Gamunex OR Flebogamma OR Intragam OR Evogam OR Panzyga OR Hyqvia OR Intratect OR Octagam OR Kiovig OR Gammanorm OR Cuvitru OR GammaSTAN OR BayGam OR Polygam OR GAMMAGARD OR Sandoglobulin OR Panglobulin OR Carimune OR GAMMAKED OR Iveegam OR Bivigam OR Gammaplex OR Intratect OR IQYMUNE OR SUBCUVIA OR Subgam OR Vigam OR CUTAQUIG OR GAMASTAN OR GAMIMUNE OR IGIVNEX OR RESPIGAM OR VIVAGLOBIN OR GammaQuin OR Nanogam OR CLAIRYG OR ENDOBULINE OR SANDOGLOBULINE OR TECTASIM OR TEGELINE OR "Kenketu Glovenin")
Comparator (if applicable)	–
Outcomes (if applicable)	–
Limits	–

mh = Medical Subject Heading, based on a PubMed platform

Table 76 Further searches for bone marrow transplantation (Pubmed example)

Pubmed search terms
Population
(Hypogammaglobulinemia OR Hypogammaglobulinaemia OR hypogamma* OR “low immunoglobulin” OR “immunoglobulin deficiency”[mh] OR "low Ig" OR "low IgG" OR "immunoglobulin deficiency" OR "immunoglobulin deficient" OR "Ig deficiency" OR "IgG deficiency" OR immunoparesis) AND (“bone marrow transplant”[mh] OR (bone AND marrow AND transplant*))
Intervention
AND (”Immunoglobulin G”[mh] OR immunoglob* OR “immune globulin” immunoglobulin OR “gamma globulin” OR gammaglobulin OR IVIg OR SCIg OR IgG OR Ig OR Intragam OR Privigen OR Hizentra OR Gamunex OR Flebogamma OR Intragam OR Evogam OR Panzyga OR Hyqvia OR Intratect OR Octagam OR Kiovig OR Gammanorm OR Cuvitru OR GammaSTAN OR BayGam OR Polygam OR GAMMAGARD OR Sandoglobulin OR Panglobulin OR Carimune OR GAMMAKED OR Iveegam OR Bivigam OR Gammaplex OR Intratect OR IQYMUNE OR SUBCUVIA OR Subgam OR Vigam OR CUTAQUIG OR GAMASTAN OR GAMIMUNE OR IGIVNEX OR RESPIGAM OR VIVAGLOBIN OR GammaQuin OR Nanogam OR CLAIRYG OR ENDOBULINE OR SANDOGLOBULINE OR TECTASIM OR TEGELINE OR “Kenketu Glovenin”)

mh = Medical Subject Heading, based on a PubMed platform

APPENDIX C STUDIES INCLUDED IN THE SYSTEMATIC REVIEW

Table 77 List of the included studies

Study ID	Title	Citation
Randomised studies – IVIg vs No IVIg		
Boughton et al., 1995	Randomized trial of intravenous immunoglobulin prophylaxis for patients with chronic lymphocytic leukaemia and secondary hypogammaglobulinaemia	Clin Lab Haematol 17(1): 75-80.
Chapel et al., 1991	Hypogammaglobulinaemia in low grade B cell tumours; significance and therapy	Immunol Invest 20(2): 187-191.
Chapel et al., 1994	Randomised trial of intravenous immunoglobulin as prophylaxis against infection in plateau-phase multiple myeloma. The UK Group for Immunoglobulin Replacement Therapy in Multiple Myeloma.	Lancet 343(8905): 1059-1063.
Kobayashi et al., 2014	Effect of meropenem with or without immunoglobulin as second-line therapy for pediatric febrile neutropenia.	Pediatrics International 56(4): 526-529.
Molica et al., 1996	Prophylaxis against infections with low-dose intravenous immunoglobulins (IVIG) in chronic lymphocytic leukemia. Results of a crossover study	Haematologica 81(2): 121-126.
Musto et al., 1995	Prophylaxis against infections with intravenous immunoglobulins in multiple myeloma.	Br J Haematol. 1995;89(4):945–6.
Sullivan et al., 1990	Immunomodulatory and antimicrobial efficacy of intravenous immunoglobulin in bone marrow transplantation."	N Engl J Med 323(11): 705-712.
Randomised studies – SCIg vs No SCIg		
Vacca et al., 2018	Subcutaneous immunoglobulins in patients with multiple myeloma and secondary hypogammaglobulinemia: a randomized trial	Clinical Immunology 191: 110-115.
Other comparative studies – IVIg vs No IVIg		
Ammann et al., 2016	Intravenous immune globulin and thromboembolic adverse events in patients with hematologic malignancy	Blood 127(2): 200-207.
Blombery et al., 2011	Prophylactic intravenous immunoglobulin during autologous haemopoietic stem cell transplantation for multiple myeloma is not associated with reduced infectious complications	Ann Hematol 90(10): 1167-1172.
Paxton et al., 2016	Selecting haematological malignancy patients for intravenous immunoglobulin	Intern Med J 46(10): 1216-1218.
Van Winkle et al., 2018	Prevalence and Safety of Intravenous Immunoglobulin Administration During Maintenance Chemotherapy in Children with Acute Lymphoblastic Leukemia in First Complete Remission: A Health Maintenance Organization Perspective.	Perm J 22: 17-141.
Non-comparative studies – IVIg case series		
Besa, 1992	Recent advances in the treatment of chronic lymphocytic leukemia: defining the role of intravenous immunoglobulin.	Semin Hematol 29(3): 14-23.
Brenner, 1996	Clinical experience with Octagam, a solvent detergent (SD) virus inactivated intravenous gammaglobulin	Clin Exp Rheumatol 14 Suppl 15: S115-119.
Günther & Dreger 2013	Post-marketing observational study on 5% intravenous immunoglobulin therapy in patients with secondary immunodeficiency and recurrent serious bacterial infections	Microbiol Immunol 57(7): 527-535.
Jurlander et al., 1994	Treatment of hypogammaglobulinaemia in chronic lymphocytic leukaemia by low-dose intravenous gammaglobulin	Eur J Haematol 53(2): 114-118.
Non-comparative studies – SCIg case series		
Dimou et al.,	Efficacy-safety of Facilitated Subcutaneous Immunoglobulin in	Anticancer Res 38(7):

Study ID	Title	Citation
2018	Immunodeficiency Due to Hematological Malignancies. A Single-Center Retrospective Analysis	4187-4191.
Any IgG (IVIg and SCIg) case series		
Benbrahim et al., 2018	A French observational study describing the use of human polyvalent immunoglobulins in hematological malignancy-associated secondary immunodeficiency	Eur J Haematol 101(1): 48-56.
Benbrahim et al., 2019	The use of octagam and gammanorm in immunodeficiency associated with hematological malignancies: a prospective study from 21 French hematology departments	Hematology 24(1): 173-182.
Duraisingham et al., 2014	Primary vs. secondary antibody deficiency: clinical features and infection outcomes of immunoglobulin replacement.	PLoS One 9(6): e100324.
Reiser et al., 2017	Management of patients with malignancies and secondary immunodeficiencies treated with immunoglobulins in clinical practice: Long-term data of the SIGNS study	Eur J Haematol 99(2): 169-177.
[Supportive] Non-comparative studies – IVIg v SCIg case series		
Sundin et al., 2012	Subcutaneous IgG replacement after pediatric SCT	Pediatric Transplantation 16(8): 866-871.
Windegger et al. 2019	Cost-utility analysis comparing hospital-based intravenous immunoglobulin with home-based subcutaneous immunoglobulin in patients with secondary immunodeficiency.	Vox Sang. 2019 Apr;114(3):237-246.
[Supportive] Other (IVIg or SCIg) – dosing studies		
Chapel, Dicato et al. 1994	Immunoglobulin replacement in patients with chronic lymphocytic leukaemia: a comparison of two dose regimes	Br J Haematol 88(1): 209-212.
Stump et al., 2017	Comparison of Weight-Based Dosing Strategies for Intravenous Immunoglobulin in Patients with Hematologic Malignancies	Pharmacotherapy 37(12): 1530-1536.

Table 78 List of the included studies as they apply to the NBA-funded conditions

Study	Study type	Risk of bias	N	Studied indication(s)
Acute Leukaemia				
Kobayashi et al., 2014	RCT	Low (SIGN)	N=61	[ALL(34); AML(12); other leukaemia(2); NHL(2); solid tumours(11) Of whom 22 received HSCT (which ones not specified)
Van Winkle et al., 2018	Cohort study	Moderate (SIGN)	N=118	ALL
Stump et al., 2017	Case series	RoB: high (IHE)	N=79 (n=209 infusions)	CLL(74); AL(65); MM(26); NHL(32); HL(7); CML(5)
CLL				
Boughton et al., 1995	RCT	RoB: moderate (SIGN)	N=42	CLL
Chapel et al., 1991	RCT cross-over	RoB: low (SIGN)	N=12	CLL, NHL (breakdown not given; NHL likely v small)
Molica et al., 1996	RCT cross-over	RoB: moderate (SIGN)	N=42	CLL
(Ammann et al. 2016)	Registry study	RoB: moderate (IHE)	N= 10,759	CLL(76%), MM(24%)
Paxton et al., 2016	Cohort study	RoB: high (SIGN)	N=92	CLL (42); MM (18); NHL (27); other (5)
Besa, 1992	Case series	RoB: high (IHE)	N=23	CLL
Brenner, 1996	Time series	RoB: moderate (IHE)	N=54 (26 patients SID)	CLL(22), MM(4)
Dimou et al. 2018	Before/after time series	RoB: moderate (SIGN)	N=33	CLL(25); MM(3); NHL(3); HL(1)
Jurlander et al., 1994	Time series	RoB: moderate (SIGN)	N=15	CLL
Reiser et al., 2017	Case series	RoB: moderate (IHE)	N=307	CLL(130); indolent lymphoma(77);

Study	Study type	Risk of bias	N	Studied indication(s)
				MM(43); NHL(22); other(35)
Benbrahim et al., 2019 (Follow-up report)	Case series (prospective)	RoB: low (IHE)	N=160	MM(54), CLL(54), aggressive NHL(19), indolent NHL(29), HL(4)
Chapel, Dicato et al. 1994	Case series	RoB: low	N=34	CLL
Stump et al., 2017	Case series	RoB: high (IHE)	N=79 (n=209 infusions)	CLL(74); AL(65); MM(26); NHL(32); HL(7); CML(5)
MM				
Chapel et al., 1994	RCT	RoB: low (SIGN)	N=83	MM
Musto et al., 1995	RCT cross-over	RoB: low (SIGN)	N=25	MM
Vacca et al., 2018	RCT	RoB: low (SIGN)	N=46	MM
(Ammann et al. 2016)	Registry study	RoB: moderate (IHE)	N= 10,759	CLL(76%), MM(24%)
Paxton et al., 2016	Cohort study	RoB: high (SIGN)	N=92	CLL (42); MM (18); NHL (27); other (5)
Benbrahim et al., 2019 (Follow-up report)	Case series (prospective)	RoB: low (IHE)	N=160	MM(54), CLL(54), aggressive NHL(19), indolent NHL(29), HL(4)
Reiser et al., 2017	Case series	RoB: moderate (IHE)	N=307	CLL(130); indolent lymphoma(77); MM(43); NHL(22); other(35)
Stump et al., 2017	Case series	RoB: high (IHE)	N=79 (n=209 infusions)	CLL(74); AL(65); MM(26); NHL(32); HL(7); CML(5)
NHL				
Paxton et al., 2016	Cohort study	RoB: high (SIGN)	N=92	CLL (42); MM (18); NHL (27); other (5)
Benbrahim et al., 2019 (Follow-up report)	Case series (prospective)	RoB: low (IHE)	N=160	MM(54), CLL(54), aggressive NHL(19), indolent NHL(29), HL(4)
Reiser et al., 2017	Case series	RoB: moderate (IHE)	N=307	CLL(130); indolent lymphoma(77); MM(43); NHL(22); other(35)
Stump et al., 2017	Case series	RoB: high (IHE)	N=79 (n=209 infusions)	CLL(74); AL(65); MM(26); NHL(32); HL(7); CML(5)
HSCT				
Sullivan et al., 1990	RCT	RoB: low (SIGN)	N=369	BMT
(Blombery et al. 2011)	Cohort study	RoB: high (SIGN)	N=240	MM+HSCT (autologous)
Sundin et al., 2012	Case series	RoB: moderate	N=58 (26 had HM)	HSCT
Other haematological malignancies				
None identified.				
Included studies that could not be used for any of the NBA-funded conditions				
Günther & Dreger 2013	Case series	RoB: moderate (IHE)	N=10	CLL(5), FL(2), plasmacytoma; WM(1), MDS(1)
Benbrahim et al., 2018 (preliminary report)	Case series (prospective)	RoB: low (IHE)	N=231	MM(64), CLL(84), NHL(71), AL(6); HL(6)
Duraisingham et al., 2014	Case series (PID vs SID)	RoB: moderate (IHE)	N=39 SID patients, of which 15 had HM	CLL(1), MM(1), NHL(11); MDS(1); MGUS(1)
Windegger et al. 2019	Before/after time series	RoB: moderate (IHE)	N=13 (N=84 for QoL survey)	Haem. malignancy (unspecified)

Abbreviations are the same as those for Table 15. Orange shading indicates RCTs; grey is supportive only. .

APPENDIX D EVIDENCE PROFILE TABLES

Table 79 Included study profiles for safety and effectiveness – RCTs

Author, Year Country	Study design Risk of bias (RoB)	Population characteristics (at baseline unless specified)	Eligibility criteria Objectives	Intervention	Comparator	Outcomes assessed Statistical Analyses Duration of follow-up	Comments
Randomised studies – IVIg vs No IVIg							
Boughton et al., 1995 UK Multi-centre (20 sites)	RCT, double-blind RoB: moderate (SIGN)	N=42 (CLL) Sex, ♀/♂: 16/26 Mean age±sd, yr IVIg/placebo: 61±7/63±7 Mean weight±sd, kg IVIg/placebo: 66±11/72±14 Disease stage, A/B/C: 20/7/15 Mean serum IgG±sd, g/L: IVIg: 3.5±0.7 No IVIg: 3.6±0.6	Inclusion: CLL patient with serum IgG levels <5.5 g/L (excluding paraprotein) and a history of 2+ recent infections Exclusion: if prophylactic antibiotics in prior 2 weeks; if severe infection at trial entry; if any IVIg or human plasma in 3 months prior to trial entry; prior severe reactions to IV blood products. Objectives: investigation of IVIg in preventing infections in CLL and to identify high risk patients for whom IVIg prophylaxis may be cost effective.	IVIg (n=24): 18g every 3 weeks for 12 months (Sandoglobulin, Sandoz). If 3 infections, classified as tx failure and weekly dose increased to 24g. *7 patients failed tx after 9-11 mo; were switched to higher dose 24g IVIg.*	Placebo (n=18): 0.6g albumin for 12 months. If 3 infections, classified as tx failure and switched to IVIg. *11 placebo patients failed tx; were switched to IVIg after 5-9 mo.*	Outcomes: infections, serious infections, tx outcome (success or failure); liver function (for viral safety, not presented) Analyses: statistical comparisons used Fisher's Exact test or Wilcoxon Rank Sum, and statistical correlation was calculated by least squares Follow-up: Not stated. Fig 1 suggests 1 mo after 12-mo tx period. 1 IVIg patient withdrew due to infusion-related pyrexia; 3 patients died due to disease progression. No patients lost to follow-up.	Ethics: Local hospital ethical committee permission was obtained at each site Funding: Authors supported by the Leukaemia Research Fund; Sandoz provided logistical and analytical support (study coordination; biostatistician) and Sandoglobulin study drug. *Outcomes pooled in 6mo or 12mo groups, no info on which /how many completed 24mo protocol; when did discontinuations occur; nor if any wash-out period.*
Chapel et al., 1991 UK Single centre	Comparative, double-blind, crossover. Not stated if randomised allocation used. RoB: low (SIGN)	N=12 (CLL or NHL) *No serum IgG or other parameters described. Numbers of CLL or NHL patients not given.*	Inclusion: Patients with CLL or low-grade NHL and had either IgG <50% of LLN or a previous major infection. Exclusion: Not described. Objectives: investigation of IVIg on infections in CLL and NHL patients based on crossover design.	IVIg 400mg/kg 3-weekly As for Gale, 1988. Crossover at 12 months for a further year's tx (24 mo total).	No IVIg (equivalent infusion volume of saline) As for Gale, 1988. Crossover at 12 months for a further year's tx (24 mo total).	Outcomes: Incidence of infections. Analyses and follow-up not described. Only 5 patients remained at 24 mo (3 died, 1 discontinued due to futility, 2 moved away in the 2nd yr, 1 refused cross-over)	Funding: grant received from Baxter (manufacturer of Gammagard used in this study) *Study heavily based on earlier trial by same authors in Gale et al., 1988 New England journal of medicine 319(14): 902-907. (excluded as pre-1990)*
Chapel et al., 1994	RCT, double-blind	N=83 (MM)(analysis set N=82 due to patient	Inclusion: plateau phase MM; expected to survive 6+ months; well enough for infusions and	IVIg (n=42*): 0.4g/kg, every 4 weeks for 12 months (Gammagard,	Placebo (n=41): 0.4% HSA, every 4 weeks for	Outcomes: Incidence and type of infections; adverse reactions including death; time to infection;	Same trial as described in Chapel & Lee 1994.

