Review of Immunoglobulin (Ig) for

Primary Immunodeficiency Diseases (PID)

with Antibody Deficiency

July 2020

MSAC application no. 1592

Contracted Assessment

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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

| Main issues for MSAC consideration |
| --- |
| * Ig was generally associated with mild adverse events. Severe events are rare and mostly resolved by treatment cessation. * Ig was associated with lowered infection rates, (including upper and lower respiratory tract infections, pneumonia, otitis media, sinusitis and diarrhoea) lower hospitalisation rates and higher IgG levels. * Data on the safety and effectiveness of Ig in patients with PID is limited, at high risk of bias and rated as low-very low quality for effectiveness outcomes. * Despite the significant limitations associated with the evidence base, it is unlikely that higher quality studies addressing these issues will be forthcoming. * The Assessment group has identified potential areas for future research for patients with PID in Australia:   + From a clinical effectiveness point of view, research into the impact of co-interventions on outcomes would be helpful to resolve the confounding issues identified in the evidence base.   + It may be useful to establish a registry or database for PID patients and document the treatment(s) they are receiving. This would be helpful to understand Ig therapy coverage and true population prevalence in Australia.   + It would be beneficial to have more granular information on how Ig is used for PID in Australia. Ideally, future research would focus on each PID subgroup separately and be aimed to answer the questions such as; usage patterns for children compared to adults, how disease severity may impact Ig usage, patterns of Ig usage, trial periods off Ig and which patients successfully stop or reduce their Ig usage. |

**Immunoglobulin (Ig) for Primary Immunodeficiency Diseases (PID) with Antibody Deficiency**

This Assessment of immunoglobulin (Ig) for the treatment of primary immunodeficiency diseases (PID) with antibody deficiency is intended for the Medical Services Advisory Committee (MSAC). Immunoglobulin replacement therapy for this indication is presently funded by the National Blood Authority (NBA) under the national blood supply arrangements, but the cost-effectiveness of this use has not previously been established. The target population is people with PID currently eligible for Ig treatment under *the Criteria for Clinical Use of Immunoglobulin in Australia[[1]](#footnote-2)* (herein described as *‘the Criteria Version 3’*)

Alignment with agreed PICO Confirmation

This Assessment of Ig for the treatment of PID with antibody deficiency addresses most of the PICO elements that were pre-specified in the PICO Confirmation that was ratified by the Immunoglobulin Review Reference Group. Insufficient comparative evidence in patients with PID was identified; therefore, the Assessment also includes single arm studies. These were limited to patients with common variable immune deficiency (CVID) in accordance with the PICO Confirmation.

### Proposed Medical Service

The intervention under review is Ig for immunoreplacement therapy in people with PID with antibody deficiency. Ig replacement therapy is a blood-based treatment whereby Ig is administered into the bloodstream of a person with PID in order to provide them with the antibodies needed to adequately fight infections.

In Australia, Version 3.1 of *the Criteria Version 3* outlines which patients are eligible for Government funded Ig treatment. *The Criteria Version 3* provides a list of medical conditions and specific circumstances around entitlement for publicly funded Ig treatment, as well as an outline of the approved Ig dosage and recommended duration of use. Table 5 (Section A.2.) summarises the approved dosage and medical review conditions described in *the Criteria Version 3* for patients with PID with antibody deficiency.

Ig can be delivered in one of two ways; intravenously (IVIg) or via subcutaneous injection (SCIg), both of these administration methods are used for publicly funded Ig in Australia. The main difference between the two delivery methods is that IVIg requires venous access, can deliver larger volumes (therefore fewer doses) and is carried out by skilled healthcare professionals in a hospital setting. SCIg, which delivers smaller volumes, may be self-administered at home (following appropriate training by a registered nurse or technician).

Ig products used for replacement therapy in PID are funded under the National Blood Authority (NBA). The NBA has contracts with suppliers to source products both domestically (from plasma collected by the Australian Red Cross Blood Service) and through a range of international suppliers. The sixteen Ig items on the ARTG that are relevant to this application are shown in Table 6 (Section A.2.).