Author, Year Country	Study design Risk of bias (RoB)	Population characteristics (at baseline unless specified)	Eligibility criteria Objectives	Intervention	Comparator	Outcomes assessed Statistical Analyses Duration of follow-up	Comments
UK multi-centre (9 sites)	RoB: low (SIGN)	withdrawal after 1 dose) Mean age±sd, yr: IVIg: 65.6± 6.6 Placebo: 66.3±9.2 Sex ♀/♂: IVIg, n/n: 17/25 Placebo, n/n: 24/17 Total Ig >LLN/<LLN: IVIg, n/n: 10/32 Placebo, n/n: 15/26 Disease, n (%) Stage I: 23 (28) Stage II: 35 (42) Stage III: 25 (30)	travel to clinic. Exclusion: Any prior IgG therapy during the month before entry; Prior anaphylaxis to a blood product; Total selective deficiency of serum IgA. Patients stratified by serum Ig (below or above non-paraprotein Ig LLN). Objectives: investigation of IVIg as prophylaxis against infection in MM patients in plateau phase.	Baxter). No prophylactic antibiotics permitted. *n=42 includes a patient that withdrew after 1 dose (analysis set n=41). *12 patients did not complete the IVIg therapy and 10 did not complete the placebo treatment*	12 months. No prophylactic antibiotics permitted. *12 patients did not complete the IVIg therapy and 10 did not complete the placebo treatment*	infections in an immunised sub-set (n=54; immunised prior to study start). Analyses: Chi-square test was used to compare qualitative data and two-sample t-test (2-tailed p value) for quantitative data; time to first infection was determined by Kaplan-Meier plots and distributions compared by Cox-Mantel. See paper for further analyses. Follow-up not described.	One author (M Lee) an employee of Baxter (IVIg manufacturer) Ethics: protocol approved by each hospital ethics committee; formal written consent obtained from all participants. Funding: The authors thank Baxter for a financial grant for this study. [Baxter manufactures Gammagard, IVIg used in this study]
Kobayashi et al., 2014 Japan Single centre	RCT, open-label, sub-study [August 2008 – April 2012] RoB: low (SIGN)	N=61 patients with 146 (range 1-9) febrile neutropenic episodes. [ALL(34); AML(12); other leukaemia(2); NHL(2); solid tumours(11)] In 22 tx episodes patients had received HSCT, but not clear which ones. Age, median (range): 6.0 years (0–22). Sex ♀/♂: 29/32 Serum IgG, mg/dL, median (range): MEPM+IVIG: 673 (236–1344) MEPM: 667.5 (292–2047)	Inclusion: paediatric chemo or HSCT patients with febrile neutropenia who failed 1st line antibiotics. Exclusion: none described Objectives: meropenem (MEPM) ± IVIG as 2nd line tx for paediatric oncology patients with febrile neutropenia	MEPM + IVIG (62 episodes): 100 mg/kg/d (max 5g/day) for 3 days (Venoglobulin IH 5% Mitsubishi Tanabe/ Benesis). MEPM as described for MEPM only arm. G-CSF permitted.	MEPM without IVIG (84 episodes): MEPM only for 3 days as follows: Aug2008-Apr2010;: 60 mg/kg/d (max 1.5g/d) Apr2010-Apr2012: 120mg/kg/d (max: 3g/d) G-CSF permitted.	Outcomes: tx success vs failure evaluated 120h after the start of therapy (failure defined as defined as persistence of fever or infecting organism, any required modification of antibiotic tx, new infections, or infection-related death) Analyses: Differences between groups were analysed using Fisher's exact test and the Mann–Whitney U-test. Follow-up: not stated. 2 deaths were due to invasive fungal infection in MEPM only group.	Ethics: research was approved by the hospital IRB. Written informed consent was obtained from all patients or parents of patients. Funding: no funding sources were declared nor competing interests statement provided. *17/74 MEPM episodes had received HSCT compared with 5/62 MEPM + IVIg episodes.*
Molica et al., 1996 Italy Multi-centre (5	RCT (crossover study with random allocation);	N=42 (CLL) ♀/♂: 12/30 Age mean±sd: 64±11.5 Rai stage, n(%)	Inclusion: serum IgG <600mg/dL or a history of at least one serious infection in 6-months prior to study 31% of patients had	IVIg: 300 mg/kg every 4 weeks for 6 months (Ig-Vena N, Sclavo). Then crossover to observation for 12	No IVIg: observation (empirical treatment) for 6 months. Then crossover to IVIg for 12 months; finally	Outcomes: infections (incidence, type, severity) Analyses: The number of infections occurring during the treatment or observation period	All patients gave informed consent. No mention of ethics committee approval. Funding: this work was

Author, Year Country	Study design Risk of bias (RoB)	Population characteristics (at baseline unless specified)	Eligibility criteria Objectives	Intervention	Comparator	Outcomes assessed Statistical Analyses Duration of follow-up	Comments
sites)	open-label RoB: moderate (SIGN)	0: 2 (4.7%) I–II: 14 (33.3%) III-IV: 36 (61.9%) IgG level mg/dL(%): <500: 16 (38) >500<650: 13 (30.9) >650: 13 (30.9)	IgG>650mg/dL at entry and 40% had a history of infections. Exclusion: Not described. Objectives: to investigate effect on infections of low-dose IVIg given to CLL patients in a cross-over setting.	months; finally crossover to IVIg for further 6 months. Prophylactic antibiotics not allowed.	crossover to observation for further 6 months. Prophylactic antibiotics not allowed.	were compared by the chi-square test and also by the McNemar test for non-parametric data corrected for continuity. Follow-up duration not described. 2 withdrawals due to IVIg toxicity; 2 patients lost to follow-up (2 and 18 mo). 13 deaths were due to disease progression (5), second neoplasm (2); surgical sequelae (1); infections (5; of which 4 occurred during observation).	supported by a grant from Sclavo (Siena, Italy) which sells immunoglobulins in Italy.
Musto et al., 1995 Italy Single centre	RCT, open-label, crossover RoB: moderate (SIGN)	N=25 (MM) 22 patients had extended (stage III) disease, of which 3 had moderate renal failure (serum creatinine 1.8-2.5mg/dL). No baseline data reported.	Inclusion: serum IgG <LLN or a recent history of recurrent infections. Exclusion: Not described. Objectives: to investigate IVIg efficacy in preventing infections in MM patients selected for hypo-GG and history of infections.	IVIg (0.3g/kg every 4 weeks) for 6 months. Crossover to no IVIg for further 12 months. Crossover back to IVIg for final 6 months. No antibiotic prophylaxis permitted	No IVIg (observation) for 6 months. Crossover to IVIg for further 12 months. Crossover back to no IVIg for final 6 months. No antibiotic prophylaxis permitted	Outcomes: minor infections; serious infections. Analyses and follow-up not described. *9 patients did not complete the study; due to disease progression (4) or lethal infections (5, all during the observation period).*	No mention of research ethics approval. No description of funding source or conflict of interest declaration.
Sullivan et al., 1990 USA Single centre.	RCT, open-label RoB: low (SIGN)	N=382 eligible; 369 received tx in line with criteria. AA(13)/MDS(20); AL(207), CML(77), lymphoma(43), other(13), no BMT(9) Age <20yo: 124(32%) >20yo: 258(68%) BMT source: ▪Allo: 342(90%) ▪Auto: 40(10%) *Sex, serum IgG not reported.*	Inclusion: undergoing BMT for haematological malignancy; either CMV seropositive or, if CMV seronegative receiving BMT from CMV+ donor (May 1986 – Nov 1987) Exclusion: none described Objectives: Investigation of the effect of IVIg on acute GVHD, severe infections and survival in haematological malignancy patients.	IVIg (n=191, of which 184 evaluable): 500mg/kg weekly from d-7 to d90; then monthly to d360 post BMT (Gamimune, Cutter Biologicals), plus supportive care. All patients received S+T prophylaxis until d120 for *Pneumocystis* spp. Acyclovir prophylaxis for baseline CMV+ patients.	No IVIg (n=191, of which 185 evaluable): supportive care. All patients received S+T prophylaxis until d120 for *Pneumocystis* spp. Acyclovir prophylaxis for baseline CMV+ patients. 2 patients developed severe hypo-GG [IgG<4g/L] and recurrent bacterial infections – were given IVIg.	Outcomes: acute GVHD, infection**, interstitial pneumonia, death. ***Infections of oral cavity, URT or infection with herpes simplex not recorded.* Analyses: survival (censored at last contact) and mortality (censored at relapse) analyses included all 382 eligible patients. Analyses of infection and interstitial pneumonia included only 359 evaluable patients. Log-rank test (2-sided p) used to	Ethics: consent forms were approved by the IRB. Funding: grants disclosed from NIH, Cutter Biological Inc (manufacturer of Gamimune, the IVIg product used in this study) and NIAID. *Cutter Biological is now part of Grifols.* *1st 6 patients recruited inadvertently received antibiotic prophylaxis.* *A continuation study for this*

Author, Year Country	Study design Risk of bias (RoB)	Population characteristics (at baseline unless specified)	Eligibility criteria Objectives	Intervention	Comparator	Outcomes assessed Statistical Analyses Duration of follow-up	Comments
						compare times to: death; relapse; acute GVHD; interstitial pneumonia. More details in paper. Follow-up: median duration of follow-up since randomisation: ▪Surviving IVIg (n=66): 1.9 yr ▪Surviving no IVIg (n=69): 2 yr (no ranges given)	*cohort is described in (Sullivan et al. 1996) alongside a 2nd cohort of patients recruited at the same time as this group of BMT recipients, but was excluded as neither tx group had hypo-GG by that stage.*
Randomised studies – SCIg vs No SCIg							
Vacca et al., 2018 Italy Single-centre	RCT, open-label RoB: low (SIGN)	N=46 (MM) Sex ♀/♂: 21/25 Age, mean (range): 71 (56–85) Stage, n (%): IIA: 3 (6.5) IIIA: 39 (84.8) IIIB: 4 (8.7) [Durie & Salmon] IgG g/L, mean (range): 3.1 (1.3–5.2)	Inclusion: adult (<18 yo); serum IgG <500mg/dL; life expectancy >1 year; self or carer able to administer SCIg at home Exclusion: other cause of immunodeficiency; active HCV/ HBV/HIV infection; unable to administer SCIg at home. All patients were free of infection at trial entry, and none were inpatients. Objectives: evaluation of effect of SCIg tx on rate of severe infections in MM patients.	SCIg (n=24): 4 weekly infusions to give a total dose of 0.4–0.8g/kg/ month (Hizentra, CSL Behring). Dosing was adjusted according to normal IgG monthly trough levels. Mean administered dose was 80mg/kg/week. Tx until discontinuation or withdrawal of consent (mean duration 18 mo [range 10–28]). No patient received antibiotic prophylaxis or G-CSF. At the end of the first 6mo tx, 21 of 24 SCIg patients accepted to continue, whereas 3 patients withdrew from the study due to side effects.	Controls (n=22): No SCIg No patient received antibiotic prophylaxis or G-CSF. Monthly serum IgG levels measured as for active arm.	Outcomes: annual rate of severe infections; days of hospitalisation due to severe infections; days of treatment with antibiotics; improvement of HRQoL (SF-36). AEs were reported though not defined as an endpoint. Analyses: Continuous variables, including rate of infections, were assessed as mean, median, sd, and range. Groups were compared by Student-Fisher t-test, and Chi-square test. The Wilcoxon correlation and Mann-Whitney U test assessed the correlation by rate of infection and other variables. Follow-up: patients followed for mean 18mo duration of tx (10-28 mo range).	Ethics: study was approved by the local Ethical Committee. A signed patient informed consent was an inclusion criterion. Funding: *Hizentra's manufacturer had no role in support of the study. None of the authors has received honoraria or consulting fees from [CSL Behring] and none of them has conflicts of interest with any other commercial entity.* [funding sources declared derive from Italian non-profit organisations and from EU Framework 7]

Units conversion: 100mg/dL (units used in older studies) equals 1g/L

Risk of Bias was assessed using the SIGN checklist for controlled trials (for RCTs only); the SIGN checklist for cohort studies, and the IHE checklist for case series.

AA=aplastic anaemia (underlying disease not specified); AEs=adverse events; AL=acute leukaemia (AML+ALL); ALL=acute lymphoblastic leukaemia; AML=acute myeloid leukaemia; ARCBS=Australian Red Cross Blood Service; BMT=bone marrow transplant; CLL=chronic lymphocytic leukaemia; CMV=cytomegalovirus; DLBCL=diffuse large B-cell lymphoma (Richter's syndrome); ECOG-PS=Eastern Cooperative Oncology Group – Performance Status; FL=follicular lymphoma; G-CSF=granulocyte colony stimulating factor (filgrastim); GVHD=graft versus host disease; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HL=Hodgkin lymphoma; HM=haematological malignancy; HR=hazard ratio; HRQoL=health-related quality of life; HSA=human serum albumin; HSCT=haematopoietic stem cell transplant; hypo-GG=hypogammaglobulinaemia; IgA=alpha immunoglobulin; IgG=gamma immunoglobulin; IgM=immunoglobulin M; IMIg=intramuscular immunoglobulin; IQR=interquartile range; IRB=institutional review board (USA); ITP=idiopathic thrombocytopenic purpura; IVIg=intravenous immunoglobulin; LLN=lower limit of normal (laboratory reference range); MAb=monoclonal antibody; MCL=mantle cell lymphoma; MDS=myelodysplastic syndrome; MEPM=meropenem; MGUS=monoclonal gammopathy of undetermined significance; MM=multiple myeloma; MZL=marginal zone lymphoma; NHL=non-Hodgkin lymphoma; NNH=number needed to harm; OS=overall survival; PAPS=primary antiphospholipid syndrome; PID=primary immunodeficiency; RCT=randomised controlled trial; RT=replacement therapy; SCIg=subcutaneous immunoglobulin; sd=standard deviation; SCID=severe combined immunodeficiency; SID=secondary immunodeficiency; SLL=small lymphocytic lymphoma; S+T=sulfamethoxazole+trimethoprim; tx=treatment; TEEs= thromboembolic events; URT=upper respiratory tract; WM=Waldenström macroglobulinaemia.

Table 80 Included study profiles for safety and effectiveness – cohort studies

Author, Year Country	Study design Risk of bias (RoB)	Population characteristics (at baseline unless specified)	Eligibility criteria Objectives	Intervention	Comparator	Outcomes assessed Statistical Analyses Duration of follow-up	Comments
Other comparative studies – IVIg vs No IVIg							
Ammann et al., 2016 USA SEER national cancer registry	Cancer registry retrospective cohort [1992-2010] RoB: moderate (IHE)	N=10,759 CLL/MM: 76%/24% Mean age±sd IgG/non-users: 75.8±6.4/75.9±6.6 ♀/♂ IgG, %: 41/59 ♀/♂ non-users, %: 42/58 Neutropenia, %, IgG/nonusers: 27/26 *No baseline serum IgG described.* *Not clear how hypo-GG status assessed.*	Inclusion: IgG users and non-user controls who were ≥66years old, diagnosed with CLL within 16 years or MM within 8 years, with evidence of US healthcare utilisation Exclusion: hospice care within the previous year; prevalent users (defined as patients who already on IgG prior to reaching eligible age for US Medicare coverage and thus study inclusion) Objectives: to assess rates of clinically serious TEEs in new users of IVIg versus a propensity-matched control group of non-users.	IgG (n=2724 [25%]): one year of monthly infusions; includes IVIg, SCIg, IMIg *No further dose information described; only days since last IVIg per TEE event.*	Non-user controls (no IgG) (n=8035 [75%]): IgG and non-user individuals matched by cancer type (CLL or MM) and utilization status and using time-dependent propensity scores derived from Cox regression models to yield a cohort of patients balanced for factors including disease stage, TEE risk and treatment start date.	Outcomes: TEEs; NNH. *Infections not reported as outcomes but as disease covariates.* Analyses: Cox regression used to assess hazards of arterial and venous TEEs (IgG vs nonusers). 1-year cumulative incidence difference and NNH for each TEE type, representing the estimated absolute risk attributable to IgG. Estimates were based on the Kaplan-Meier cumulative TEEs observed in the unexposed patients and the model-based HR in IgG at follow-up. Follow-up: one year.	Funding: University of Iowa Holden Comprehensive Cancer Center Population Research Core, supported by a National Institutes of Health National Cancer Institute grant. Financial interests declared relate to US government funding only. Ethics: approved by the University of Iowa Institutional Review Board.
Blombery et al., 2011 Australia (Peter MacCallum) Single centre	Retrospective cohort [1 Jan 2000 – 31 Dec 2009] RoB: high (SIGN)	N=240 (MM; auto-HSCT) Median age (range) IVIg/noIVIg: 58(34–74)/60(31–79) Median total Ig, g/L (range) IVIg/no IVIg: 3(0–8)/3(1–7) Median days of neutropenia ANC <0.5x10^9/L (range): IVIg: 5 (3–24) No IVIg: 5 (3–18)	Inclusion: MM patients receiving auto-HSCT; pre-transplant hypo-GG (defined as combined IgG/A/M <8g/L excluding paraprotein). Exclusion: none described. Objectives: does peri-transplant IVIg (0.4g/kg) reduce infectious complications in MM patients after HSCT?	IVIg (n=130): one 0.4g/kg IVIg dose (123 patients (94.6%) received this dose) Single dose given peri-transplant (d−30 to d+30)(104 patients, [80%] received IVIG between days −2 to +2). >95% received Intragam P, (CSL). 25 patients (19.2%) received IVIg as part of ongoing (multi-dose) replacement tx for MM.	No IVIg (n=110): auto-HSCT patients receiving no IVIg in peritransplant period (days −30 to +30) *Cefepime (until 2004) or piperacillin–tazobactam (2004–2009) given to patients with febrile neutropenia. Management of febrile neutropenia and use of G-CSF was according to institutional guidelines.*	Outcomes: infections within 30 days post-transplant (days of intravenous antimicrobial agents number of febrile days); survival post-ASCT Analyses: Association of categorical variables tested using Fisher's exact test; quantitative variables using Student's t test and Mann–Whitney rank-sum test. Survival data analysed by log-rank test. Follow-up: 30 days (not including survival outcomes culled from patient records.	Ethics: *study approved by the institutional ethics committee.* Funding: *none (one author employed by ARCBS).* *IVIg tx is physician's preference – no formal unit policy for IVIg in HSCT.* *Patients typically received antifungal prophylaxis (fluconazole 200mg daily) and antiviral prophylaxis (valacyclovir 500mg daily) whilst neutropenic.*

Author, Year Country	Study design Risk of bias (RoB)	Population characteristics (at baseline unless specified)	Eligibility criteria Objectives	Intervention	Comparator	Outcomes assessed Statistical Analyses Duration of follow-up	Comments
				Management of febrile neutropenia same as for control group.			
Paxton et al., 2016 Australia (Canberra Hospital) Single centre	Retrospective cohort [2009-2013] RoB: high (SIGN)	N=92 [CLL(42); MM(18); B-cell NHL(27); other(5) (AML, T-cell NHL, amyloidosis, post-HSCT)] Sex ♀/♂: 42/50 Age, mean±sd yrs IVIg/NoIVIg: 68.2±12/66.7±11 Mean IgG g/L±sd IVIg: 2.8±1.6 No IVIg: 4.0±1.6 Low IgG, n(%): <4g/L: 56 (61) ≥4g/L: 36 (39)	Inclusion: haematological malignancy patients who either (1) received IVIg for infection prophylaxis or (2) untreated controls with at least 1 serum IgG value <LLN. Exclusion: IVIg for indications other than infection prophylaxis. Objectives: a retrospective study to determine the absence of a history of recurrent or severe infections affects efficacy and safety of IVIg in patients with haematological malignancy and hypo-GG.	IVIg, n (%)=35 (38) *Antibiotics are not routine practice for hypo-GG but co-trimoxazole and fluconazole are given [routinely] with chemotherapy involving high-dose steroids, purine analogues or transplantation.* *Penicillin prophylaxis in 1 patient after allo-HSCT.* No further details given – tx according to hospital practice.	No IVIg, n (%)=57 (62) *Antibiotics/anti-infective prophylaxis as for IVIg.* No further details given – tx according to hospital practice.	Outcomes: rate of serious infections, defined as those requiring hospital admission. Hospitalisation compared before and after HSCT. Analyses: Group characteristics compared using Fisher's exact test for categorical variables or Student's t-tests; event rates expressed as rate ratios with estimated variance to determine 95% confidence limits. Patients stratified by IgG level±4g/L, diagnosis, age, sex. Follow-up not described.	Funding: None. Ethics: approval was received from the ACT Health Human Research Ethics Committee. *The untreated group had fewer cases with severe hypogammaglobulinaemia (51% vs 77%, P < 0.01)* [Comment: The untreated group had a much higher number of patients with IgG>4g/L who would be expected to do better]
Van Winkle et al., 2018 USA Mutli-centre within single organisation (5 sites)	Retrospective cohort RoB: moderate (SIGN)	N=118 Sex (%) ♀/♂: 55(47)/63(53) Age, mean yrs at diagnosis (range): IVIg: 7.9(0.8-19.8) No IVIg: 7.1(1.5-18.7) High risk, Y/N (%): IVIg: 20(56)/16(44) No IVIg:30(37)/52(63) Serum IgG, mean mg/dL (range): IVIg*: 474(89–785) No IVIg: no data. *only available for n/N=31/36; 24/31 patients had IgG<LLN	Inclusion: ALL; 9 mo – 19 yr; tx between 1 January 2008 – 1 July 2014; completion of 12+ months maintenance tx. Exclusion: <6 months old at diagnosis; relapsed ALL without 12 months maintenance tx; receipt of BMT, concurrent or prior additional malignancies, and Down syndrome. Objectives: Study of IVIg in children with ALL in remission receiving maintenance chemotherapy; including indications for initiation and discontinuation.	IVIg (n=36): 400mg/kg at 1 month intervals is standard in patients with serum IgG<LLN, decision to treat was physician's choice and actual dosing may vary. Duration not stated. Reason for IVIg (n=36): Infect. before chemo: 5 Infect. during chemo: 16 Viral exposure: 4 Hypo-GG: 11 Reason ceased (n=36): End of chemo: 16 IgG return to normal: 7 Single dose only: 6 Patient refused: 2 [others: ongoing at study	No IVIg (n=82): tx per patient medical records	Outcomes: infectious complications before and during maintenance tx (including episodes of infection; hospitalisations and days of hospitalisation) Analyses: Groups were compared using nonparametric statistics (χ2, Wilcoxon rank sum, signed rank tests as appropriate). Univariate logistic regression of each variable with the outcome 'IVIG given (group membership)' was also computed. Multivariate analysis with all variables from univariate analysis with p<0.25 available	Ethics: study approved by Kaiser Permanente Southern California IRB. Funding: *This research was supported by a grant from the Regional Research Committee of Kaiser Permanente Southern California.* *The author(s) have no conflicts of interest to disclose.* *The LLN […] for IgG ranged from 501 mg/dL to 757 mg/dL*

Author, Year Country	Study design Risk of bias (RoB)	Population characteristics (at baseline unless specified)	Eligibility criteria Objectives	Intervention	Comparator	Outcomes assessed Statistical Analyses Duration of follow-up	Comments
				end (3); relapsed, excl. from analysis (2)]		prior to maintenance tx. Further details in paper. Follow-up: Not applicable.	