### Proposal for Public Funding

There are no proposed MBS items relevant to this Assessment.

### Population

PID refers to a large heterogeneous group of disorders where one or more components of the immune system is compromised, leading to absent or impaired immune function. The specific conditions (as diagnosed by an Immunologist) described in *the Criteria Version 3* for patients with PID with antibody deficiency to be eligible for publicly funded Ig treatment in Australia are:

* Severe combined immunodeficiency (SCID)
* Combined immunodeficiency (e.g. thymoma)
* Combined immunodeficiency with associated or syndromal features
* Common variable immunodeficiency (CVID)
* Possible CVID – below normal serum IgG but normal serum IgA
* Severe reduction in all Ig isotypes with decreased or absent B-cells
* Severe reduction in at least two Ig isotypes with low/normal B-cells (e.g. CVID)
* Severe reduction in serum IgG and IgA with normal/elevated IgM
* Transient hypogammaglobulinaemia of infancy
* Lymphoproliferative syndromes

People with immunodeficiency disorders are prone to infection (increased frequency and severity), abnormal inflammation, cancer and autoimmune diseases.

PID are considered rare disorders; however, their true incidence and prevalence (individually or collectively) is unknown. The Australasian Society of Clinical Immunology and Allergy PID Register conducted a cumulative, cross-sectional survey of PID patients in Australia and New Zealand and identified 1,209 patients across 88 centres and 56 PID syndromes ([Kirkpatrick and Riminton, 2007b](#_ENREF_48)). Based on these data the estimated prevalence of PID was 5.6 cases per 100,000 population for Australia. However, using 2018-19 data on Ig use for PID provided by the NBA, the prevalence of PID is calculated as being approximately 9.09 per 100,000 population. The differences between these prevalence estimates over the past 20 years may be due to one or more reasons such as: increasing diagnostic capabilities; changes in disease definitions; or improved access to treatments. It is also important to note that PID patients (diagnosed or undiagnosed) who are not on Ig therapy are not included in the Ig usage data from the NBA. Consequently, the NBA data might underestimate the total (potentially eligible) population in Australia with PID.

Table 1 describes the number of patients in 2018/19 accessing Ig therapy funded by the NBA. The total number of patients treated for that period was 2,292.

Table 1 Ig usage, patient and episode numbers for PID with antibody deficiency in 2018-19 ([NBA, 2019](#_ENREF_59))

| Specific condition name | Ig usage (grams) | Patient count | Treatment episodes | | |
| --- | --- | --- | --- | --- | --- |
| **Total** | **Private** | **Public** |
| SCID | 10,496 | 42 | 550 | 86 | 464 |
| CID | 1,094 | 8 | 52 | 1 | 51 |
| Wiskott-Aldrich syndromeA | 845 | 5 | 52 | 13 | 39 |
| CVID | 639,109 | 1,847 | 26,590 | 5,740 | 20,850 |
| Possible CVID | 7,801 | 55 | 319 | 71 | 248 |
| Severe reduction in all Ig isotypes with decreased or absent B-cells | 826 | 5 | 33 | - | 33 |
| X-linked agammaglobulinaemiaB | 40,221 | 118 | 1,725 | 211 | 1,514 |
| Severe reduction in at least two Ig isotypes with low/normal B-cells | 9,560 | 67 | 504 | 68 | 436 |
| Severe reduction in serum IgG and IgA with normal/elevated IgM | 308 | 2 | 16 | 5 | 11 |
| Transient hypogammaglobulinaemia of infancy | 332 | 3 | 30 | 13 | 17 |
| Lymphoproliferative syndromes | 348 | 1 | 15 | - | 15 |
| Other PID | 35,377 | 139 | 1,741 | 267 | 1,474 |
| TOTAL | 746,316 | 2,292 | 31,627 | 6,475 | 25,152 |

**Source:** Personal Communication from National Blood Authority: Phase 2 HTA conditions, received January 2020.([NBA, 2019](#_ENREF_59))

**Abbreviations:** CID: combined immunodeficiency; CVID: Common variable immunodeficiency; Ig: immunoglobulin; Ig A: immunoglobulin A; IgG: immunoglobulin G; IgM: immunoglobulin M; SCID: severe combined immunodeficiency.