Units conversion: 100mg/dL (units used in older studies) equals 1g/L; Risk of Bias was assessed using the SIGN checklist for controlled trials (for RCTs only); the SIGN checklist for cohort studies, and the IHE checklist for case series. Abbreviations are as for Table 79.

Table 81 Included study profiles for safety and effectiveness – case series

Author, Year Country	Study design Risk of bias (RoB)	Population characteristics (at baseline unless specified)	Eligibility criteria Objectives	Intervention	Comparator	Outcomes assessed Statistical Analyses Duration of follow-up	Comments
Non-comparative studies – IVIg case series							
Besa, 1992 USA Single centre.	Case series (prospective); Open-label RoB: moderate (IHE)	N=23 (CLL) Age, median (range): 64.3 (31-83) ♀/♂: 6/17 Disease stage A (0): 1; A (I): 2 B (II): 8 C (III): 7; C (IV): 5 Serum IgG, mean mg/dL (range): 572 (200–1720) *18/23 patients (78%) had hypo-GG (serum IgG <700mg/dL)*	Inclusion: CLL patients with stage A(0) to A(II) disease with increased lymphocyte doubling time; or stage B(II), C (III and IV) disease. Exclusion: none described. Objectives: to investigate whether IVIg has anti-leukaemic effects in CLL patients with lymphocytosis, based on previous pilot study in 3 patients	IVIg: 400 mg/kg daily for 5 days, followed by a maintenance dose at 21-day intervals for 12 months	–	Outcomes: lymphocyte counts; leukaemic response. Infections reported as a complication/ prognostic variable (before/after comparison presented). Analyses and follow-up not described.	Funding: Supported by the Hematology-Oncology Research Fund of the Medical College of Pennsylvania. No conflict of interest statement included. IVIg (Sandoglobulin) supplied by Sandoz. Ethics: no statement of ethics committee oversight included.
Brenner, 1996 Israel Single centre	Before/after time series RoB: moderate (IHE)	N=54 [CLL(22); MM(4); ITP(20); PAPS(8)] Sex, ♀/♂: 26/28 Median age yr (range), CLL: 61(39-80); MM: 65(61-70)	Inclusion: for CLL – serum IgG <700mg/dL and/or recurrent infections with at least one infection requiring hospital admission; for MM – recurrent infections Exclusion: none described. Objectives: to investigate the safety of Octagam in patients with CLL, MM, ITP and PAPS. To evaluate ability of Octagam to prevent infections in patients with CLL and MM.	IVIg: 0.4g/kg every four weeks for six consecutive courses (Octagam, Octapharma).	–	Outcomes: adverse events; viral safety parameters (not presented); infections; infections requiring hospitalisation. History of infections is presented in a naïve comparison with the infections observed during the study for CLL patients (MM patient numbers too small). Analyses: none presented Follow-up: 6 months after last infusion.	Funding: the article makes no funding disclosures but as a study that aims to demonstrate safety and efficacy of a single brand of IVIg, it is very likely a sponsor-funded study. Ethics: Informed consent approved by Rarnbam Medical Center ethical committee. Outcomes due to ITP and PAPS (both autoimmune diseases) are not relevant to this evaluation.
Günther & Dreger 2013 Germany	Before/after time series: [Apr 1997–Nov 2010]	*N=10 patients [CLL(5), FL(2), immunocytoma(1), plasmacytoma(1),	Inclusion: adults indicated for IVIG with recurrent serious bacterial infections due to haematological malignancy	IVIg: 0.35 g/kg body weight every 3–4 weeks (Flebogamma, Grifols)	–	Outcomes: incidence of bacterial infections; non-bacterial infections; antibiotic/anti-infective use; adverse events including	Work was supported by Grifols (manufacturer of Flebogamma). Serum IgG at baseline not

Author, Year Country	Study design Risk of bias (RoB)	Population characteristics (at baseline unless specified)	Eligibility criteria Objectives	Intervention	Comparator	Outcomes assessed Statistical Analyses Duration of follow-up	Comments
Single centre	Level IV RoB: Moderate (IHE)	MDS(1)] Sex ♀/♂: 7/3 Weight (kg): 77 (57–100) Age, median (range): 63 yr (38–73) Disease stage (n): Binet A (2); Binet B/Rai II (3); Rai III (4); not specified (1)	Exclusion: not described. Objectives: Effect of IVIg on severe recurrent infections in 10 patients with various haematological malignancies.			death. Analyses and follow-up not described.	reported.
Jurlander et al., 1994 Denmark Single centre.	Before/after time series Level IV RoB: Moderate (SIGN)	N=15 (CLL) (results reported for 14 only) Age median (range): 66 (50–81) Sex ♀/♂: 6/9 Binet stage, n: A(3); B(4): C(8) Disease duration median (range): 8.0 (2–19.5) Serum IgG mean±sd: 12.5±5.0 micromol/L	Inclusion: B-cell CLL, hypo-GG (serum IgG<LLN); history of recurrent infections; able to be treated as outpatient Exclusion: Not described. Objectives: whether a 10g dose 3-weekly of IVIg in CLL patients with hypo-GG and a history of recurrent infections will show a benefit in terms of infection related events.	IVIg: 10g every 3 weeks (Gammagard, Baxter) Dose duration not pre-specified. Paper describes tx until serum IgG normalised (or discontinuation) Number of infusions median (range): 19.5 (4–25), or ~13 mo	–	Outcomes: serum IgG levels; infection status; antibiotic use; hospital admission for infection; febrile episodes Analyses: comparison of infection-related events in 12 months prior to IVIg and in 12 months after IVIg using Wilcoxon-Pratt test for paired nonparametric data. Follow-up: Median observation period 14 months (range 3–20)	No mention of research ethics approval. No description of funding source or conflict of interest declaration.
Non-comparative studies – SCIg case series							
(Dimou et al. 2018) Greece Single centre	Interrupted time series without a concurrent control group Level III-3 RoB: moderate (IHE)	N=33 [CLL(25); MM(3); B-NHL(3); HL(1)] 5 treatment naïve (all CLL); 29 pretreated, 13 with IVIg Sex ♀/♂: 16/17 Age, mean (range): 66.1 yrs (38-88)	Inclusion: secondary hypogammaglobulinaemia due to haematological malignancy Exclusion: not stated	SCIg: 0.4-0.8mg/kg/month with dose intervals between 3-4 weeks. Administered using a variable rate portable pump.	Historical comparison (12 months prior to SCIg) 13 patients on IVIg	Outcomes: infections, adverse events Analyses: none performed	No funding or CoI stated.
Non-comparative studies – any IgG (IVIg and SCIg) case series							
Benbrahim et al., 2018	Case series (prospective)	N=231 [MM(64), CLL(84), aggressive NHL(32), indolent NHL(39), AL(6),	Inclusion: Consecutive adult patients with HM-associated 2° immunodeficiency who were	IgRT with IVIg (N=106): median prescribed dose 385mg/kg/mo IVIg	IgRT with SCIg (N=113) median prescribed dose 99 mg/kg/wk SCIg	Baseline data only. Outcomes, analyses and follow-	Ethics: study conducted under French Regulations for non-interventional

Author, Year Country	Study design Risk of bias (RoB)	Population characteristics (at baseline unless specified)	Eligibility criteria Objectives	Intervention	Comparator	Outcomes assessed Statistical Analyses Duration of follow-up	Comments
France Multi-centre (29 sites)	RoB: low (IHE)	HL(6)] *23% of patients had received auto-HSCT, and 1% allo-HSCT* Age, yr, mean±sd: 66±12 years old ♀/♂: 80(35%)/ 151(65%) ECOG-PS 0: 100 (43.7%) 1: 84 (36.7%) 2: 34 (14.9%) ≥3: 11 (4.8%). Serum IgG, median IgG: 4.20g/L IgA: 0.44g/L IgM: 0.20g/L [no ranges given, n=195/231] 134/195 patients tested (68.7%) had serum IgG <5g/L	newly prescribed IgG-RT (IVIg or SCIg). Exclusion: Patients having received IgG-RT at any time within the last 12 months. Patients also excluded from analysis due to: age <18 y; no haematological malignancy or diagnosis of MGUS. Objectives: efficacy and safety of IgRT with IVIg or SCIg, patient adherence and satisfaction of physician expectations over the follow-up period (preliminary report).	(Octagam, Octapharma). *For both groups, antibiotic prophylaxis was reported except S+T which is conventional tx in France for immuno-compromised patients at risk of Pneumocystis spp. and valaciclovir for herpesviruses activation (zoster, CMV)*	(Gammanorm, Octapharma). *For both groups, antibiotic prophylaxis was reported except S+T which is conventional tx in France for immuno-compromised patients at risk of Pneumocystis spp. and valaciclovir for herpesviruses activation (zoster, CMV)*	up: reported in Benbrahim et al., 2019.	studies (confirmed by French ethics committee (Comité de Protection des Personnes Ile-de-France VI). Funding: *"study was funded by Octapharma-France"* 2 authors were pharma industry employees (CRO Soladis, Octapharma). Other authors declared wide range of advisory board and speaking engagements but no conflicts of interest.
Benbrahim et al., 2019 France Multi-centre (21 sites)	As above.	N=160 [MM(54), CLL(54), aggressive NHL(19), indolent NHL(29), HL(4)]. Age, yr, mean±sd: 67.3±11.2 ♀/♂: 61(38.1%)/ 99(61.9%) 133/160 (83.1%) were ECOG-PS ≤1 138/160 patients (86.3%) had Ig levels tested.	Inclusion: available for follow-up since study initiation (see preliminary report). Exclusion and objectives: As for preliminary report.	IgRT with IVIg (N=50): 387±78 mg/kg/mo IVIg. Otherwise as for preliminary report.	IgRT with SCIg (N=110): 97±45mg/kg/wk SCIg (equals 388mg/kg/mo). Otherwise as for preliminary report.	Outcomes: change in serum IgG from baseline; annual incidence of infections. Analyses: Characteristics were compared according to route of administration, using χ^2 test or Fisher's exact test for categorical variables and Student's t test for continuous variables. Follow-up: Mean follow-up duration was 8.7±4.0 months (median 10.8 months).(during which 17 patients died, 5 after developing sepsis)	Ethics: as for preliminary report. This protocol was approved by the French CCTIRS and CNIL. Funding and disclosures – as for preliminary report. Aggressive NHL: lymphomas incl. T-cell ,T-lymphoblastic, Burkitt, DLBCL, and angio-immunoblastic T-cell. Indolent NHL: incl. FL and Waldenström macro-globulinemia.
Duraisingham	Case series	N=167, of which:	Inclusion: Adults with primary	SID (n=39): initial dose of	PID (n=126): IVIg initial	Outcomes: Patient	Ethics: in accordance with

Author, Year Country	Study design Risk of bias (RoB)	Population characteristics (at baseline unless specified)	Eligibility criteria Objectives	Intervention	Comparator	Outcomes assessed Statistical Analyses Duration of follow-up	Comments
et al., 2014 United Kingdom Single centre	(retrospective) RoB: moderate (IHE)	PID (113); PID (prob.)(13); SID(26); SID(prob.)(13); undetermined(2) Haem. malignancy patients (15) in SID group: CLL(1), MM(1), NHL(11); MDS(1); MGUS(1) Sex ♀/♂: 98/ 69 Median age, yr: SID 64.5; SID (prob.) 58 hypo-GG (IgG <5.5g/L): SID 80.8%; SID (prob.) 69.2% Median 12mo serum IgG (SID): 3.30 g/L) Lung disease (SID): Bronchiectasis:28.2% Asthma and/or COPD: 34.1%	(PID) or secondary immuno-deficiency (SID) receiving IgG-RT at data cut-off (May 2013) Exclusion: patients whose diagnosis as either PID or SID was not confirmed Objectives: comparison of PID and SID patients receiving IgG-RT; comparison of infection outcomes before and after tx.	0.1g/kg/week with adjustment based on infection IVIg: 13 (33.3%) SCIg: 26 (66.6%) SID+SID(prob.) group had patients with haem. malignancy (14+1) and autoimmune/ rheumato-logical disease (12+12).	dose of 0.1g/kg/week with adjustment based on infection *(PID patients not relevant to PICO – for further details see paper)*	demographics, causes of immunodeficiency, diagnostic delay, clinical and laboratory features, infection frequency. Analyses: comparisons by 2-tailed unpaired t-test with Welch's correction (unequal variance t-test). 2-tailed paired t-test compared infection frequency pre-/post-treatment. Comparison between diagnostic sub-groups used Kruskal-Wallis test. Bronchiectasis data, only available for few patients, analysed using Mann-Whitney test. P <0.05 considered significant. Follow-up: 12 months	approval by the City and East London Research Ethics Committee. Funding: primary author's salary funded by CSL Behring. Other authors disclosed a range of interests with plasma products manufacturers including CSL Behring, Baxter, Octapharma, Grifols, BPL and LFP. Supplementary data: the 11 NHL patients had: MCL(1); DLBCL(1); B lymphoblastic lymphoma(1); FL(4); MZL(2); unspecified NHL(2) 1 patient with Waldenström macroglobulinaemia was not included in the analysis as being 'undetermined' rather than SID.
Reiser et al., 2017 Germany Multi-centre (48 sites)	Case series (2009-2016) (Prospective) RoB: moderate (IHE)	N=307 [CLL(130); indolent lymphoma (77); MM(43); NHL(22); other(35)] Mean age±sd, yr: 63.7±14.4 ♀/♂: 47.6%/52.4% New IgG starters (tx <3mo): 31.3% Median (IQR) IgG tx duration: 3mo (0-13) Median IgG level: 5.8g/L (mean 7.2±6.9 g/L).	Inclusion: receiving IgG maintenance or newly initiated on any IgG preparation as long-term therapy; due to CLL, MM, indolent lymphoma, other malignancies such as NHL or HIV (if infection or tumours). Exclusion: none described Objectives: to systematically collect data on patient characteristics, IgG utilisation, and outcomes with respect to infection rates and QoL under real life conditions.	IgG: Variable. Median (IQR) 4-weekly dose: IVIg (n=287); 163mg/kg (116-258) SCIg (n=20); 330mg/kg (255-420) Average dose: 205mg/kg per 4 weeks. Duration not reported.	–	Outcomes: Infection rate; severe infections; IgG trough levels; side-effects; QoL; mortality; IgG utilisation Analyses: continuous variables were compared with t test, Mann-Whitney or Wilcoxon test depending on the underlying distribution. Categorical data were compared with the $\chi 2$-test. Survival was evaluated with Kaplan-Meier analysis. Follow-up: average follow-up 20.5 months	Ethics: It was approved by the ethics committee of the Medical Faculty of the Technical University of Dresden and further local ethics committees in Germany. Funding: study supported with unrestricted grant by Baxalta. The company had no influence on the concept, analysis and interpretation of data.

Author, Year Country	Study design Risk of bias (RoB)	Population characteristics (at baseline unless specified)	Eligibility criteria Objectives	Intervention	Comparator	Outcomes assessed Statistical Analyses Duration of follow-up	Comments
Non-comparative studies – IVIg v SCIg case series							
Sundin, 2012 Sweden Single centre	Case series [2003 – 2010] (designed as a cohort study SCIg v IVIg) RoB: moderate (IHE)	N=58 (HSCT), of which 26 had haem. malignancy: ALL(11); AML(7); JMML(3); NHL(2); MDS(3). Sex ♀/♂: 18/39 Mean age, yr (range) IVIg: 7.2 (0–17) SCIg: 2.6 (0–9)	Inclusion: paediatric (<18 yo) patients receiving HSCT who had hypo-GG for at least 3 mo post-HSCT. Exclusion: not described. Objectives: the use of SCIg vs. IVIg in 58 hypo-GG children post-HSCT with a prolonged need of IgG replacement.	IVIg (n=46): 0.3–0.5 g/kg, every 2-4 weeks IgG initiated at median 3 mo post-HSCT (range 1-8 mo). 24 of 46 patients had haem malignancy.	SCIg (n=12): 0.1–0.2g/kg every 1-2 weeks IgG initiated at median 3 mo post-HSCT (range 0-8 mo). Most SCIg patients were initiated in the hospital on IVIg before switch to SCIg. 2 of 12 patients had haem. malignancy.	Outcomes: rates of infections, IgG levels and family attitudes (in survivors) Analyses: Proportions were compared using Fisher's exact test. For individual samples Mann–Whitney's test was used. Statistic significance was set at p <0.05. Follow-up: Data cut-off December 2011 (HSCT received between 2003 – 2010)	Ethics: approved by the Regional Ethical Review Board in Stockholm, Funding: funding disclosed from government and charitable sources, though no conflict of interest declaration was included. JMML is juvenile form of CML
(Windegger et al. 2019) Australia Single-centre Sunshine Coast Hospital and Health Service	Case series Level IV RoB: Moderate (IHE)	N=13 with acquired hypogammaglobulinaemia secondary to malignancy or associated treatment Sex ♀/♂: 8/5 Age mean 62.5 (range 39-76)	Inclusion: adult patients with acquired hypogammaglobulinaemia secondary to malignancy or associated treatment, who were on IVIg for at least 12 months before switching to SCIg Objectives: to determine whether SCIg is a cost-effective treatment in SID patients	IVIg administered by a registered nurse once every 4 weeks. Mean usage: 29.46 g/month SCIg: administered weekly at a place convenient to them. Mean usage: 31.15 g/month	–	Outcome: infections, length of hospital stay per infection,	Funding: University of the Sunshine Coast, the National Blood Authority, the Wishlist Coast Health Foundation and CSL Behring Australia. CoI not stated.
(Windegger et al. 2019) Australia Multi-centre	As above.	N=84 patients with acquired hypogammaglobulinaemia secondary to malignancy or associated treatment (including those who did not switch or switched without 12 months of IVIg data)	Inclusion: adult patients with acquired hypogammaglobulinaemia secondary to malignancy or associated treatment Objectives: to determine whether SCIg is a cost-effective treatment in SID patients	IVIg or SCIg	–	Outcomes: utilities associated with disease and infections	As above. Institutions: Sunshine Coast Hospital and Health Service and Gold Coast University Hospital
Other (IVIg or SCIg) – dosing studies							
Chapel, Dicato	Case series,	N=34 (CLL)	Inclusion: CLL and an IgG level	High dose IVIg (n=16)	–	Outcomes: adverse events,	One author (M Lee) an