**Notes:** A = Wiskott-Aldrich syndrome is one example of CID with syndromal features. B = X-linked agammaglobulinaemia is one example of a PID where all Ig isotypes are reduced, and B-cells are decreased/absent.

### Comparator Details

The comparator for Ig replacement therapy for the treatment of PID with antibody deficiency in this Assessment is no Ig (no active treatment). This may or may not include supportive care including antibiotic treatment, prophylactic antibiotics and antimicrobials.

The Immunoglobulin Review Reference Group, when advising on the Referral Form, agreed that given the heterogeneous patient group comprising PID with antibody deficiency, ‘no Ig’ is the most appropriate comparator for this condition (PICO Confirmation page 18). The Immunoglobulin Review Reference Group also confirmed that there are no active comparators to IVIg for the treatment of PIDs available in Australia (PICO Confirmation page 18).

### Clinical management algorithm(s)

Figure 1 and Figure 2 (Section A.6.) describe the current management of patients with PID with antibody deficiency using IVIg, funded by the National Blood Authority (for initial access to Ig and continued access to Ig, respectively). For eligible patients, Ig therapy is funded for 6 months, at which point a review by an immunologist is required.

Figure 3 (section A.6.) describes the current management of patients with PID with antibody deficiency, where IVIg is not a treatment option. This is either due to contraindications or ineligibility according to *the Criteria Version 3* (including patients who were previously eligible for treatment under *the Criteria Version 3* but are no longer, for example, due to treatment failure). For these patients, best supportive care is the only treatment available.

### Key Differences in the Delivery of the Proposed Medical Service and the Main Comparator

The main comparator for Ig therapy, for the purposes of this Assessment, is no Ig. The way in which Ig therapy is delivered has been described above. For the comparator (no Ig) standard of care may or may not include supportive treatment including antibiotics and antimicrobials.

Clinical Claim

The following clinical claims have been made regarding Ig use for the treatment of PID with antibody deficiency:

* Ig has superior effectiveness and inferior safety compared to no Ig.

### **Approach T**aken to the **E**vidence **A**ssessment

A systematic review of published literature was undertaken on 20/11/2019 (PubMed) and 25/11/2019 (Embase) to identify relevant published studies and systematic reviews. Searches were conducted of the databases and sources described in Appendix B. Search terms are described in Section B.1.

A PRISMA flowchart (Figure 2, Section B.2.) provides a graphic depiction of the results of the literature search and the application of the study selection criteria.

Comparative studies on the safety and effectiveness of Ig in patients with PID were included. Single arm studies on patients with CVID were also included in accordance with the PICO Confirmation. The searches identified four comparative studies, seventeen single arm studies providing pre- and post-Ig treatment data and/or Ig safety data.

A profile of each included study is given in Appendix C and summarised in Section B.4. Supplementary evidence is presented at the end of Section B.6. This evidence does not directly inform on the comparative safety and effectiveness of Ig compared to no treatment in patients with PID; however, it is evidence that the Assessment Group felt provided additional context on the use of Ig to treat PID which may be of interest to the Immunoglobulin Review Reference Group, MSAC and the NBA.

Risk of bias was assessed using the Cochrane ROBINS-1 tool for the comparative studies and the Institute of Health Economics quality appraisal tool for the case series studies. GRADE methodology was used to appraise the overall quality of the evidence base for each outcome.

### **Characteristics of the Evidence Base**

Four non-randomised comparative studies and seventeen case series studies were identified for inclusion in this Assessment. The characteristics of the evidence base are detailed in Section B.4.