Author, Year Country	Study design Risk of bias (RoB)	Population characteristics (at baseline unless specified)	Eligibility criteria Objectives	Intervention	Comparator	Outcomes assessed Statistical Analyses Duration of follow-up	Comments
et al. 1994 UK, LU, DE Multi-centre (4 hospitals)	though designed as RCT between two different doses of Ig (no 'no Ig' arm); double-blind Level IV RoB: low (IHE)	High dose (n=16) Mean age±sd, yr: 63.5±8.4 Sex ♀/♂: 7/9 Disease stage (IWCLL), n (%) 1: 4 (25%) 2: 5 (31%) 3:7 (44%) Low dose (n=18) Mean age±sd, yr: 64.2±8.7 Sex ♀/♂: 5/13 Disease stage (IWCLL), n (%) 1: 7 (39%) 2: 4 (22%) 3:7 (39%)	below lower limit of normal for the local hospital laboratory or a recent history of one or more serious infections. Exclusion: taking prophylactic antibiotics, had total IgA deficiency or history of anaphylaxis to blood product. Objectives: to determine whether a reduction in the dose of immunoglobulin would still protect against bacterial infections in patients with CLL and NHL	500 mg/kg body weight every 4 weeks as outpatient for 12 months Low dose IVIg (n=18) 250 mg/kg body weight every 4 weeks as outpatient for 12 months Gammaguard (Baxter Biotech Group)		infections Analyses: infection rates compared using Poisson rates with two-tailed p value. Numbers of infected patients compared by chi-square test for independence. Follow-up: 9 patients did not complete the study, (6/3 low/high dose) 4 of these patients died, 2 in each tx group; the 1 infective death was a low dose patient who died of meningitis.	employee of Baxter (IVIg manufacturer) Ethics: protocol approved by each hospital ethics committee; formal written consent obtained from all participants. Funding: The authors thank Baxter for a financial grant for this study. [Baxter manufactures Gammagard, IVIg used in this study] No declaration of CoI made.
Stump, 2017 USA Single centre	Case series (interrupted time series comparison of different dosing strategies) [April 2014 – September 2016] RoB: high	N=79 (209 evaluable of 238 IVIg encounters) Pre-dose not baseline values as number of IgG naïve recipients not reported. Infusions – condition: CLL(74); AL(65); MM(26); NHL(32); HL(7); CML(5) Age yr, mean±sd ABW: 57.7±14.8 IBW: 49.4 ±19.6 ♀/♂: 106(51)/103(49) IgG levels: tested prior to 133 of 238 infusions (56%) Of which, hypo-GG	Inclusion: patients ≥18 yo with hematologic malignancies who received IVIG either as an inpatient or outpatient, including HSCT patients for malignancy. Exclusion: Patients who were pregnant, incarcerated, primary immunodeficiency, or received IVIG for indication unrelated to hematologic malignancy. Objectives: effectiveness of ideal body weight (IBW) versus actual body weight (ABW) dosing strategy for IVIG in patients with hematologic malignancies or undergoing HSCT	IVIg-ABW (n=125 infusions): *no information on dose level, frequency, duration or supportive care (including antibiotic use) provided.* *NB: some patients receiving consecutive doses had ABW and IBW calculated doses on different occasions.* *Note: Authors advise that median IVIg dose per patient during study period (30mo or 2.5yr) was 1 (range 1-18) or a mean of 2.6 doses (S Stump, pers.*	IVIg-IBW (n=84 infusions): *no information on dose level, frequency, duration or supportive care (including antibiotic use) provided.* *NB: some patients receiving consecutive doses had ABW and IBW calculated doses on different occasions.* *See note in ABW column regarding doses per patient.*	Outcome: primary outcome was infection rate within 30 days of IVIg administration; Secondary outcomes incl. 60-day infection rate, IgG-level response (>400mg/dL), realised and potential IVIg savings. Infection defined as defined as a positive culture, respiratory viral panel, *Clostridium difficile* assay, or a chest radiograph. Analyses: A χ^2 test used to analyse primary outcome and other categorical data; Student t test used for continuous data. Statistical significance defined as $p<0.05$ Follow-up: 30 days for each	Ethics: The study was approved by the University of North Carolina institutional review board. Funding: the paper includes no statement of funding source nor conflict of interest declaration. *But no 'no IVIg' baseline against which to measure infection rate.* *Type of infections, total patient numbers, how many infusions were received as consecutive doses by the same patient, dose levels, dose duration were not reported.*

Author, Year Country	Study design Risk of bias (RoB)	Population characteristics (at baseline unless specified)	Eligibility criteria Objectives	Intervention	Comparator	Outcomes assessed Statistical Analyses Duration of follow-up	Comments
		(<400mg/dL): 47/133 (35%) Existing infection, IBW/ABW: 51.2%/33.6% Neutropenia ANC <0.5x10^9/L IBW/ABW: 65.5%/58.4%		*comm. May 2019)*		infusion received during the period 1 April 2014 to 30 September 2016. *N=209 did not include 26 patients who died in the initial 30 day period and 1 patient lost to follow-up who were excluded from the analysis.*	*49% of infusions were in patients who received HSCT*

Units conversion: 100mg/dL (units used in older studies) equals 1g/L; Risk of Bias was assessed using the SIGN checklist for controlled trials (for RCTs only); the SIGN checklist for cohort studies, and the IHE checklist for case series. Abbreviations are as for Table 79.

*Notes: Günther & Dreger 2013 – the plasmacytoma case was IgA-secreting which is most likely not included in the WHO definition of MM depending on other clinical features (if extramedullary), thus is an 'other haematological malignancy'; FL is included in the WHO definition of NHL; the case of WM (described by authors as an IgM-secreting immunocytoma) is an 'other haematological malignancy'.

APPENDIX E EXCLUDED STUDIES

Table 82 List of the excluded systematic reviews or meta-analyses

Study	Title+citation	Indication (# RCTs)	Reason for exclusion
Ahn et al., 2018.	Effectiveness of immunoglobulin prophylaxis in reducing clinical complications of hematopoietic stem cell transplantation: a systematic review and meta-analysis', Transfusion, 58: 2437-52.	HSCT(27)	The review included all studies of IgG regardless of baseline infections risk and/or hypogamma-globulinaemia.
Bass et al., (1993)	Efficacy of immune globulin in preventing complications of bone marrow transplantation: a meta-analysis. Bone Marrow Transplant. 1993;12(3):273-82.	HSCT/BMT	Included studies (k=12) were a mix of interventions, outcomes and only included some randomised trials.
Raanani et al., 2008	Immunoglobulin prophylaxis in hematological malignancies and hematopoietic stem cell transplantation Cochrane Database Syst Rev(4): CD006501.	HSCT(30), haem. malignancies (10)	The review included all studies of IgG and CMV-IgG regardless of baseline infections risk and/or hypogamma-globulinaemia.
Raanani et al., 2009	Immunoglobulin prophylaxis in chronic lymphocytic leukemia and multiple myeloma: Systematic review and meta-analysis. Leukemia and Lymphoma 50(5): 764-772.	CLL or MM (9)	The review included all studies of IgG regardless of baseline infections risk and/or hypogammaglobulinaemia.
Raanani, Gafter-Gvili et al., 2009	Immunoglobulin prophylaxis in hematopoietic stem cell transplantation: Systematic review and meta-analysis. J Clin Oncol 2009 Feb;27(5):770-81.	HSCT (30)	As above.

Abbreviations are the same as those in Table 79

Table 83 List of the excluded studies

Study	Title+citation	Indication (N patients)	Reason for exclusion
Azik et al., (2015).	Comparison of prophylactic use of immunoglobulin M-enriched polyclonal immunoglobulin (Pentaglobins) versus standard immunoglobulin after pediatric hematopoietic stem cell transplatation. Bone marrow transplantation. 50: S573.	HSCT N=59	IgG tx commenced prior to conditioning; no record of serum IgG or infection history prior to tx.
Abdel-Mageed et al., (1999)	Comparison of two doses of intravenous immunoglobulin after allogeneic bone marrow transplants. Bone Marrow Transplant. 1999;23:929-32.	HSCT (allo-BMT) N=350	No serum IgG levels at baseline or during study; nor infections with/without IgG
Casulo et al., (2013)	Incidence of hypogammaglobulinemia in patients receiving rituximab and the use of intravenous immunoglobulin for recurrent infections. Clin Lymphoma Myeloma Leuk 13(2): 106-111.	Sub-study: N=14 (NHL, CLL/SLL)	All patients received B-cell depletion therapy, excluded under *Criteria Version 3*. Symptomatic IgG with IVIg tx only in n=14 sub-study.
Chapel et al., (1993).	Intravenous immunoglobulin therapy in patients with multiple myeloma. Immunodeficiency 4(1): 77-78.	N=82 (MM)	Preliminary report – results reported in Chapel & Lee, 1994; Chapel et al., 1994.
Chapel & Lee (1994).	The use of intravenous immune globulin in multiple myeloma. Clinical and Experimental Immunology, Supplement 97(1): 21-24.	N=82 (MM)	Same study as reported in Chapel et al., 1994 (Lancet). The Lancet paper was chosen to include as it presented better description of trial particulars.
Compagno et	Subcutaneous immunoglobulin in lymphoproliferative disorders and rituximab-	N=61 (B-CLL[40];	B-cell depletion therapy, excluded under *Criteria Version 3*; n=42/61 patients

Study	Title+citation	Indication (N patients)	Reason for exclusion
al., 2014	related secondary hypogammaglobulinemia: a single-center experience in 61 patients. Haematologica, 99: 1101-6.	NHL[21])	(69%) received anti-CD20 MAbs prior to onset of hypo-GG
Cordonnier et al., (2003).	Should immunoglobulin therapy be used in allogenic stem-cell transplantation? Ann Intern Med 139(1): 8-18.	Allo-HSCT (N=200)	Prophylactic tx (no evidence of infection); no evidence of hypo-GG status or history of infection at baseline.
Demitrovicova et al., (2017).	Infectious complications in chronic lymphocytic leukemia- a retrospective analysis: single institution experience. Neoplasma 64(3): 474-481.	CLL (N=110)	IgG given in an unidentified subset of patients with no outcomes reported according to IgG/No IgG received.
Foster et al., (2018).	Immunoglobulin prophylaxis in pediatric hematopoietic stem cell transplant. Pediatric Blood and Cancer 65(12).	HSCT N=150	Both tx groups received prophylactic IgG (no evidence of infection); only in 2nd group was tx based on hypo-GG status or serum IgG levels monitored. Viral infections only reported.
Frangoul et al., (2013).	Incidence and risk factors for hypogammaglobulinemia in pediatric patients following allo-SCT. Bone Marrow Transplant 48(11): 1456-1459.	Allo-HSCT (paeds) N=185	'No IgG' control patients all had normal IgG levels, compared to IgG recipients who had hypo-GG. No infections reported, only transplant-related mortality.
Gimesi A, Eibl M, Koós R, et al. (1992)	Immunoglobulin prophylaxis during intensive treatment of acute lymphoblastic leukemia in children. Acta Paediatr Hung 1992;32(2):115-25.	ALL (N=60)	Prophylactic use (no evidence of infection), without mention of hypo-GG status, infection history, or IgG levels.
Hensel, M., et al. (2003)	Disease activity and pretreatment, rather than hypogammaglobulinaemia, are major risk factors for infectious complications in patients with chronic lymphocytic leukaemia. Br J Haematol 122(4): 600-606.	CLL N=187	Prophylactic use (no evidence of infection). More than half patients had no hypo-GG; only 10 patients received IVIg. Not possible to identify infections occurring only in those receiving IVIg or in those with hypo-GG.
Howell et al., (2012).	Retrospective analysis of weekly intravenous immunoglobulin prophylaxis versus intravenous immunoglobulin by IgG level monitoring in hematopoietic stem cell transplant recipients. Am J Hematol 87(2): 172-174.	Allo-HSCT N=229	Both tx groups received prophylactic IgG (no evidence of infection); only in 2nd group was tx based on hypo-GG status or serum IgG levels monitored.
Hussein et al., (2016).	Incidence and risk factors of bacterial infections in children following autologous hematopoietic stem cell transplantation: Single-center experience from Jordan. Pediatr Transplant 20(5): 683-686.	HSCT (paed) N=65, of which HL(12); NHL(6)	Mixed population, mostly solid tumours. Patients that had HM and hypo-GG who also received IgG were not identifiable in infections data.
Locatelli et al., (2017).	Outcome of children with acute leukemia given HLA-haploidentical HSCT after ab T-cell and B-cell depletion. Blood 130(5): 677-685.	Haplo-HSCT (ALL or AML) N=80 (paed)	IgG-RT given to (all?) patients as part of supportive care (timing, dose, criteria for initiation unspecified). Serum IgG levels suggest patients include those with and without hypo-GG, but no outcomes reported based on hypo-GG status.
Park et al., (2015).	Incidence of infection according to intravenous immunoglobulin use in autologous hematopoietic stem cell transplant recipients with multiple myeloma. Transpl Infect Dis 17(5): 679-687.	Auto-HSCT (N=162 MM patients)	No criterion required or information reported regarding IgG serum levels at baseline nor infection history/risk. HSCT patients all given IVIg from d1 of transplant.
Ruutu et al., (1997)	No prevention of cytomegalovirus infection by anti-cytomegalovirus hyperimmune globulin in seronegative bone marrow transplant recipients. The Nordic BMT Group. Bone Marrow Transplant. 1997 Feb;19(3):233-6.	HSCT (BMT) N=28	Intervention: CMV hyperimmune globulin only

Study	Title+citation	Indication (N patients)	Reason for exclusion
Spadaro et al., (2016).	Intravenous versus subcutaneous immunoglobulin replacement in secondary hypogammaglobulinemia. Clin Immunol 166-167: 103-104.	N=14 NHL(12); CLL(2)	All patients received B-cell depletion therapy, excluded under *Criteria Version 3*.
Sullivan et al., (1996).	A controlled trial of long-term administration of intravenous immunoglobulin to prevent late infection and chronic graft-vs.-host disease after marrow transplantation: clinical outcome and effect on subsequent immune recovery. Biol Blood Marrow Transplant 2(1): 44-53.	BMT N=254	Extension study for Sullivan et al., 1990. Not clear that patients continue to meet criteria for tx. Untreated group serum IgG levels suggest patients no longer have hypo-GG.
Visentin et al., (2015).	Clinical profile associated with infections in patients with chronic lymphocytic leukemia. Protective role of immunoglobulin replacement therapy. Haematologica 100(12): e515-518.	CLL N=706	No information on infections at baseline, most patients did not have hypo-GG, nor was there any subsequent monitoring of IgG levels.
Winston et al., (2001)	A multicenter, randomized, double-blind comparison of different doses of intravenous immunoglobulin for prevention of graft-versus-host disease and infection after allogeneic bone marrow transplantation. Bone Marrow Transplant. 2001 Jul;28(2):187-96.	HSCT N=618	Tx commenced prior to transplant; no infection history or IgG levels at baseline.
Winston DJ, Ho WG, Bartoni K, Champlin RE (1993)	Intravenous immunoglobulin and CMV-seronegative blood products for prevention of CMV infection and disease in bone marrow transplant recipients. Bone Marrow Transplant 12:283–288	HSCT	Prophylactic Ig use (not limited to treating hypo-GG)
Winston et al., (1993)	Ganciclovir prophylaxis of cytomegalovirus infection and disease in allogeneic bone marrow transplant recipients. Results of a placebo-controlled, double-blind trial. Ann Intern Med. 1993;118:179-84.	HSCT	Prophylactic Ig use (not limited to treating hypo-GG)
Wolff et al., (1993)	High-dose weekly intravenous immunoglobulin to prevent infections in patients undergoing autologous bone marrow transplantation or severe myelosuppressive therapy. A study of the American Bone Marrow Transplant Group. Ann Intern Med 118:937–942	Auto-BMT (125); AL (26); 'other' (19) N=170	Only 8% of patients had hypo-GG; results not reported according to hypo-GG status. No information on history of infections.
Zikos et al., (1998)	A randomized trial of high dose polyvalent intravenous immunoglobulin (HDIgG) vs. cytomegalovirus (CMV) hyperimmune IgG in allogeneic hemopoietic stem cell transplants (HSCT). Haematologica 83:132–137	HSCT (adults and paeds) (N=128)	Wrong comparator (CMV globulin not 'No IgG'), no evidence of hypo-GG in recipients prior to treatment; no untreated group to enable comparison of infection rates. Prophylactic tx prior to HSCT.

Abbreviations are the same as those in Table 79

APPENDIX F SUPPORTING CLINICAL DATA

Table 84 Antibiotic use and infection prophylaxis in the included studies

Study	Infection prophylaxis	Antibiotic prescribing
Randomised studies – IVIg vs No IVIg		
Boughton et al., 1995	On-study – none noted. Immediately prior to study, patients excluded if antibiotic prophylaxis received within 2 weeks.	As prescribed by GP
Chapel et al., 1991	None noted (likely the same as (Gale et al. 1988), not allowed on study.)	Not described, though infection severity was defined in terms of requirement for antibiotics – oral (moderate) IV (major) or none required (minor)
Chapel et al., 1994	Not allowed in 2 weeks prior to entry; *'patients were not expected to receive such treatment during the study'.*	As required, by treating physician (blinded to study drug)
Kobayashi et al., 2014	Sub-study patients those who failed main study antibiotic prophylaxis received 2nd line MEPM: -until Apr 2010 60 mg/kg/d, [max 1.5g/d] for 72h; -after Apr 2010 120mg/kg/d [max 3.0g/d] for 72h G-CSF was used in 28 of 61 patients. Main study patients received one of two potential 1st line prophylactic agents: -until Apr 2010 cefepime or cefozopran -after Apr 2010 cefepime or piperacillin/ tazobactam	Sub-study patients: Anti-fungal drugs (micafungin or liposomal amphotericin) were given to patients with suspected fungal infections, other anti-infectives not described (noting 72h sub-study tx duration).
Molica et al., 1996	Not allowed on study.	Not described.
Musto et al., 1995	Not allowed on study.	Not described.
Sullivan et al., 1990	*Pneumocystis* spp. antibiotic prophylaxis until d120 (likely S+T or similar); enteric decontamination (presumably with non-absorbed antibiotics); other antibiotic prophylaxis was not permitted; the 1st 6 consecutive patients 'inadvertently' received unidentified antibiotic prophylaxis.	Not described.
Randomised studies – SCIg vs No SCIg		
Vacca et al., 2018	Antibiotic prophylaxis not allowed on study. All patients receiving bortezomib received acyclovir for the study duration. No antifungals were given.	Prescribed on diagnosis of infection as they arose.
Other comparative studies – IVIg vs No IVIg		
Ammann et al., 2016	Not reported (variable)	Not reported (variable)
Blombery et al., 2011	Not allowed on study.	Antibiotics if any febrile neutropenia.
Paxton et al., 2016	Antibiotic prophylaxis was not routine practice for hypo-GG, but S+T and fluconazole were given with chemotherapy involving high-dose steroids, purine analogues or HSCT. Penicillin prophylaxis used in 1 patient after allo-HSCT.	Per patient records.
Van Winkle et al., 2018	None noted.	Per treating physician.