All the included studies were at high risk of bias and several potential applicability issues were identified:

* The evidence only included patients with CVID
* The age of patients was markedly lower than the average age of CVID patients receiving Ig funded by the NBA
* The included studies used a different diagnostic criterion to those listed in *The Criteria Version 3*
* The included studies only reported results for IVIg; SCIg is also used for PID in Australia
* Co-interventions and other confounding factors were rarely reported or adequately assessed.

### Results

#### Safety

No comparative safety data was identified. Given the comparator is ‘no treatment’ there are not expected to be any safety issues relevant to the comparator.

Ig use was associated with mostly mild adverse events (chills, flushing, fever, nausea, headache, muscle ache, mild anxiety, pharyngolaryngeal pain, fatigue and hypotension) occurring in 14% to 67% of patients and 2% to 22% of infusions.

Moderate events (rash, severe headache, abdominal pain, joint pain, chest tightness, vomiting, wheezing and mild dyspnoea) occurred in 6.7% to 24% of patients and 0.2% to 1.5% of infusions and were resolved by slowing or stopping the infusions.

Severe events (severe chest pain, severe wheezing/breathlessness, severe headache, severe dizziness, tightness of the throat pressure in the chest sensation, collapse and moderate events that were persistent and could not be prevented by pre-infusion treatment with steroids and antihistamines) were rare occurring in 0% to 5% of patients and 0% to 0.2% of infusions. These events required adrenaline, hospitalisation, withdrawal of treatment, or changing to SCIg administration.

#### Effectiveness

One comparative study was identified which retrospectively compared a group of patients on Ig treatment to a group of patients not on Ig treatment due to delayed diagnosis. IVIg treatment was associated with improved patient outcomes (including lower infection rates, hospital admissions, bronchiectasis and mortality). This study was assessed as being at high risk of bias.

Data from single arm studies of patients with CVID comparing pre- and post-treatment outcomes reported consistent findings. The post-Ig outcomes (infection rates, IgG levels and hospitalisation rates) were improved compared to those measured pre-Ig treatment.

Data from three studies reporting a mean age similar to that of Australian patients receiving NBA-funded Ig were consistent with the overall results of the Assessment. All three studies reported that Ig use was associated with reductions in infection rate compared to pre-treatment rates.

Supplementary evidence from one RCT and five systematic reviews of observational studies found SCIg was at least non-inferior to IVIg. Therefore, it was considered reasonable to extrapolate the results of this review to patients on SCIg therapy for CVID. SCIg may be associated with high rates of minor local adverse events at the infusion site but lower rates of systemic adverse events.

Key issues with the evidence base were identified which may have a substantial effect on effectiveness results. Confounding factors and co-interventions were generally not reported and not investigated; therefore, it is not clear how these influence results. Unadjusted co-intervention use may bias results in favour of Ig. Most studies were retrospective; it was not clear that all patient information was captured consistently and comprehensively. Further, it was not clear if any eligible patients were excluded from analysis. The impact these issues may have on results is uncertain.

Despite the significant limitations associated with the evidence base, it is unlikely that higher quality studies will be forthcoming to investigate the comparative effectiveness of Ig therapy in patients with PID. No relevant upcoming clinical trials were identified, and due to the low incidence of PID, recruiting enough patients for a large prospective trial may not be feasible and/or ethical.

The summary of findings is shown in Table 2.

Table 2 Balance of clinical benefits and harms of intervention, relative to comparator, and as measured by the critical patient-relevant outcomes in the key studies

| Outcome  (units, follow-up) | No. of studies and study design | Risk of bias | Effect Ig | Effect no treatment | Quality | Importance |
| --- | --- | --- | --- | --- | --- | --- |
| Adverse events  follow up: range 1 years to 12 years (count) | 8 observational studies | Serious | 184/434 (42.4%) | NA | ⨁⨁⨁⨀  **Moderate quality** | Critical |
| Serious adverse events (count) | 5 observational studies | Serious | 20/519 (3.9%) | NA | ⨁⨁⨁⨀  **Moderate quality** | Critical |
| Lower respiratory infection rates (per patient per year) | 8 observational studies | Very serious | Range of means  0.16-0.34 | Range of means  0.28-2.04 | ⨁⨀⨀⨀  **Very low quality** | Critical |
| IgG trough levels (mg/dl) | 7 observational studies | Serious | Range of means  455-891 | Range of means  195-416 | ⨁⨁⨀⨀  **Low quality** | Critical |
| Hospitalisations (per patient per year) | 4 observational studies | Very serious | Range of means  0.13-0.7 | Range of means  1.35-3.4 | ⨁⨀⨀⨀  **Very low quality** | Critical |

**Abbreviations**: Ig: immunoglobulin, IgG: immunoglobulin G, NA: not applicable. Source: GRADE Working Group grades of evidence (Guyatt et al., 2013)

⨁⨁⨁⨁ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect. ⨁⨁⨁⨀ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. ⨁⨁⨀⨀ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. ⨁⨀⨀⨀ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

On the basis of the benefits and harms reported in the evidence base (summarised above)**, it is suggested that, relative to no treatment, Ig has inferior safety and may have superior effectiveness noting that there is only low- to very low-quality evidence available to support these conclusions.**

### Translation Issues

Translation of the clinical evidence was not undertaken.

### Economic Evaluation

To understand the cost-effectiveness profile of Ig replacement therapy for PID patients, a review of literature on published economic evaluations were conducted. Results of the literature review were used to inform feasibility of performing a model-based economic evaluation.

The literature searches and selection identified 15 relevant studies where six were model-based economic evaluations, six were cost analyses on disease burden and budgetary impact, and the remaining three were reviews of economic studies. None of the identified studies compared Ig use to non-Ig standard care for PID patients. Comparative studies were all focused on how IVIg and SCIg is compared in terms of clinical and economic outcomes. Despite the diversity in modelling approaches and evaluation results, there was a consistent finding across all studies: SCIg is likely to be substantially more cost-effective compared to IVIg.

Given the limitations with the available evidence , it was determined in consultation with the Immunoglobulin Review Reference Group that conducting a modelled economic evaluation comparing Ig and non-Ig standard of care would not be feasible or meaningful for decision-making. Furthermore, as Ig use for patients with PID is considered to be the standard clinical management strategy (particularly for patients with common subtypes of PID including common variable immunodeficiency (CVID) and X-linked agammaglobulinemia (XLA)) further evidence for ‘no Ig’ use (required to populate an economic model) is unlikely to be forthcoming.

A simplified cost-consequence (CCA) analysis was conducted to estimate the economic impact of Ig for PID patients. The CCA was limited to a one-year time horizon and considered the cost differences between Ig and no Ig in terms of Ig itself, Ig administration costs, and the incremental costs of treating serious infections and managing bronchiectasis. The overall incremental cost was estimated at $18,281.01 per year per patient, driven largely by the direct cost of Ig (with some cost offsets associated with avoidance of hospitalisations due to serious infections). More detailed results are provided in Section D.4 together with sensitivity analyses around uncertainties in the cost estimates for managing serious infections and bronchiectasis.

### Estimated Extent of Use and Financial Implications

Financial estimates are primarily based on the Ig usage figures from the past two financial years (2017 to 2019) provided by the NBA, as well as externally sourced epidemiological studies conducted in Australia. The base case relies on the population prevalence for PID of 9.09 per 100,000 Australians, projected over five years assuming annual population growth of 1.5%.

The total Ig costs, including delivery costs, are summarised in Table 3.

Table 3 Total Ig costs including delivery

| FY | 2021 | 2022 | 2023 | 2024 | 2025 | Source | Calculation reference |
| --- | --- | --- | --- | --- | --- | --- | --- |
| IVIg number | 1805 | 1832 | 1860 | 1888 | 1916 | Table 25 | A |
| SCIg number | 570 | 579 | 587 | 596 | 605 | Table 25 | B |
| **Total cost of Ig delivery** | $6,879,371 | $6,982,561 | $7,087,300 | $7,193,609 | $7,301,513 | **Calculated** | **C** |
| Ig product costs | $43,566,409 | $44,219,905 | $44,883,204 | $45,556,452 | $46,239,799 | Table 30 | D |
| **Grand total of Ig for PID patients** | **$50,445,780** | **$51,202,467** | **$51,970,504** | **$52,750,061** | **$53,541,312** | **Calculated** | **E = C + D** |
| *% of delivery from the total* | 13.64% | 13.64% | 13.64% | 13.64% | 13.64% | *Calculated* | *F = C ÷ E* |