Study	Infection prophylaxis	Antibiotic prescribing
Non-comparative studies – IVIg case series		
Besa, 1992	None noted.	Not described
Brenner, 1996	None noted.	Not described
Günther & Dreger 2013	None noted.	9 (out of 10) patients were on (unspecified) antibiotics at enrolment and continued to receive these as concomitant medication. Antibiotics prescribed during the study were reported by infection type. For example, the antibiotics prescribed for the 17 lower respiratory tract infections that occurred on study were: azithromycin, roxithromycin, ceftriaxone, ciprofloxacin, cefuroxime, clarithromycin and carbacephem. See Table 4 of the article for other antibiotics prescribed on study.
Jurlander et al., 1994	None noted	Number of prescriptions reported only.
Non-comparative studies – SCIg case series		
Dimou et al., 2018	None noted.	Not described.
Any IgG (IVIg and SCIg) case series		
Benbrahim et al., 2018	N/A (preliminary report)	N/A (preliminary report)
Benbrahim et al., 2019	Prophylaxis with valaciclovir and S+T was acceptable but usage was not reported.	8 patients (5%) received antibiotic prophylaxis at least once during follow-up (apart from the conventional [use] of valaciclovir and S+T, which was not reported).
Duraisingham et al., 2014	Patients on prophylactic antibiotics in SID group (N=39, of which 15 had HM): Before Ig-RT: 27 (69.2%) After Ig-RT: 23 (60.0%)	Antibiotics other than prophylactic not described. Days on antibiotics before IgG-RT recorded but not after IgG-RT.
Reiser et al., 2017	As recorded in medical records.	Not described.
Non-comparative studies – IVIg v SCIg case series		
Sundin et al., 2012	Refers to previously published paper (Remberger et al. 2011) that cited prophylaxis with antivirals (ganciclovir, acyclovir, foscarnet) and lysosomal amphotericin B for potential fungal infections, though it is not known how many patients received these in this study.	Not described.
Windegger et al. 2019	None noted.	Not described.
Other (IVIg or SCIg) – dosing studies		
Chapel, Dicato et al. 1994	Patients on prophylactic antibiotics ineligible for study entry; and it was implied though not explicit that this also applied to on-study tx.	Not described.
Stump et al., 2017	None noted.	Not described.

Table 85 Randomised studies presenting infections – IVIg vs no IVIg

Study	Outcome	Intervention	Comparator	Comparison
Boughton et al., 1995	**Infections in 12 mo (%)(N=42)**	**IVIg (n=24)**	**No IVIg (albumin) (n=18)**	**p value**
CLL	**Patients with infections (n/N)**	**18/42 (43%) (figures for tx groups not reported)**		

	Number of infections	122 (figures for tx groups not reported)		
	Patients with infections ≥3 infections in 12mo <3 infections in 12mo	 7 (29%) 17 (71%)	 11 (61%) 7 (39%)	 p=0.04
	Patients with serious infections ≥3 serious infections in 12mo <3 serious infections in 12mo	 5 (21%) 19 (79%)	 10 (56%) 8 (44%)	 p=0.02
Chapel et al., 1991	**Infection incidence during 24 mo including cross-over (N=12)**	**IVIg (n=6)**	**Placebo (saline)(n=6)**	
CLL, NHL	Patients free of serious infection	6/6 (100%)	1/6 (17%)	
	Total 3-weekly cycles (infusions)	191	162	
	Years, mean/patient	1.84	1.56	
	Major infections per patient	*0.3*	*1.7*	
	Major infections/patient/year	*0.182*	*1.070*	
	Major infections/patient/month	*0.015*	*0.089*	p=0.001
	Major infections • Bacterial • Viral • Fungal **Total major infections**	 0 1 1 **2**	 9 1 0 **10**	
	Moderate infections • Bacterial • Viral • Fungal • Unknown infection **Total moderate infections**	 3 3 0 1 **7**	 11 0 1 1 **13**	
	Trivial infections	**23**	**22**	
	Total overall infections	***32***	***45***	
Chapel et al., 1994	**Infections during 12 mo (N=82 not including 1 IVIg withdrawal)**	**IVIg (n=41)**	**Placebo (albumin)(n=41)**	**p (2-tailed)**
MM	*Patients – any infection* *Patients – no infections*	*24* *6*	*26* *5*	
	Serious infections – major • septicaemia • pneumonia **Total serious (major) infections**	 0 0 **0**	 3 7 **10**	 0.045 0.005 **0.002**
	Serious infections – moderate • other chest infections • UTIs • skins sepsis/abscess/cellulitis • pyrexia of unknown origin • other **Total serious (moderate) infections**	 6 8 2 2 1 **19**	 18 5 0 0 5 **28**	 0.0097 n.r. n.r. n.r. n.r. **n.r.**
	Total serious infections (57 of 138 infections of any severity) Serious infections rate (/patient/mo)	**19** *0.042*	**38** *0.081*	**p=0.019 (95% CI 0.007-0.071)** n.r.
	Serious infections, bacterial *Serious bacterial infections/patient/month*	15 *0.033*	29 *0.062*	0.05
	Serious infections, bacterial Secondary comparison (not incl. outlier patient with 5 UTIs)	10	29	0.007
	Total patient months Mean months per patient Serious infections /patient/month	449 *11.0* n.r. *(calculated: 0.042)*	470 *11.5* n.r. *(calculated: 0.081)*	– 0.019 (95% CI 0.007-0.071)
	Minor infections*	**n.r.**	**n.r.**	
	Recurrent infections any severity during	IVIg	Placebo (albumin)	p (2-tailed)

	12 mo			
	Patients at risk	30	31	
	1 infection	12	4	
	2 infections	4	11	
	3 infections	4	7	
	4+ infections	4	4	
	Patient months	*360*	*372*	
	Recurrent infections /patient/month	n.r.	n.r.	0.021
Kobayashi et al., 2014	**Tx success rate*, % of episodes (N=61; 146 episodes)**	**MEPM+IVIg (n=62 episodes)**	**MEPM alone (n=84 episdoes)**	
AL	Tx success rate overall	69.4%	65.5%	p=0.862
	Tx success, patients with serum IgG <500 mg/dL	81.3%	62.5%	p=0.238
	Tx success, patients with serum IgG >500 mg/dL	66.0%	66.7%	p=1.000
	Tx success patients with ANC <0.5×10^9/L	64.3%	53.7%	p=0.460
Molica et al., 1996	**Type and site (N=42; crossover tx in 2 groups of randomised n=21)**	**IVIg therapy phase (N=42)**	**Empirical phase (N=42)**	
CLL	**Major infections**			
	• Sepsis	2	1	
	• Bacterial pneumonia	3	5	
	• Peritonitis	0	1	
	• Mycotic pneumonia	0	1	
	• Varicella	0	1	
	Total major infections	***5***	***9***	
	Minor infections			
	• Bronchitis	14	19	
	• Bacterial skin infection	1	2	
	• Bacterial stomatitis	0	2	
	• Lower urinary tract infection	1	0	
	• Fever of unknown origin	13	15	
	• Herpes zoster	1	4	
	Total minor infections	***30***	***42***	
	Total serious (major+minor) infections	***35***	***51***	
	Trivial infections	**6**	**11**	
	Total overall infections	***41***	***62***	
	Patients with no infections	22*	10*	*p<0.02 (χ-square).
	Calculated infections rates			
	Patient-months, total	376	368	
	Patient months, mean	*8.95*	*8.76*	
	Infections per patient	*0.98*	*1.48*	
	Rate, infections /patient/month	*0.109*	*0.168*	
	Major infections per patient	*0.119*	*0.214*	
	Rate, major infections /patient/month	*0.013*	*0.024*	
Musto et al., 1995	**Infections outcomes (6+12+6 mo crossover of either IVIg or No IVIg [observation])**	**During IVIg phases (N=25 received IVIg + observation)**	**During No IVIg phases (N=25 received IVIg + observation)**	**p-value**
MM	**Serious infections**	**10**	**30**	**p<0.002**
	Of which, life-threatening (septicaemia or pneumonia)	0	9	
	Serious infections per patient	*0.4*	*1.2*	
	Minor infections	**23**	**27**	**n.s.**
	Total infections	***33***	***57***	
	Patient months, total	261	250	
	Patient months, mean	*10.4*	*10.0*	
	Rate serious infections / patient /month	*0.04*	*0.12*	
Sullivan et	**Infectious Outcomes**	**IVIg (n=184)**	**No IVIg (n=185)**	

al., 1990	from d0 to d100 or discharge (N=369)					
BMT	Infections	No.	Rate/100 d	No.	Rate/100 d	Relative risk (p-value)
	Patient days at risk	13,415		13,878		
	Septicaemia					
	• gram-positive	14	0.1	19	0.14	1.69 (n.s.)
	• gram-negative	11	0.08	33	0.24	2.65 (0.0039)
	• fungal	13	0.1	16	0.12	1.32 (n.s.)
	• other	1	–	0	–	
	Total, septicaemia	39	0.29	68	0.49	2.15 (0.0022)
	Rate, septicaemia per patient month	*0.088*		*0.149*		
	Bacteraemia					
	• gram-positive	121	0.90	122	0.88	0.98 (n.s.)
	• gram-negative	41	0.31	38	0.27	0.88 (n.s.)
	• fungal	16	0.12	13	0.09	0.83 (n.s.)
	Total, bacteraemia	178	1.33	173	1.25	0.97 (n.s.)
	Rate, bacteraemia per patient month	*0.404*		*0.379*		
	Local infection					
	• gram-positive	18	0.13	27	0.19	1.32 (n.s.)
	• gram-negative	9	0.07	12	0.09	0.96 (n.s.)
	• fungal	10	0.07	22	0.16	1.82 (n.s.)
	• viral	33	0.25	43	0.31	1.36 (n.s.)
	• other	2	–	3	–	
	• clinical only	22	0.16	37	0.27	1.46 (n.s.)
	Total, local infection	94	0.70	144	1.04	1.36 (0.029)
	Rate, local infection per patient month	*0.213*		*0.316*		

Notes: Values in italics have been calculated for this evaluation. Boughton et al., (1995) – infections reported were mostly respiratory tract infections. Specific types of infection not reported, except where positive bacterial culture obtained (19/122 infectious episodes). Chapel et al., 1994 – 'other chest infections' included acute bronchitis and pleurisy not requiring hospitalisation; 'all infections' incidence was not reported by group thus recurrent infection rates could not be calculated; minor infections were not reported in the article though the authors state theses were mostly viral URT infections with similar rates in each group, thus total infections numbers were not derived either. Molica et al., 1996 – infections were pooled according to tx status (Ig or observation) not reported by randomised group or study part (group 1 or 2; part 1 [1st 6mo], part 2 [12mo after 1st crossover], part 3 [6mo after 2nd crossover]); The authors reported that 30 (of 42) patients completed 6 months of treatment and 17 completed 12 months (and that a further 17 did not complete the study) but not report how many patients completed the full 6+12+6 months protocol. Sullivan et al., 1990 – infections of URT or oral cavity and herpes simplex infections were not reported.

ALL=acute lymphoblastic leukaemia; BMT=bone marrow transplant; BSI=bloodstream infections; CLL=chronic lymphocytic leukaemia; GI=gastrointestinal; IgG=immunoglobulin gamma; IVIg=intravenous immunoglobulin; HSCT=haematopoietic stem cell transplant; LRTI=lower respiratory tract infection; MM=multiple myeloma; mo=month; n.r.=not reported; n.s.=not significant; SEM=standard error of the mean; tx=treatment; URTI=upper respiratory tract infection; UTI=urinary tract infection; yr=year.

Table 86 Randomised studies presenting infections – SCIg vs no SCIg

Study	Outcome	Intervention	Comparator	Comparison
Vacca et al., 2018	**Infectious episodes (all outcomes adjusted to 365d)**	**SCIg (n=24)**	**No SCIg (n=22)**	
MM	**Major infections**			
	• Sepsis	0	24	
	• Bacterial pneumonia	0	18	
	• Bronchitis with sepsis	0	43	
	• Pharyngo-tracheitis with sepsis	2	24	
	• Acute sinusitis	0	5	
	• Erysipelas (skin infection)	0	12	
	• Urinary infection with sepsis	1	32	
	• Fever of unknown origin	13	32	
	Major infections in 365d	***16***	***190***	
	Minor infections			
	• Tracheobronchitis	32	64	

	• Bacterial skin infection	11	16	
	• Bacterial stomatitis	6	12	
	• Lower UTI	19	36	
	• Thoracic herpes zoster	1	15	
	Minor infections in 365d	***69***	***143***	
	Upper respiratory tract infections	*2*	*29*	
	Lower respiratory tract infections	*32*	*125*	
	Total overall infections	*85*	*333*	
	Infection rates	SCIg (n=24)	No SCIg (n=22)	p value
	Major infections/patient/mo	*0.056*	*0.720*	p<0.001
	Minor infections/patient/mo	*0.240*	*0.542*	p<0.001
	Upper respiratory infections/patient/yr	*–*	*–*	p<0.001
	Lower respiratory infections/patient/yr	*–*	*–*	p<0.001
	Duration of infections	SCIg (n=24)	No SCIg (n=22)	p value
	Total infection days per yr (range)	62 (26-87)	135 (88-194)	p<0.01

Notes: Values in italics have been calculated for the evaluation. Vacca et al., 2018 – The article describes infections as serious vs nild/non-serious in the graphs; major vs minor in tables and severe in the text – it is assumed Upper and lower respiratory tract infection rates were not calculated as patient numbers for these events were not reported. Infection rates presented as bar charts without values , thus rates were derived using the infection episodes above, assuming 365d and N=46 patients. Numbers approximating the authors' graphs could not be replicated for the 'No SCIg' major infections rate.

CLL=chronic lymphocytic leukaemia; GI=gastrointestinal; IVIg=intravenous immunoglobulin; HSCT=haematopoietic stem cell transplant; MM=multiple myeloma; mo=month; n.r.=not reported; n.s.=not significant; SCIg=sub-cutaneous immunoglobulin; SEM=standard error of the mean; tx=treatment; UTI=urinary tract infection; yr=year.

Table 87 Cohort studies presenting infections – IVIg vs no IVIg

Study	Outcome	Intervention	Comparator	Comparison
Blombery et al., 2011	**Patients with infectious complications until d30 (fever; infections) (%)**	**IVIg (n=130)**	**No IVIg (n=110)**	**p value**
MM+HSCT	• Fever (%)	111 (85.4)	93 (84.5)	p=0.86
	• BSI (%)	46 (35.4)	35 (31.8)	p=0.59
	• Pneumonia (%)	23 (17.7)	16 (14.5)	p=0.60
	• UTIs (%)	2 (1.5)	2 (1.8)	p=1.00
	• GI infections (%)	6 (4.6)	11 (10.0)	p=0.13
	Total HSCTs with infections	*188*	*157*	
	Crude rate infections per patient (30 d)	*1.45*	*1.43*	
	Crude rate / patient / year	*17.59*	*17.37*	
	Total HSCTs with infections, not including fever	*77*	*64*	
	Crude rate, not including fever (30 d)	*0.59*	*0.58*	
	Median no. febrile d [range]	2 [0–15]	2 [0–12]	p=0.17
Van Winkle et al., 2018	**Infectious complications during maintenance chemo.±IVIg,**	**IVIg (N=36)**	**No IVIG, (N=82)**	**p-value**
ALL	*Treatment duration mo, mean (range) (based on mean # infusions which were given monthly)*	*10.5 mo (range 1-31)*	*–*	
	Prior: Days of treatment from induction to maintenance chemotherapy *(taken to be equivalent to patient days of observation)(SEM)*	279 (11.0)	244 (6.7)	0.004
	Prior: mean episodes of bacteremia or fungemia (SEM)	0.89 (0.2) [32.0 episodes]	0.26 (0.1) [21.3 episodes]	0.002
	Prior rate, bacteraemia or fungaemia	*0.097*	*0.032*	
	During: Days of chemotherapy, mean patient-days*(taken to be equivalent to patient days at risk)* (SEM)	713 (33.2)	736 (22.8)	p=0.617
	During: mean episodes of bacteraemia (SEM)	0.25 (0.09) [9.0 episodes]	0.15 (0.04) [12.3 episodes]	0.336
	During: rate, bactermaemia (/patient/month)	*0.011*	*0.006*	

	Mean no. infections treated with antibiotics, outpatient (SEM)	4.8 (0.8) [172.8 episodes]	4.7 (0.4) [385.4 episodes]	0.756
	During: rate, infection + antibiotics (/patient/mo)	*0.205*	*0.194*	

Notes: Van Winkle et al., 2018 – p values took into account days of chemotherapy; otherwise no information about duration of observation or IgG treatment was provided in the paper. Days of chemotherapy were assumed to be equivalent to patient daysof observation or at risk for the purpose of this evaluation.

Table 88 Studies presenting infections within sub-groups – Blombery et al., 2011

Study, Indication	Outcome	Intervention 1	Intervention 2	Comparison
Blombery et al., 2011	**Patients with infections (%) – single vs multi-dose sub-groups**	**IVIg (multi-dose RT) (n=25)**	**IVIg (single dose only) (n=105)**	**p value**
MM+HSCT	• BSI (%)	9 (36.0%)	37 (35.2%)	p=1.00
	• Pneumonia (%)	8 (32.0%)	15 (14.3%)	p=0.046
	• UTIs (%)	0	2 (1.9%)	p=1.00
	• GI infections (%)	2 (8.0%)	4 (3.8%)	p=0.33
	Total patients with infections	*19*	*58*	
	Crude rate per patient	*0.76*	*0.55*	

BSI=bloodstream infections; GI=gastrointestinal; HSCT=haematopoietic stem cell transplant; IVIg=intravenous immunoglobulin; MM=multiple myeloma; RT=replacement therapy; UTI=urinary tract infection.