**Abbreviations:** PID = primary immunodeficiency diseases; IVIg = intravenous immunoglobulin; SCIg = subcutaneous immunoglobulin; FY = financial year

Sensitivity analyses were conducted to test assumptions in patient number estimates, the price of Ig and Ig dosage. These are summarised in the table below.

Table 4 Sensitivity analyses considering only Ig costs (not delivery)

| Year | 2021 | 2022 | 2023 | 2024 | 2025 |
| --- | --- | --- | --- | --- | --- |
| Base case  Ig cost alone | $43,566,409 | $44,219,905 | $44,883,204 | $45,556,452 | $46,239,799 |
| ***Ig cost alone***  ***Sensitivity analysis*** |  |  |  |  |  |
| PID patients via Method 2  *Uncertainty range by Method 1 and Method 3* | $41,896,385  ($40.5m, $47.9m) | $41,849,003  ($40.0m, $49.9m) | $41,801,621  ($39.5m, $51.9m) | $41,754,239  ($39.1m, $53.8m) | $41,706,857  ($38.5m, $55.8m) |
| Price of Ig at lowest cost ($44.94) | $32,409,774 | $32,895,920 | $33,389,359 | $33,890,200 | $34,398,553 |
| Price of Ig at highest ($140.18) | $101,094,839 | $102,611,262 | $104,150,431 | $105,712,687 | $107,298,378 |
| Price of Ig at weighted average ($94.51) | $68,158,605 | $69,180,984 | $70,218,699 | $71,271,980 | $72,341,059 |
| 10% increase in dosage | $47,923,050 | $48,641,896 | $49,371,524 | $50,112,097 | $50,863,779 |
| 10% decrease in dosage | $39,209,768 | $39,797,915 | $40,394,884 | $41,000,807 | $41,615,819 |

**Abbreviations:** PID = primary immunodeficiency diseases; IVIg = intravenous immunoglobulin; SCIg = subcutaneous immunoglobulin; FY = financial year

### Consumer impact summary

The draft Referral Form was released for Targeted Consultation in August 2019 and the PICO Confirmation was released to Sponsor companies in December 2019. Four submissions were received; three from industry and one from a consumer group.

Overall, both industry and the consumer group were supportive of the use of Ig to treat PID as set out by *the Criteria Version 3* and depicted in the Referral Form. Industry discouraged further limitation to access of Ig in Australia and expressed concerns about the feasibility of conducting clinical comparisons across a highly heterogeneous population and the Assessment’s ability to draw meaningful conclusions. One sponsor provided feedback on the approach outlined in the PICO Confirmation and was supportive of the approach noting that allogenic transplantations may be a relevant comparator to Ig and there were 26 such transplants performed in Australia in 2016.

The consumer representative was highly supportive of Ig therapy for PID; and provided personal examples of significant improvements in quality of life. Noted disadvantages included adverse events, regular attendance to hospital for Ig infusions, and time spent travelling and waiting due to delays in day units. However, consumers considered that the advantages of Ig therapy outweigh any potential disadvantages.

### Other Relevant Considerations

The Assessment group has identified the following areas for future research on PID in Australia:

* Currently, most evidence considers all forms of PID together; having studies that report data separately for each subtype would be informative. This may be difficult due to the rare nature of these conditions.
* From a clinical effectiveness point of view, research into the impact of co-interventions on outcomes would be helpful to resolve the confounding issues identified in the evidence base.
* More broadly, it may be useful to establish a registry or database for PID patients and document the treatment(s) they are receiving. This would be helpful to understand Ig therapy coverage and true population prevalence in Australia.
* It would be beneficial to have more granular information on how Ig is used for PID in Australia. Ideally, future research would focus on each PID subgroup separately and be aimed to answer the questions such as:
  + Is there any difference is usage patterns for children compared to adults?
  + Does severity of disease impact Ig usage?
  + Which patients are trialling periods off Ig and which of these patients are able to successful stop or reduce Ig usage?
  + Is the pattern of Ig usage consistent over time for each PID subtype?