Table 89 Case series presenting within-patient (before/after) infections outcomes – IVIg

Study, Indication	Outcome	Comparator		Intervention	Comparison
Besa, 1992	**Infections – episodes**	**Before IVIg (3 yrs)(N=23)**		**During IVIg tx (3 yrs)(N=23)**	
CLL	Bacterial				
	• Pneumonia	8		0	
	• Sepsis	2		0	
	• Sinusitis	5		0	
	• Cellulitis	4		2	
	Bacterial infections (n patients)	19 (in 13 patients)		2 (in 1 patient)	
	Viral				
	• Zoster	1		0	
	Total n/N patients (%)	13/23 (57)		1/23 (4)	
	Infections per patient per month	*0.023*		*0.002*	
Brenner, 1996	**Infections in CLL patients (N=54, of which 26 SID patients)**	**Patient history**	**Equivalent to study period (no IVIg)**	**During study period (~12mo)(+IVIg)**	
CLL(22), MM(4)*	Evaluable patients, N	21	21	21	
	Patients with infections	21	n.r.	8	
	Patients with no infections	0	n.r.	13	
	Infections requiring hospitalisation				
	• Sepsis	6	4	2	
	• Pneumonia	11	6	3	
	• UTI	5	3	2	
	• Cellulitis	6	5	7	
	All requiring hospitalisation*	32*	21*	14	

	Rate /patient/month		*0.083*	*0.056*	
	Treated ambulatory				
	• Fever, URI	5	6	9	
	• Bronchitis	7	4	3	
	• Others	3	1	0	
	All treated ambulatory	15	11	12	
	All infections in CLL patients	47	32	26	
	Infections in MM patients				
	Evaluable patients n/N	3/4	n.r.	3/4	
	Bacterial infections	n.r.	n.r.	0	
Günther & Dreger 2013	**Infections before/during IVIg (N=10)**	**Prior to IVIg (N=10) (3 mo)**		**During IVIg (N=10) (mean tx 51.2±25.4 mo)**	
Various*	Severe bacterial infections	24 infections (≥2 in 7/10 patients) *Or 96 events in 12mo*		29 infections *Or 6.8 events in 12mo*	
	• URTIs	5		6	
	• LRTIs	11 *(or 44 events in 12mo)*		17 *(or 4 events in 12mo)*	
	• Ear infections	0		2	
	• Sinusitis	1		0	
	• Skin & soft tissue infection	0		1	
	• GI infection	0		1	
	• Not specified	7		2	
	Mean severe bacterial infections (/patient/yr)	9.7		0.7	
	(rate /patient /month)	*0.808*		*0.058*	
	Non-bacterial infections	n.r.		17 viral 6 unclear 4 fungal	
Jurlander et al., 1994	**Infection-related outcomes (N=15)***	**12 months prior to study (N=14)**		**12 months during study (median 14mo, range 3-20) (n=14)**	**p-value**
CLL	Patient months	168		169	
	Febrile episodes	63		31	p=0.004
	Severe infection (septicaemia, pneumonia, meningitis)	6		3	p>0.05
	Rate of severe infections (/patient month)	*0.036*		*0.018*	
	Death due to infection (septicaemia)	–		2	

*Notes: Brenner, 1996 studied a population (N=54) of CLL(22), MM(4) and also ITP and PAPS patients. The CLL and MM patient results are reported separately where possible. For CLL, the total numbers of infections requiring hospitalisation did not correspond with the individual contributing infections but this was not explained by the authors. No further MM data were presented due to small patient numbers. Günther & Dreger 2013 – underlying disease types: CLL(5), FL(2), WM(1), IgA-plasmacytoma (1), MDS(1)]; duration of IVIg ranged from 22.5 months to more than 9 years; LRTIs included acute bronchitis, bronchopulmonary infection and pneumonia. Jurlander et al., 1994 – 1 of 15 patients discontinued after 4 infusions and is not included, thus N=14.

CLL=chronic lymphocytic leukaemia; ITP=idiopathic thrombocytopenic purpura; IVIg=intravenous immunoglobulin; MM=multiple myeloma; n.r.=not reported; PAPS= primary antiphospholipid syndrome; URI=upper respiratory tract infection.

Table 90 Non-comparative studies presenting within-patient (before/after) infections outcomes – SCIg

Study, Indication	Outcome	Comparator	Intervention
Dimou et al. (2018)	**Patients with events (N=33)**	**12 mo prior to SCIg commencement**	**During SCIg (median follow up 11.2 mo)**

CLL(25), MM(3); NHL(3), HL(1)**	Total patients with events	26/33 (*79%*)	6/33 (*18%*)
	• Lower respiratory tract infection	15	4
	• Upper respiratory tract infection	7	0
	• Renal infections	3	0
	• Soft tissue infections	2	0
	• Herpes zoster reactivation	1	0
	• Nail infection	0	1
	• Flu-like infection and dermal infection (*staphylococcus aureus*)	0	1
	Infections other than LRTIs	*13*	*2*
	Total infections	*28*	*6*
	Infections/patient/month	*0.071*	*0.016*
	Patients with no events	7	27
	Infections incidence	78.8%	18.2%

*Notes: Dimou et al., 2018 – the individual haematological malignancy totals do not add up to N=33. In 12 mo prior to SCIg, 13/33 patients were receiving IVIg; 18/33 were tx naïve. Patients switching from IVIg to SCIg (n=13) had a minimum 28 days washout period prior to SCIg commencement. 7 patients switching to SCIg had no history of infection but, as they were already receiving IVIg, it was assumed these individuals met the ESMO 2015 and BCSH 2012 guidelines criteria specified by the authors prior to IVIg commencement.

Table 91 IVIg+SCIg studies – infections outcomes as a single group

Study, Indication	Outcome	Comparator	Intervention	Comparison
Benbrahim et al., 2019	**Infectious episodes**	**Baseline Total (N=160) (IVIg n=50, SCIg n=110)**	**Last visit (N=160) (IVIg n=50, SCIg n=110)**	
MM(54), CLL(54), NHL(48), HL(4)	Patients with hypo-GG	69.2%	15.9%	p=0.14
	Incidence of infectious episodes /patient/year:	**Prior to study (95% CI)**	**During follow-up (95% CI)**	**p-value**
	• Sepsis	2.43 (2.18–2.70)	1.90 (1.46–2.49)	p=0.001
	total events	*389*	*304*	
	rate /patient/month	*0.203*	*0.158*	
	• WHO grade >2 infections	0.51 (0.39–0.67)	0.30 (0.21–0.42)	p=0.09
	total events	*82*	*48*	
	rate /patient/month	*0.043*	*0.025*	
Duraisingham et al., 2014	**Infections before / after IgG-RT (SID group N=39)**	**Infections before IgG (1 yr)**	**Infections during IgG (1 yr)**	**p-value**
CLL(1), MM(1) NHL(11); MDS(1) MGUS(1)	Evaluable patients, n/39 IVIg: 13 (33.3%) SCIg: 26 (66.6%)	28/39	37/39	
	Serious infections	25	7	p=0.0058
	Serious infections in haem. malignancy patients, n=15	*11 (in 6 of 15 patients)*	*3 (in 2 of 15 patients)*	
	Serious infections per /patient /month in HM subset	*11 infections in 15 patients: 0.061*	*3 infections in 15 patients: 0.017*	
	• Pneumonia	13 (52.0%)	0 (0.0%)	
	• Sepsis	8 (32.0%)	3 (42.9 %)	
	• Meningitis	0 (0.0%)	0 (0.0%)	
	• Infective exacerbation, asthma or COPD	1 (4.0%)	2 (28.6%)	
	• Other	3 (12%)	2 (28.6%)	
	Non-serious infections	122	56	p=0.0023
	(Haem. malignancy patients n/N=15/39)	*(37)*	*(21)*	
	Non-serious infections per /patient /month in HM subset	*37 infections in 15 patients: 0.206*	*21 infections in 15 patients: 0.117*	
	• Respiratory	95 (77.9%)	44 (75.9%)	

	• UTI	3 (2.5%)		4 (6.9%)	
	• Diarrhoea	6 (4.9%)		2 (3.4%)	
	• Skin	2 (1.6%)		1 (1.7%)	
	• Sinusitis	7 (5.7%)		3 (5.2%)	
	• Otitis	6 (4.9%)		0 (0.0%)	
	• Conjunctivitis	1 (0.8%)		1 (1.7%)	
	• HSV	1 (0.8%)		1 (1.7%)	
	• Other	1 (0.8%)		0 (0.0%)	
	Infection-free subjects	1 (2.6%)		9 (23.1%)	

Reiser et al., 2017	**Infections (N=307; IVIg=287; SCIg=20)**	**Infections in 12mo before study**		**Infections on study**	
CLL(130); NHL (99); MM(43); other(35)	Groups:	IgG new starters *(n=96)*	IgG ongoing *(n=211)*	IgG new starters (n=96)	IgG ongoing (n=211)
	Patients with any infection	79/96 (82%)	137/211 (65%)	6mo: 35% 12mo: 21% 18mo: 29% 24mo: 42%	6mo: 39% 12mo: 41% 18mo: 43% 24mo: 44%
	Patients with serious bacterial infections	6/96 (6.3%)	6/211 (2.9%)	6mo: 2.4% 12mo: 1.5% 18mo: 0% 24mo: 3.8%	6mo: 0.5% 12mo: 1.2% 18mo: 1.9% 24mo: 0.7%
	Patients with other serious infections	9/96 (9.4%) 17 events	5/211 (2.4%)	6mo: 2.4% 12mo: 3.0% 18mo: 8.6% 24mo: 0%	6mo: 2.6% 12mo: 1.2% 18mo: 3.2% 24mo: 1.4%
	Patients with 'general infections' (non-serious)	73/96 (76%)	131/211 (62%)	6mo: 30% 12mo: 16% 18mo: 21% 24mo: 38%	6mo: 38% 12mo: 39% 18mo: 39% 24mo: 42%
	*3 or more serious infections	2/*96* (2.1%)	n.r.	n.r.	n.r.
	Serious bacterial infection rate (/patient-yr) *Serious bacterial infection rate (/patient-month)*	0.250 *(equals 77 events)* *0.021*		0.036 *(equals 11 events)* *0.003*	
	All serious infections rate (bacterial+other)(/patient/yr) All serious infections rate (bacterial+other)(/patient/mo)	n.r. –		0.122 *(equals 37 events)* *0.010* *(equals 3 events)*	

Notes: Benbrahim et al., 2019 – study did not report total infections per patient or for the cohort; although the study reported rates per patient year, figures equivalent to 24 months prior/26 months during IgG treatment were used for the forest plots; Sepsis is a serious subset of septicaemia involving potential organ damage or organ failure (Singer et al. 2016). Sepsis numbers were higher than total infections requiring antibiotics and five times higher than those requiring IV antibiotics. Based on event numbers, this would be more consistent with a diagnosis of 'fever' or 'clinical signs of infection' instead of sepsis. The authors did not define sepsis. Duraisingham et al., 2014 – only data from n=39 SID patients presented; p-values are from Figure 3 (E & F) of the publication; figures for n=15 haematological malignancy subset in italics extracted from raw data in supplementary spreadsheet, note this included one patient with MGUS and excluded another with WM.
CLL=chronic lymphocytic leukaemia; COPD=chronic obstructive pulmonary disease; HL=Hodgkin lymphoma; HM=haematological malignancy; HSV=herpes simplex virus; hypo-GG=hypogammaglobulinaemia; IgG=gamma immunoglobulin; IVIg=intravenous immunoglobulin; MDS=myelodysplastic syndrome; MGUS=monoclonal gammopathy of undetermined significance; MM=multiple myeloma; mo=month; NHL=non-Hodgkin lymphoma; n.r.=not reported; SCIg=subcutaneous immunoglobulin; UTI=urinary tract infection; WHO=World Health Organization; WM=Waldenström macroglobulinaemia; yr=year.

Table 92 Studies comparing infections outcomes between routes of administration – IVIg vs SCIg

Study, Indication	**Outcome**	**Intervention 1**	**Intervention 2**	**Comp-arison**
Sundin et al.,	**IgG replacement**	**IVIg (N=46)**	**SCIg (N=12)**	**p-value**

2012		n=24 haem. malignancy	n=2 haem. malignancy	
HSCT	Initiation post-HSCT, at median months (range)	3 (0–8)	3 (1–8)	
	Duration, median months from initiation (range)	9 (6–20)	5 (3–47)	
	Number of patients (%) with chronic need for IgG-RT	4 (8.7%)	5 (41.7%)	p=0.01
	Number of clinical infections	mean (range)	mean (range)	
	• Bacterial	1.5 (0–8	1.8 (0–5))	
	• Viral	2.1 (0–9)	2.1 (1–4)	
	• Fungal	0.5 (0–5)	0.1 (0–1)	
	• Unidentified	2 (0–10)	2.5 (0–4)	
	Total clinical infections per patient	5.5 (0–23)	6.4 (3–13)	
Windegger et al. (2019)	**Infections requiring hospitalisation/total annual (N=13)**	**Initial 12 mo IVIg Mean per patient**	**Subsequent 12 mo SCIg Mean per patient**	
(undefined)	Mean annual no. infections	1.85	2.31	n.s.
	Rate, infections/patient/mo	*0.15*	*0.19*	

Notes: Sundin et al., 2012 – no observation period for events reported thus infection rate per patient month not derived. GP=general practitioner; IgG-RT=immunoglobulin gamma replacement therapy; LoS = length of hospital stay; n.s.=not statistically significant

Table 93 Supportive studies comparing infections outcomes between dose levels

Study, Indication	Outcome	Intervention 1	Intervention 2	Comparison
Chapel, Dicato et al (1994)	**Infections overall**	**High dose IVIg 500mg/kg (n=16)**	**Low dose IVIg 250 mg/kg (n=18)**	**p-value**
CLL (N=34)	Patient months	180	198	
	patient years	*15*	*16.5*	
	Total infections	23 episodes	22 episodes	p=0.64
	Serious infections			
	• Bacterial	5	7	
	Serious bacterial infections (/patient year)	0.33	0.42	p=0.68
	Rate infection (/patient/mo)	*0.028*	*0.035*	
	• Viral	0	2	
	• Fungal	0	0	
	• Unknown	1	2	
	Minor infections			
	• Bacterial	2	2	
	• Viral	5	7	
	• Fungal	1	1	
	• Unknown	9	1	
Stump et al., 2017	**Infections post-infusion episode (n/N (%) episodes)**	**IgG-ABW**	**IgG-IBW**	**p-value**
*Various	Within 30 days	20/125 (16%)	13/84 (15.5%)	0.823
	Within 60 days	24/121 (19.8%)	19/82 (23.2%)	0.568

*Notes: Stump et al., 2017 – patients who died within 30 / 60 days of receiving IVIG were not included in the respective totals. 'Various' = CLL(74); AL(65); MM(26); NHL(32); HL(7); CML(5); numbers represent patient encounters (i.e. infusions); patient numbers were not reported in the publication however the authors advised that the median IVIg dose per patient during the study period (30mo or 2.5yr) was 1 (range 1-18) or a mean of 2.6 doses and a total of 79 patients (S Stump, pers. comm. May 2019).

ABW=actual body weight dosing; AL=acute leukaemia; CLL=chronic lymphocytic leukaemia; IBW=ideal (lean) body weight dosing; IgG=immunoglobulin gamma; IVIg=intravenous immunoglobulin; MM=multiple myeloma; mo=month; NHL=Non-Hodgkin lymphoma; HL=Hodgkin lymphoma; CML=chronic myeloid leukaemia

APPENDIX G ECONOMIC ANALYSIS APPENDICES

OVERVIEW

Table 94 Decision algorithm for undertaking an economic evaluation in the setting of the Ig Review

Comparative safety of Ig	Comparative effectiveness of Ig				
	Inferior		Uncertain	Non-inferior	Superior
	No active comparator	Active comparator			
Inferior	x	F	?	F[b]	F[a]
Uncertain	x	F[a]	?	?	F[a]
Non-inferior	x[c]	F	?	$	F
Superior	x[c]	F[a]	?	F[b]	F

Ig = immunoglobulin

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

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

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

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

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

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

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

STRUCTURE AND RATIONALE OF THE ECONOMIC EVALUATION

Table 95 Economic literature search terms

Search	Query	Items found
Pubmed		
#1	Hypogammaglobulinemia OR Hypogammaglobulinaemia OR hypogamma* OR "low immunoglobulin" OR "immunoglobulin deficiency"[mh] OR "low Ig" OR "low IgG" OR "immunoglobulin deficiency" OR "immunoglobulin deficient" OR "Ig deficiency" OR "IgG deficiency" OR immunoparesis OR immunodeficiency	374,761

Search	Query	Items found
#2	"secondary immunodeficiency" OR leukaemia* OR leukemia* OR "Leukemia, Lymphoid"[mh] OR "Leukemia, Mast-Cell"[mh] OR "Leukemia, Myeloid"[mh] OR "Leukemia, plasma cell"[mh] OR "Leukemia, Radiation-Induced"[mh] OR "Multiple myeloma"[mh] OR "multiple myeloma" OR "Lymphoma"[mh] OR lymphoma OR lymphoproliferative OR "non-hodgkin" OR nonhodgkin OR (("B-cell" OR haematological OR hematological) AND (malignancy OR malignancies OR neoplasm[mh])) OR "Hematologic Neoplasms"[mh] OR "Hematopoietic Stem Cell Transplantation"[mh] OR HSCT OR (("stem cell" OR "progenitor cell") AND (transplantation OR transplant OR transplants))	650,396
#3	"Immunoglobulin G"[mh] OR immunoglob* OR "immune globulin" OR immunoglobulin OR "gamma globulin" OR gammaglobulin OR IVIg OR SCIg OR IgG OR Ig OR Intragam OR Privigen OR Hizentra OR Gamunex OR Flebogamma OR Intragam OR Evogam OR Panzyga OR Hyqvia OR Intratect OR Octagam OR Kiovig OR Gammanorm OR Cuvitru OR GammaSTAN OR BayGam OR Polygam OR GAMMAGARD OR Sandoglobulin OR Panglobulin OR Carimune OR GAMMAKED OR Iveegam OR Bivigam OR Gammaplex OR Intratect OR IQYMUNE OR SUBCUVIA OR Subgam OR Vigam OR CUTAQUIG OR GAMASTAN OR GAMIMUNE OR IGIVNEX OR RESPIGAM OR VIVAGLOBIN OR GammaQuin OR Nanogam OR CLAIRYG OR ENDOBULINE OR SANDOGLOBULINE OR TECTASIM OR TEGELINE OR "Kenketu Glovenin")	957,682
#4	"economics"[MeSH Terms] OR "costs and cost analysis"[MeSH Terms] OR "cost allocation"[MeSH Terms] OR "cost benefit analysis"[MeSH Terms] OR "cost control"[MeSH Terms] OR "cost savings"[MeSH Terms] OR "cost of illness"[MeSH Terms] OR "health care costs"[MeSH Terms] OR "drug costs"[MeSH Terms] OR "health expenditures"[MeSH Terms] OR "economics, medical"[MeSH Terms] OR "economics, pharmaceutical"[MeSH Terms] OR "fees and charges"[MeSH Terms] OR "budgets"[MeSH Terms] OR "cost"[All fields] OR "high cost"[All Fields] OR "low cost"[All Fields] OR "cost utility"[All Fields] OR "cost-utility"[All Fields] OR "economics"[All Fields] OR "financial"[All Fields] OR "finance"[All Fields] OR "healthcare cost"[All Fields] OR "health care cost"[All Fields] OR "cost estimate"[All Fields] OR "unit cost"[All Fields] OR "economics, pharmaceutical"[MeSH Terms] OR ("economics"[All Fields] AND "pharmaceutical"[All Fields]) OR "pharmaceutical economics"[All Fields] OR "pharmacoeconomic"[All Fields] OR "commerce"[MeSH Terms] OR "commerce"[All Fields] OR "price"[All Fields] OR (("costs"[All Fields] OR "cost"[All Fields]) AND "analysis"[All Fields]) OR "costs and cost analysis"[All Fields] OR "pricing"[All Fields] OR "cost-effectiveness"[All Fields] OR "cost effectiveness"[All Fields] OR "economic evaluation"[All Fields]	1,148,753
#5	#1 AND #2 AND #3 AND #4	67
Embase		
#1	'immunoglobulin deficiency'/exp OR 'immunoglobulin deficiency' OR 'immunoparesis'/exp OR immunoparesis OR 'hypogammaglobulinaemia'/exp OR hypogammaglobulinaemia OR 'hypogammaglobulinemia'/exp OR hypogammaglobulinemia OR 'low immunoglobulin' OR 'low ig' OR 'low igg' OR 'immunoglobulin deficient' OR 'ig deficiency' OR 'igg deficiency'/exp OR 'igg deficiency' OR 'immunodeficiency'/exp OR immunodeficiency	634,524
#2	'secondary immunodeficiency' OR leukemia OR leukaemia OR 'acute leukemia' OR 'myeloid leukemia' OR 'multiple myeloma' OR lymphoma OR 'nonhodgkin lymphoma' OR 'acute lymphoblastic leukemia' OR 'chronic lymphatic leukemia' OR 'chronic lymphocytic leukemia' OR 'small lymphocytic lymphoma' OR 'b cell malignancy' OR 'haematological malignancy' OR 'hematopoietic stem cell transplantation' OR 'progenitor cell transplant'	788,651
#3	'immunoglobulin' OR 'immune globulin' OR immunoglobulin OR 'gamma globulin' OR gammaglobulin OR ivig OR scig OR igg OR ig OR privigen OR hizentra OR gamunex OR flebogamma OR intragam OR evogam OR panzyga OR hyqvia OR octagam OR kiovig OR gammanorm OR cuvitru OR gammastan OR baygam OR polygam OR gammagard OR sandoglobulin OR panglobulin OR carimune OR gammaked OR iveegam OR bivigam OR gammaplex OR intratect OR iqymune OR subcuvia OR subgam OR vigam OR cutaquig OR gamastan OR gamimune OR igivnex OR respigam OR vivaglobin OR gammaquin OR nanogam OR clairyg OR endobuline OR sandoglobuline OR tectasim OR tegeline OR 'kenketu glovenin'	742,290