# Acronyms and Abbreviations

| Acronym/abbreviation | Meaning |
| --- | --- |
| AIHW  ARAG | Australian Institute of Health and Welfare  autosomal recessive agammaglobulinemia |
| ARTG | Australian Register of Therapeutic Goods |
| CD40L | CD40 ligand |
| CI | confidence interval |
| CID | combined immunodeficiency |
| CVID | common variable immunodeficiency |
| HESP | Health Expert Standing Panel |
| HRQoL | Health-Related Quality of Life |
| HTA | Health Technology Assessment |
| ICER | Incremental Cost-Effectiveness Ratio |
| Ig | immunoglobulin |
| IgA | immunoglobulin A |
| IgE | immunoglobulin E |
| IgG | immunoglobulin G |
| IgM | immunoglobulin M |
| IMIg | intramuscular immunoglobulin |
| IVIg | intravenous immunoglobulin |
| LPS | lymphoproliferative syndromes |
| MA | meta-analysis |
| MBS | Medicare Benefits Schedule |
| MD | mean difference |
| MSAC | Medical Services Advisory Committee |
| NHMRC | National Health and Medical Research Council |
| NK | natural killer |
| PASC | PICO Confirmation Advisory Sub-Committee of the MSAC |
| PID | primary immunodeficiency diseases |
| QALY  QoL | Quality Adjusted Life Year  Quality of life |
| RCT | randomised controlled trials |
| SBI | serious bacterial infection |
| SCID | severe combined immunodeficiency |
| SCIg | subcutaneous immunoglobulin |
| TGA | Therapeutic Goods Administration |
| THI | transient hypogammaglobulinaemia of infancy |
| WAS | Wiskott-Aldrich Syndrome |
| XLA | X-linked agammaglobulinaemia |

# Section A Context

This Assessment of immunoglobulin (Ig) for the treatment of primary immunodeficiency diseases (PID) with antibody deficiency is intended for the Medical Services Advisory Committee (MSAC). MSAC evaluates new and existing health technologies and procedures 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.

Immunoglobulin replacement therapy for this indication is presently funded by the National Blood Authority (NBA) under the national blood supply arrangements, but the cost-effectiveness of this use has not previously been established. As of 2017, the National Blood Agreement provides for MSAC to undertake evidence-based evaluation of blood products funded under the national blood supply arrangements at the request of the Jurisdictional Blood Committee (JBC). All Australian Governments, through the JBC, have agreed to conduct robust Health Technology Assessments of immunoglobulin use (Ig Reviews) funded under the National Blood Agreement. The Australian Government Department of Health has convened an Immunoglobulin Review Reference Group to provide advice to the Ig Reviews. The Population, Intervention, Comparator, Outcome (PICO) Confirmations for these products have been considered by the Immunoglobulin 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 new items on the Medical Benefits Schedule (MBS).

ASERNIP-S, of the Royal Australasian College of Surgeons, has been commissioned by the Department of Health to conduct a systematic literature review of Ig replacement therapy for the treatment of PID with antibody deficiency. This Assessment has been undertaken to inform MSAC’s advice to the JBC regarding the clinical safety, effectiveness and cost-effectiveness of Ig replacement therapy for this indication. This contracted assessment complements the NBA Immunoglobulin Governance Program, which aims to strengthen clinical governance and authorisation of government-funded Ig in Australia.

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

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

## Items in the agreed PICO Confirmation

This Assessment of Ig for the treatment of PID with antibody deficiency addresses most of the PICO elements that were pre-specified in the PICO Confirmation that was ratified by the Immunoglobulin Review Reference Group. Insufficient comparative evidence in patients with PID was identified; therefore, the Assessment also includes single arm studies. These were limited to patients with common variable immune deficiency (CVID) in accordance with the PICO Confirmation.