Search	Query	Items found
#4	'health economics'/exp OR 'cost'/exp OR 'cost effectiveness analysis'/exp OR 'health care cost'/exp OR 'drug cost'/exp OR 'pharmacoeconomics'/exp OR 'budget'/exp OR 'cost utility analysis'/exp OR 'cost' OR 'cost effectiveness analysis' OR 'cost utility analysis' OR 'health economics'	1,157,537
#5	#1 AND #2 AND #3 AND #4	253
	Total, after duplicates were excluded	292
	Studies identified from pearling	0
	Total studies included	1

Note: Searches were conducted on 3/4/19

INPUTS TO THE ECONOMIC EVALUATION

RESOURCE USE

Table 96 Estimation of Ig costs

2017/18 Ig Report	Price in $(m)	Grams (weight,%)	Price/gram in $	Reference to Ig report section
Domestic IVIg including plasma fractionation (excluding hyperimmune plasma) Intragam P* Intragam 10	443.2	3,161,673 (51.6%)	140.18	Calculation required for cost: Plasma fractionation costs of $252.2M (expenditure section) + total domestic product cost of $195M (Table 6) – Evogam product cost of $4M (Table 6) = $443.2M Calculation for grams: Total domestic grams 3,225,722 (Table 6) – Evogam grams 64,049 = 3,161,673
Domestic IVIg excluding plasma fractionation Intragam P* Intragam 10	191	3,161,673 (51.6%)	60.41	Table 6: Calculation for price: Total domestic price – Evogam price Calculation for grams: Total domestic grams – Evogam grams
Imported IVIg Flebogamma Privigen	124	2,759,266 (45.0%)	44.94	Table 6: Calculation for price: Total imported price – Hizentra price Calculation for grams: Total imported grams – Hizentra grams
SCIg domestic Evogam	4	64,049 (1.0%)	62.45	Table 6
SCIg imported Hizentra	8	143,729 (2.3%)	55.66	Table 6
Total domestic Ig grams		3,225,722		Expenditure
Total imported Ig grams		2,902,995		Expenditure

Ig = immunoglobulin; IVIg = intravenous immunoglobulin; SCIg = subcutaneous immunoglobulin.
Source: NBA (2019b)

SENSITIVITY ANALYSES

Table 97 Sensitivity analyses

	Inc. cost	Inc. QALYs	ICER	% change
Base case analysis	**$41,011**	**0.4109**	**$99,803**	**-**
Baseline annual infection rates (base case: Paxton, Hawkins & Crispin 2016, serious 0.43, non-serious 1.05)				
Chapel et al. (1991): serious 1.07, non-serious 3.75	$53,054	0.6163	$86,079	–14%
Molica et al. (1996): serious 0.29, non-serious 1.73	$50,160	0.3819	$131,328	32%
Chapel et al. (1994): serious 0.26, non-serious 1.75	$51,346	0.3653	$140,555	41%
Musto, Brugiatelli & Carotenuto (1995): serious: 0.43, non-serious 2.30	$51,163	0.4612	$110,936	11%
Vacca et al. (2018): serious 8.64, non-serious 6.50	$69,310	0.6529	$106,160	6%
Sullivan et al. (1990): serious 1.79, non-serious 3.79	$48,062	0.7121	$67,493	–32%
Duraisingham et al. (2014): serious 0.73, non-serious 2.47	$46,868	0.5604	$83,627	–16%
IRR of Ig treatment effect (base case: serious, 0.15; non-serious 0.61)				
Serious infections, 0.05	$36,936	0.4450	$82,992	–17%
Serious infections, 0.43	$52,526	0.3139	$167,315	68%
Non-serious infections, 0.51	$35,828	0.4694	$76,328	–24%
Non-serious infections, 0.72	$46,236	0.3523	$131,233	31%
Non-randomised IRRs, serious: 0.25, 0.46	$37,625	0.4620	$81,436	–18%
Dose of Ig (base case: 0.37 g/kg), 0.4 g/kg	$45,885	0.4109	$111,666	12%
Duration of Ig treatment (base case: 2.2 years)				
1 year	$19,162	0.2450	$78,222	–22%
3 years	$55,209	0.4771	$115,716	16%
5 years	$84,261	0.5430	$155,168	55%
10 years	$125,097	0.5457	$229,233	130%
Exclude development of bronchiectasis	$41,213	0.0141	$2,927,525	2833%
Time horizon (base case: 10 years)				
2.2 years (as per Ig treatment duration)	$38,869	0.0322	$1,208,343	1111%
5 years	$39,552	0.1509	$262,086	163%
Discount rate (base case: 5%)				
0%	$43,815	0.5525	$79,305	–21%
3%	$42,068	0.4610	$91,256	–9%
Ratio of non-serious to serious infections (base case: 2.45)				
0.75	$33,506	0.3519	$95,202	–5%
5.9	$52,953	0.4660	$113,643	14%
Transition probabilities (base case: adjusted)				
Transitions from infection health state, unadjusted	$45,309	0.3087	$146,792	47%
Transitions from bronchiectasis health state, unadjusted (exc. cost of Ig in bronchiectasis)	$27,245	0.3237	$84,176	–16%
Transitions from infection and bronchiectasis, unadjusted	$29,927	0.2335	$128,154	28%
Mortality				

	Inc. cost	Inc. QALYs	ICER	% change
Base case analysis	**$41,011**	**0.4109**	**$99,803**	**-**
RR with haematological malignancy, lower limit 2.49 (base case: 2.55)	$41,018	0.4083	$100,455	1%
RR with haematological malignancy, upper limit 2.60 (base case: 2.55)	$41,004	0.4130	$99,279	–1%
Increased mortality risk (2.34) with a history of infections above CLL (base case: none)	$39,963	0.4686	$85,283	–15%
RR with infections, −50% to 2.09 (base case: 4.18)	$40,322	0.3437	$117,317	18%
RR with infections, +50% to 6.27 (base case: 4.18)	$41,521	0.4668	$88,945	–11%
RR with bronchiectasis, 2.14 (base case: 2.20)	$40,994	0.4047	$101,301	2%
RR with bronchiectasis, 2.26 (base case: 2.20)	$41,027	0.4170	$98,375	–1%
RR with *P. aeruginosa* infections, 1.772 (base case: 2.391)	$40,847	0.3977	$102,698	3%
RR with *P. aeruginosa* infections, 3.125 (base case: 2.391)	$41,192	0.4259	$96,727	–3%
Patient weight (base case: 75 kg)				
70 kg	$37,161	0.4109	$90,434	–9%
80 kg	$44,868	0.4109	$109,190	9%
Cost of Ig per gram, $58.23 (base case: $60.41)	$38,925	0.4109	$94,727	–5%
Windegger et al. (2019) costs				
Cost of disease management (base case: MBS item costs)	$40,779	0.4109	$99,240	–1%
Cost of treating infections (base case: AR-DRG/MBS costs)	$44,097	0.4109	$107,313	8%
Cost of P. aeruginosa health state (base case: AR-DRG costs)	$41,179	0.4109	$100,213	0%
Cost of hospitalisation of serious infections (base case: $12,775)				
$9,961, based on AR-DRG E62A	$42,528	0.4109	$103,495	4%
$15,261, based on AR-DRG I67A	$39,671	0.4109	$96,542	–3%
$18,269, based on AR-DRG I64A	$38,050	0.4109	$92,597	–7%
$25,381, based on AR-DRG T60A	$34,216	0.4109	$83,268	–17%
$52,961, based on AR-DRG R01A	$19,349	0.4109	$47,088	–53%
Cost of treating non-serious infections (base case: $184)				
$92 (i.e. −50%)	$41,334	0.4109	$100,589	1%
$276 (i.e. +50%)	$40,687	0.4109	$99,016	–1%
Cost of serious bronchiectasis infections (base case: $9,143)				
$4,572 (i.e. −50%)	$43,017	0.4109	$104,685	5%
$13,715 (i.e. +50%)	$39,005	0.4109	$94,921	–5%
Cost per week in the *P. aeruginosa* health state (base case: $1,322)				
$661 (i.e. −50%)	$47,109	0.4109	$114,644	15%
$1,983 (i.e. +50%)	$34,912	0.4109	$84,962	–15%
Utilities				
No disutility for IV infusion (base case: disutility per infusion included)	$41,011	0.4146	$98,916	–1%
Utility decrement for serious infections, 0.205 (base case: 0.41)	$41,011	0.3966	$103,398	4%
Utility decrement for non-serious infections, 0.01 (base case: 0.06)	$41,011	0.3914	$104,769	5%
Utility with infections with bronchiectasis, 0.6278 (base case:	$41,011	0.3714	$110,407	11%

	Inc. cost	Inc. QALYs	ICER	% change
Base case analysis	**$41,011**	**0.4109**	**$99,803**	**-**
0.5355) Utility with infection, 0.6956 (base case: 0.5805 with Ig, 0.5532 without Ig)	$41,011	0.4042	$101,466	2%

CLL = chronic lymphocytic leukaemia; ICER = incremental cost-effectiveness ratio; Ig = immunoglobulin; IRR = incidence rate ratio; IV = intravenous; QALY = quality-adjusted life year.

APPENDIX H FINANCIAL IMPLICATIONS APPENDIX

IDENTIFICATION, ESTIMATION AND REDUCTION OF UNCERTAINTY

Table 98 Estimation of the average weighted cost per gram within the acquired hypogammaglobulinemia indictaion

	Usage (grams)	Proportion of use	Cost per gram
Domestic IVIg	1,242,051	88.6%	$140.18
Imported IVIg	117,863	8.4%	$44.94
Domestic SCIg	5,345	0.4%	$62.45
Imported SCIg	36,766	2.6%	$55.66
Weighted price			**$129.66**

Ig = immunoglobulin; IVIg = intravenous immunoglobulin; SCIg = subcutaneous immunoglobulin.
Source: Table 96, Appendix G and the 'HTA Data April2019.xlsx' workbook.

ATTACHMENT 1

IgG products TGA registered strengths and approved indications (search of January 2019 undertaken for PICO Confirmation)

Product	Route	ARTG#	Strength	TGA Approved Indications
Intragam 10	IV infusion	162489 162488 162487 162486	20g/200mL vial 10g/100mL vial 5g/50mL vial 2.5g/25mL vial	Thrombocytopenic Purpura, in adults or children at high risk of bleeding or prior to surgery to correct the platelet count • Kawasaki disease • Guillain-Barré Syndrome • Chronic Inflammatory Demyelinating Polyneuropathy • Multifocal Motor Neuropathy • Myasthenia Gravis (MG) in acute exacerbation (myasthenic crisis) or prior to surgery and/or thymectomy; as maintenance therapy for moderate to severe MG when other treatments have been ineffective or caused intolerable side effects • Short-term therapy for severely affected nonparaneoplastic Lambert-Eaton Myasthenic Syndrome patients • Treatment of significant functional impairment in patients who have a verified diagnosis of stiff person syndrome.
Privigen 10%	IV infusion	219160 143368 143337 143273	40g (100g/L, 10%) bottle 20g (100g/L, 10%) bottle 10g (100g/L, 10%) bottle 5g (100g/L, 10%) bottle	Replacement therapy • Primary Immunodeficiency Diseases (PID). • Myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections. • Symptomatic hypogammaglobulinaemia secondary to underlying disease or treatment. Immunomodulatory therapy • Idiopathic Thrombocytopenic Purpura (ITP) in patients at high risk of bleeding or prior to surgery to correct the platelet count. • Guillain-Barré Syndrome (GBS). • Kawasaki disease. • Chronic Inflammatory Demyelinating Polyneuropathy (CIDP). • Multifocal Motor Neuropathy (MMN). • Myasthenia Gravis (MG) exacerbations. • Lambert-Eaton Myasthenic Syndrome (LEMS). • Stiff Person Syndrome (SPS).
Hizentra	SC infusion	285345 285344 207386 207385	20% Solution 10 mL PFS 20% Solution 5 mL PFS 20% Solution 5 mL vial 20% Solution 10 mL vial	Replacement therapy in adults and children in: • Primary Immunodeficiency Disease (PID) and • Symptomatic hypogammaglobulinaemia secondary to underlying disease or treatment. Immunomodulatory therapy in:

Product	Route	ARTG#	Strength	TGA Approved Indications
		207384 207383	20% Solution 50 mL vial 20% Solution 20 mL vial	• Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) as maintenance therapy after stabilisation with IVIg.
Gamunex 10%	IV infusion*	117240 117239 117238 117237 116689	20g/200mL vial 10g/100mL vial 5g/50mL vial 2.5g/25mL vial 1g/10mL vial	Replacement therapy in: - Primary Immunodeficiency (PI) Diseases. - Symptomatic Hypogammaglobulinaemia secondary to underlying disease or treatment. Immunomodulation in: - Idiopathic Thrombocytopaenic Purpura (ITP), in patients at high risk of bleeding or prior to surgery to correct the platelet count. - Guillain Barré Syndrome (GBS). - Chronic Inflammatory Demyelinating Polyneuropathy (CIDP). - Kawasaki disease.
Flebogamma 10%	IV infusion	184353 182359 182358	5g/50mL vial 20g/200mL vial 10g/100mL vial	Replacement therapy indications: • Primary Immunodeficiency (PI) Diseases • Symptomatic hypogammaglobulinaemia secondary to underlying disease or treatment. Immunomodulation indications: • Idiopathic Thrombocytopaenic Purpura (ITP), in patients at high risk of bleeding or prior to surgery to correct the platelet count. • Guillain Barré syndrome. • Kawasaki disease.
Flebogamma 5%	IV infusion	143803 143802 143801 143800 140602	20g/400mL vial 10g/200mL vial 5g/100mL vial 2.5g/50mL vial 0.5g/10mL vial	Replacement therapy in: Primary immunodeficiency syndromes such as: - congenital agammaglobulinaemia and hypogammaglobulinaemia - common variable immunodeficiency - severe combined immunodeficiency - Wiskott Aldrich syndrome Myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections. Children with congenital AIDS and recurrent infections. Immunomodulation Idiopathic thrombocytopenic purpura (ITP), in children or adults at high risk of bleeding or prior to surgery to correct the platelet count. Guillain Barré syndrome. Allogeneic bone marrow transplantation.

Product	Route	ARTG#	Strength	TGA Approved Indications
Intragam P	IV infusion	68635 68634 68633 68632	0.6g/10mL vial 30g/500mL vial 12g/200mL vial 3g/50mL vial	Intragam P is indicated for replacement IgG therapy in: • Primary Immunodeficiency Diseases • Symptomatic hypogammaglobulinaemia secondary to underlying disease or treatment. Intragam P is indicated for immunomodulatory therapy in: • Idiopathic Thrombocytopenic Purpura, in adults or children at high risk of bleeding or prior to surgery to correct the platelet count • Kawasaki disease • Guillain-Barré Syndrome.
Evogam	SC infusion	173324 173323 173315	16% solution 3.2g/20mL vial 16% solution 1.6g/10mL vial 16% solution 0.8g/5mL vial	Evogam is indicated in adults and children for replacement therapy in: • Primary Immunodeficiency Diseases (PID) and • symptomatic hypogammaglobulinaemia secondary to underlying disease or treatment.
Panzyga	IV infusion	291740 291645 291648 291647 291646 291644	1g/10mL vial 2.5g/25mL vial 10g/100mL bottle 5g/50mL bottle 20g/200mL bottle 30g/300mL bottle	Replacement therapy in: Primary immunodeficiency diseases. Myeloma or chronic lymphatic leukaemia with severe secondary hypogammaglobulinaemia and recurrent bacterial infections. Symptomatic hypogammaglobulinaemia secondary to underlying disease or treatment. Immunomodulation in: Idiopathic thrombocytopenic purpura (ITP), in patients at high risk of bleedingor prior to surgery to correct the platelet count. Guillain Barré syndrome. Kawasaki disease.
Hyqvia	SC infusion	235178	10% solution	HYQVIA is indicated for replacement therapy in adults in: • Primary Immunodeficiency Disease (PID) and • Symptomatic hypogammaglobulinaemia secondary to underlying disease or treatment
Intratect	IV infusion	232085 232084 232078 232077 164551 164550 164549 164548	20g in 200 mL vial 10g in 100 mL vial 5g in 50 mL vial 1g in 10 mL vial 5% 5g in 100mL vial 5% 1g in 20 mL vial 5% 10g in 200 mL vial 5% 2.5g in 50mL vial	Replacement therapy in. * Primary Immunodeficiency Diseases. * Symptomatic hypogammaglobulinaemia secondary to underlying disease or treatment. Immunomodulation. * Idiopathic thrombocytopenic purpura, in adults or children at high risk of bleeding or prior to surgery to correct the platelet count.. *Guillain Barre syndrome. * Kawasaki disease.

Product	Route	ARTG#	Strength	TGA Approved Indications
Octagam	IV infusion	155604 155603 155602 155601 113928 113927 113926 113925	20g/200mL [100 mg/mL] 10g/100mL [100 mg/mL] 5g/50mL [100 mg/mL] 2g/20mL [100 mg/mL] 10g/200mL bottle [50 mg/mL] 5g/100mL bottle [50 mg/mL] 2.5g/50mL bottle [50 mg/mL] 1g/20mL vial [50 mg/mL]	Replacement therapy • Primary immunodeficiency syndromes: - congenital agammaglobulinaemia and hypogammaglobulinaemia - common variable immunodeficiency - severe combined immunodeficiencies - Wiskott Aldrich syndrome. • Myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections. • Children with congenital Acquired Immune Deficiency Syndrome (AIDS) who have repeated bacterial infections. Immunomodulatory effect • Idiopathic thrombocytopenic purpura, in adults or children with a high risk of bleeding or prior to surgery to correct the platelet count. • Guillain Barré syndrome • Kawasaki disease. Allogeneic bone marrow transplantation
Kiovig	See indications	198488 131973 131969 131968 131966 131953	30g/300mL vial (100 mg/mL) 20g/200mL vial (100 mg/mL) 10g/100mL vial (100 mg/mL) 5g/50mL vial (100 mg/mL) 2.5g/25mL vial (100 mg/mL) 1g/10mL vial (100 mg/mL)	KIOVIG administered intravenously is indicated for: (1) Replacement therapy indications - Primary immunodeficiency disorders (PID); - Symptomatic hypogammaglobulinaemia secondary to underlying disease or treatment. (2) Immunomodulation indications - Idiopathic thrombocytopenia purpura (ITP), in patients at high risk of bleeding or prior to surgery to correct the platelet count; - Guillain Barré Syndrome; - Kawasaki Disease; - Multifocal Motor Neuropathy (MMN). KIOVIG administered subcutaneously is indicated for: (1) Replacement therapy indications - Primary immunodeficiency disorders (PID).
Gammanorm	IM or SC infusion	128705 128703	3300mg/20mL vial 1650mg/10mL vial	• Replacement therapy in adults and children with primary immunodeficiency syndromes such as: - congenital agammaglobulinaemia and hypogammaglobulinaemia - common variable immunodeficiency - severe combined immunodeficiencies

Product	Route	ARTG#	Strength	TGA Approved Indications
				- IgG subclass deficiencies with recurrent infections Replacement therapy in myeloma or chronic lymphatic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections.
CSL NORMAL IMMUNOGLOBULIN VF	IM injection	61216 61215	800mg/5mL vial 320mg/2mL vial	Normal Immunoglobulin-VF is indicated in the management of congenital and acquired forms of primary hypogammaglobulinaemia. It may also be of value in treating secondary forms of this disorder as in leukaemia, nephrosis and acute protein-losing enteropathy, particularly when there is a tendency to recurrent infection.
CUVITRU	SC infusion	282579	20% solution vial	CUVITRU is indicated as replacement therapy in adult and paediatric patients for Primary immunodeficiency diseases (PID) and Symptomatic hypogammaglobulinaemia secondary to underlying disease or treatment.

*SC infusion only recommended for replacement therapy in patients with primary immunodeficiency

REFERENCES

Ammann, EM, Jones, MP, Link, BK, Carnahan, RM, Winiecki, SK, Torner, JC, McDowell, BD, Fireman, BH & Chrischilles, EA 2016, 'Intravenous immune globulin and thromboembolic adverse events in patients with hematologic malignancy', *Blood*, vol. 127, no. 2, Jan-14, pp. 200-207.

Benbrahim, O, Viallard, JF, Choquet, S, Royer, B, Bauduer, F, Decaux, O, Crave, JC, Fardini, Y, Clerson, P & Levy, V 2018, 'A French observational study describing the use of human polyvalent immunoglobulins in hematological malignancy-associated secondary immunodeficiency', *Eur J Haematol*, vol. 101, no. 1, Jul, pp. 48-56.

Benbrahim, O, Viallard, JF, Choquet, S, Royer, B, Bauduer, F, Decaux, O, Crave, JC, Fardini, Y, Clerson, P & Levy, V 2019, 'The use of octagam and gammanorm in immunodeficiency associated with hematological malignancies: a prospective study from 21 French hematology departments', *Hematology*, vol. 24, no. 1, Dec, pp. 173-182.

Besa, EC 1992, 'Recent advances in the treatment of chronic lymphocytic leukemia: defining the role of intravenous immunoglobulin', *Semin Hematol*, vol. 29, no. 3, Jul, pp. 14-23.

Blanchette, CM, Noone, JM, Stone, G, Zacherle, E, Patel, RP, Howden, R & Mapel, D 2017, 'Healthcare Cost and Utilization before and after Diagnosis of Pseudomonas aeruginosa among Patients with Non-Cystic Fibrosis Bronchiectasis in the U.S', *Med Sci (Basel)*, vol. 5, no. 4, Sep 23.

Blombery, P, Prince, HM, Worth, LJ, Main, J, Yang, M, Wood, EM & Westerman, DA 2011, 'Prophylactic intravenous immunoglobulin during autologous haemopoietic stem cell transplantation for multiple myeloma is not associated with reduced infectious complications', *Ann Hematol*, vol. 90, no. 10, Oct, pp. 1167-1172.

Boughton, BJ, Jackson, N, Lim, S & Smith, N 1995, 'Randomized trial of intravenous immunoglobulin prophylaxis for patients with chronic lymphocytic leukaemia and secondary hypogammaglobulinaemia', *Clin Lab Haematol*, vol. 17, no. 1, Mar, pp. 75-80.

Brenner, B 1996, 'Clinical experience with Octagam, a solvent detergent (SD) virus inactivated intravenous gammaglobulin', *Clinical and Experimental Rheumatology*, vol. 14, 1996, pp. S115-S119.

Brown, JS, Baxendale, H & Floto, RA 2011, 'Immunodeficiencies associated with bronchiectasis', in RA Floto & CS Haworth (eds), *European Respiratory Society Monographs: Bronchiectasis*, pp. 178-191.

Carlisle, PS, Gucalp, R & Wiernik, PH 1993, 'Nosocomial infections in neutropenic cancer patients', *Infect Control Hosp Epidemiol*, vol. 14, no. 6, Jun, pp. 320-324.

Chapel, HM, Dicato, M, Gamm, H, Brennan, V, Ries, F, Bunch, C & Lee, M 1994a, 'Immunoglobulin replacement in patients with chronic lymphocytic leukaemia: a comparison of two dose regimes', *Br J Haematol*, vol. 88, no. 1, Sep, pp. 209-212.

Chapel, HM, Griffiths, H, Brennan, V, Bunch, C, Lea, J & Lee, M 1991, 'Hypogammaglobulinaemia in low grade B cell tumours; significance and therapy', *Immunological investigations*, vol. 20, no. 2, 1991, pp. 187-191.

Chapel, HM, Lee, M, Hargreaves, R, Pamphilon, DH & Prentice, AG 1994b, 'Randomised trial of intravenous immunoglobulin as prophylaxis against infection in plateau-phase multiple myeloma. The UK Group for Immunoglobulin Replacement Therapy in Multiple Myeloma', *Lancet*, vol. 343, no. 8905, Apr 30, pp. 1059-1063.

de Jong, PA, Dodd, JD, Coxson, HO, Storness-Bliss, C, Pare, PD, Mayo, JR & Levy, RD 2006, 'Bronchiolitis obliterans following lung transplantation: early detection using computed tomographic scanning', *Thorax*, vol. 61, no. 9, Sep, pp. 799-804.

Dimou, M, Iliakis, T, Maltezas, D, Bitsani, A, Kalyva, S, Koudouna, A, Kotsanti, S, Petsa, P, Papaioannou, P, Kyrtsonis, MC & Panayiotidis, P 2018, 'Efficacy-safety of Facilitated Subcutaneous Immunoglobulin in Immunodeficiency Due to Hematological Malignancies. A Single-Center Retrospective Analysis', *Anticancer Res*, vol. 38, no. 7, Jul, pp. 4187-4191.

Duraisingham, SS, Buckl, , M, Dempster, J, Lorenzo, L, Grigoriadou, S & Longhurst, HJ 2014, 'Primary vs. secondary antibody deficiency: clinical features and infection outcomes of immunoglobulin replacement', *PLoS One*, vol. 9, no. 6, 2014, p. e100324.

Eibl, MM 2008, 'History of immunoglobulin replacement', *Immunol Allergy Clin North Am*, vol. 28, no. 4, Nov, pp. 737-764, viii.

Finch, S, McDonnell, MJ, Abo-Leyah, H, Aliberti, S & Chalmers, JD 2015, 'A Comprehensive Analysis of the Impact of Pseudomonas aeruginosa Colonization on Prognosis in Adult Bronchiectasis', *Ann Am Thorac Soc*, vol. 12, no. 11, Nov, pp. 1602-1611.

Gale, RP, Chapel, HM, Bunch, C, Rai, KR, Foon, K, Courter, SG & Tait, D 1988, 'Intravenous immunoglobulin for the prevention of infection in chronic lymphocytic leukemia. A randomized, controlled clinical trial', *New England journal of medicine*, vol. 319, no. 14, 1988, pp. 902-907.

Gunn, ML, Godwin, JD, Kanne, JP, Flowers, ME & Chien, JW 2008, 'High-resolution CT findings of bronchiolitis obliterans syndrome after hematopoietic stem cell transplantation', *J Thorac Imaging*, vol. 23, no. 4, Nov, pp. 244-250.

Günther, G & Dreger, B 2013, 'Post-marketing observational study on 5% intravenous immunoglobulin therapy in patients with secondary immunodeficiency and recurrent serious bacterial infections', *Microbiol Immunol*, vol. 57, no. 7, Jul, pp. 527-535.

Guyatt, G, Oxman, AD, Sultan, S, Brozek, J, Glasziou, P, Alonso-Coello, P, Atkins, D, Kunz, R, Montori, V, Jaeschke, R, Rind, D, Dahm, P, Akl, EA, Meerpohl, J, Vist, G, Berliner, E, Norris, S, Falck-Ytter, Y & Schunemann, HJ 2013, 'GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes', *J Clin Epidemiol*, vol. 66, no. 2, Feb, pp. 151-157.

Independent Hospital Pricing Authority [IHPA] 2019, *National Hospital Cost Data Collection Report, Public Sector, Round 21 (Financial year 2016-17)*, Independent Hospital Pricing Authority,, viewed 5 July 2019, <https://www.ihpa.gov.au/publications/national-hospital-cost-data-collection-report-public-sector-round-21-financial-year>.

Jurlander, J, Geisler, CH & Hansen, MM 1995, 'Treatment of hypogammaglobulinaemia in chronic lymphocytic leukaemia by low-dose intravenous gammaglobulin', *Eur J Haematol*, vol. 53, no. 2, Aug, pp. 114-118.

Kearney, PJ, Kershaw, CR & Stevenson, PA 1977, 'Bronchiectasis in acute leukaemia', *Br Med J*, vol. 2, no. 6091, Oct 1, pp. 857-859.

Knowles, GK, Stanhope, R & Green, M 1980, 'Bronchiectasis complicating chronic lymphatic leukaemia with hypogammaglobulinaemia', *Thorax*, vol. 35, no. 3, Mar, pp. 217-218.

Kobayashi, R, Suzuki, D, Sano, H, Kishimoto, K, Yasuda, K & Kobayashi, K 2014, 'Effect of meropenem with or without immunoglobulin as second-line therapy for pediatric febrile neutropenia', *Pediatr Int*, vol. 56, no. 4, Aug, pp. 526-529.

Li, AM, Sonnappa, S, Lex, C, Wong, E, Zacharasiewicz, A, Bush, A & Jaffe, A 2005, 'Non-CF bronchiectasis: does knowing the aetiology lead to changes in management?', *Eur Respir J*, vol. 26, no. 1, Jul, pp. 8-14.

Liberati, A, Altman, DG, Tetzlaff, J, Mulrow, C, Gotzsche, PC, Ioannidis, JP, Clarke, M, Devereaux, PJ, Kleijnen, J & Moher, D 2009, 'The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration', *PLoS Med*, vol. 6, no. 7, Jul 21, p. e1000100.

Moher, D, Liberati, A, Tetzlaff, J, Altman, DG & Group, P 2009, 'Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement', *PLoS Med*, vol. 6, no. 7, Jul 21, p. e1000097.

Molica, S, Musto, P, Chiurazzi, F, Specchia, G, Brugiatelli, M, Cicoira, L, Levato, D, Nobile, F, Carotenuto, M, Liso, V & et al. 1996, 'Prophylaxis against infections with low-dose intravenous immunoglobulins (IVIG) in chronic lymphocytic leukemia. Results of a crossover study', *Haematologica*, vol. 81, no. 2, 1996, pp. 121-126.

Morehead, RS 1997, 'Bronchiectasis in bone marrow transplantation', *Thorax*, vol. 52, no. 4, Apr, pp. 392-393.

Musto, P, Brugiatelli, M & Carotenuto, M 1995, 'Prophylaxis against infections with intravenous immunoglobulins in multiple myeloma', *Br J Haematol*.

National Blood Authority [NBA] 2019a, *Data Analysis and Reporting*, National Blood Authority Canberra, <https://www.blood.gov.au/data-analysis-reporting>.

National Blood Authority [NBA] 2019b, *National Report on the Issue and Use of Immunoglobulin (Ig) Annual Report 2017-18*, National Blood Authority Canberra.

Okada, F, Ando, Y, Kondo, Y, Matsumoto, S, Maeda, T & Mori, H 2004, 'Thoracic CT findings of adult T-cell leukemia or lymphoma', *AJR Am J Roentgenol*, vol. 182, no. 3, Mar, pp. 761-767.

Orange, JS, Hossny, EM, Weiler, CR, Ballow, M, Berger, M, Bonilla, FA, Buckley, R, Chinen, J, El-Gamal, Y, Mazer, BD, Nelson, RP, Jr., Patel, DD, Secord, E, Sorensen, RU, Wasserman, RL, Cunningham-Rundles, C, Primary Immunodeficiency Committee of the American Academy of Allergy, A & Immunology 2006, 'Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology', *J Allergy Clin Immunol*, vol. 117, no. 4 Suppl, Apr, pp. S525-553.

Parkman, R 2008, 'Antigen-specific immunity following hematopoietic stem cell transplantation', *Blood Cells Mol Dis*, vol. 40, no. 1, Jan-Feb, pp. 91-93.

Paxton, L, Hawkins, C & Crispin, P 2016, 'Selecting haematological malignancy patients for intravenous immunoglobulin', *Intern Med J*, vol. 46, no. 10, Oct, pp. 1216-1218.

Pijnenburg, MW, Cransberg, K, Wolff, E, Bouquet, J & Merkus, PJ 2004, 'Bronchiectasis in children after renal or liver transplantation: a report of five cases', *Pediatr Transplant*, vol. 8, no. 1, Feb, pp. 71-74.

Quint, JK, Millett, ER, Joshi, M, Navaratnam, V, Thomas, SL, Hurst, JR, Smeeth, L & Brown, JS 2016, 'Changes in the incidence, prevalence and mortality of bronchiectasis in the UK from 2004 to 2013: a population-based cohort study', *Eur Respir J*, vol. 47, no. 1, Jan, pp. 186-193.

Reiser, M, Borte, M, Huscher, D, Baumann, U, Pittrow, D, Sommer, C, Stangel, M, Fasshauer, M, Gold, R & Hensel, M 2017, 'Management of patients with malignancies and secondary immunodeficiencies treated with immunoglobulins in clinical practice: Long-term data of the SIGNS study', *Eur J Haematol*, vol. 99, no. 2, Aug, pp. 169-177.

Remberger, M, Ackefors, M, Berglund, S, Blennow, O, Dahllof, G, Dlugosz, A, Garming-Legert, K, Gertow, J, Gustafsson, B, Hassan, M, Hassan, Z, Hauzenberger, D, Hagglund, H, Karlsson, H, Klingspor, L, Kumlien, G, Le Blanc, K, Ljungman, P, Machaczka, M, Malmberg, KJ, Marschall, HU, Mattsson, J, Olsson, R, Omazic, B, Sairafi, D, Schaffer, M, Svahn, BM, Svenberg, P, Swartling, L, Szakos, A, Uhlin, M, Uzunel, M, Watz, E, Wernerson, A, Wikman, A, Wikstrom, AC, Winiarski, J & Ringden, O 2011, 'Improved survival after allogeneic hematopoietic stem cell transplantation in recent years. A single-center study', *Biol Blood Marrow Transplant*, vol. 17, no. 11, Nov, pp. 1688-1697.

Royle, JA, Baade, PD, Joske, D, Girschik, J & Fritschi, L 2011, 'Second cancer incidence and cancer mortality among chronic lymphocytic leukaemia patients: a population-based study', *Br J Cancer*, vol. 105, no. 7, Sep 27, pp. 1076-1081.

Sanchez-Ramon, S, Dhalla, F & Chapel, H 2016, 'Challenges in the Role of Gammaglobulin Replacement Therapy and Vaccination Strategies for Hematological Malignancy', *Front Immunol*, vol. 7, 2016, p. 317.

Singer, M, Deutschman, CS, Seymour, CW, Shankar-Hari, M, Annane, D, Bauer, M, Bellomo, R, Bernard, GR, Chiche, JD, Coopersmith, CM, Hotchkiss, RS, Levy, MM, Marshall, JC, Martin, GS, Opal, SM, Rubenfeld, GD, van der Poll, T, Vincent, JL & Angus, DC 2016, 'The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)', *JAMA*, vol. 315, no. 8, Feb 23, pp. 801-810.

Stump, SE, Schepers, AJ, Jones, AR, Alex, er, MD & Auten, JJ 2017, 'Comparison of Weight-Based Dosing Strategies for Intravenous Immunoglobulin in Patients with Hematologic Malignancies', *Pharmacotherapy*, vol. 37, no. 12, 2017, pp. 1530-1536.

Sullivan, KM, Kopecky, KJ, Jocom, J, Fisher, L, Buckner, CD, Meyers, JD, Counts, GW, Bowden, RA, Peterson, FB, Witherspoon, RP & et al. 1990, 'Immunomodulatory and antimicrobial efficacy of intravenous immunoglobulin in bone marrow transplantation', *N Engl J Med*, vol. 323, no. 11, Sep 13, pp. 705-712.

Sullivan, KM, Storek, J, Kopecky, KJ, Jocom, J, Longton, G, Flowers, M, Siadak, M, Nims, J, Witherspoon, RP, Anasetti, C, Appelbaum, FR, Bowden, RA, Buckner, CD, Crawford, SW, Deeg, HJ, Hansen, JA, McDonald, GB, Sanders, JE & Storb, R 1996, 'A controlled trial of long-term administration of intravenous immunoglobulin to prevent late infection and chronic graft-vs.-host disease after marrow transplantation: clinical outcome and effect on subsequent immune recovery', *Biol Blood Marrow Transplant*, vol. 2, no. 1, Feb, pp. 44-53.

Sundin, M, Nordin, K, Jostemyr, Y & Winiarski, J 2012, 'Subcutaneous IgG replacement after pediatric SCT', *Pediatric Transplantation*, vol. 16, no. 8, 2012, pp. 866-871.

Tanawuttiwat, T & Harindhanavudhi, T 2009, 'Bronchiectasis: pulmonary manifestation in chronic graft versus host disease after bone marrow transplantation', *Am J Med Sci*, vol. 337, no. 4, Apr, p. 292.

Vacca, A, Melaccio, A, Sportelli, A, Solim, o, AG, Dammacco, F & Ria, R 2018, 'Subcutaneous immunoglobulins in patients with multiple myeloma and secondary hypogammaglobulinemia: a randomized trial', *Clinical Immunology*, vol. 191, 2018, pp. 110-115.

Van Winkle, P, Burchette, R, Kim, R, Raghunathan, R & Qureshi, N 2018, 'Prevalence and Safety of Intravenous Immunoglobulin Administration During Maintenance Chemotherapy in Children with Acute Lymphoblastic Leukemia in First Complete Remission: A Health Maintenance Organization Perspective', *Perm J*, vol. 22, 2018, pp. 17-141.

Visentin, A, Compagno, N, Cinetto, F, Imbergamo, S, Zambello, R, Piazza, F, Semenzato, G, Trentin, L & Agostini, C 2015, 'Clinical profile associated with infections in patients with chronic lymphocytic leukemia. Protective role of immunoglobulin replacement therapy', *Haematologica*, vol. 100, no. 12, Dec, pp. e515-518.

Wadhwa, PD & Morrison, VA 2006, 'Infectious complications of chronic lymphocytic leukemia', *Semin Oncol*, vol. 33, no. 2, Apr, pp. 240-249.

Weeks, JC, Tierney, MR & Weinstein, MC 1991, 'Cost effectiveness of prophylactic intravenous immune globulin in chronic lymphocytic leukemia', *New England journal of medicine*, vol. 325, no. 2, 1991, pp. 81-86.

Windegger, TM, Nghiem, S, Nguyen, KH, Fung, YL & Scuffham, PA 2019, 'Cost-utility analysis comparing hospital-based intravenous immunoglobulin with home-based subcutaneous immunoglobulin in patients with secondary immunodeficiency', *Vox Sanguinis*.

Wong, J, Wood, EM, Crispin, P, Weinkove, R, McQuilten, ZK, Australasian, L & Lymphoma Group Supportive Care, G 2019, 'Managing hypogammaglobulinaemia secondary to haematological malignancies in Australia and New Zealand: a clinician survey', *Intern Med J*, vol. 49, no. 3, Mar, pp. 358-363.