## Medical Service

The intervention under review is Ig for immuno-replacement therapy in people with PID with antibody deficiency. Ig replacement therapy is a blood-based treatment whereby Ig is administered into the bloodstream of a person with PID in order to provide them with the antibodies needed to adequately fight infections. Immunoglobulin G (IgG) is one kind of antibody found in blood plasma that is necessary to fight infection; people with PID have poor IgG levels and/or function ([AAAAI, 2019](#_ENREF_1)).

Serum IgG levels (the measure of IgG in the bloodstream) in healthy people range from approximately 4g/L in early infancy to 11g/L in adulthood ([Stiehm and Fudenberg, 1966](#_ENREF_83)). Serum IgG concentrations of equal to or greater than 5g/L following Ig therapy has been recommended as adequate protection from serious infections in people with PID with antibody deficiency ([Shrestha et al., 2019a](#_ENREF_78)). Serum IgG trough levels (the concentration of IgG in the bloodstream immediately preceding the next dose of Ig) are an important guide to Ig treatment success ([Shrestha et al., 2019a](#_ENREF_78)). Ig therapy does not cure antibody deficiencies or reverse the long-term complications associated with chronic infections; however, it may help treat and prevent new infections, thus reducing the risk of (further) long-term complications ([ASCIA, 2019c](#_ENREF_12)).

Ig preparations were first used in the 1950s as replacement therapy for a range of PID ([Palabrica et al., 2013](#_ENREF_67)). Ig was initially administered intramuscularly until the 1980s where highly purified monomeric suspensions of IgG became available for intravenous or subcutaneous use ([Palabrica et al., 2013](#_ENREF_67)). Ig products are manufactured from the plasma of healthy donors. Plasma pools are derived from, on average, approximately 15,000 donors and purified via ethanol fractionation with additional steps to remove Ig aggregates ([Ness, 2019](#_ENREF_60), [Palabrica et al., 2013](#_ENREF_67)). The preparation is then stabilised using agents such as human albumin, glycine, polyethylene glycol or sugars (such as sucrose, maltose or glucose) ([Palabrica et al., 2013](#_ENREF_67)). The primary active ingredient of Ig preparations is IgG; however, preparations may vary in IgG monomer, dimer, aggregate concentrations, immunoglobulin A (IgA) and immunoglobulin M (IgM) content, the stabilisers and additives used, as well as the level of impurities present ([Ness, 2019](#_ENREF_60)).

Dosage and clinical review

In Australia, Version 3.1 of the *Criteria for Clinical Use of Immunoglobulin in Australia[[2]](#footnote-3)* (herein described as *‘the Criteria Version 3’*) outlines which patients are eligible for Ig treatment ([NBA, 2018](#_ENREF_58)). *The Criteria Version 3* provides a list of medical conditions and specific circumstances around entitlement for publicly funded Ig treatment, as well as an outline of the approved Ig dosage and recommended duration of use. Table 5 summarises the approved dosage and medical review conditions described in *the Criteria Version 3* for patients with PID with antibody deficiency.

As Ig is a finite high cost resource, the aim is to deliver the lowest dose possible of Ig that achieves the appropriate clinical outcome for each patient. Dosages outside of those parameters stipulated by *the Criteria Version 3* must be authorised following a review of the rationale of the treating doctor.

Table 5 Approved Ig dosage for replacement therapy in patients with PID with antibody deficiency (per indication) according to *the Criteria Version 3 (*[*NBA, 2018*](#_ENREF_58)*)*

| Loading Dose | Maintenance Dose | Review by an Immunologist |
| --- | --- | --- |
| **Common variable immunodeficiency (CVID) – European Society for Immunodeficiencies diagnostic criteria met** | | |
| One dose of 0.4g/kg in the first month of therapy (in addition to the maintenance dose) is permitted if the serum IgG level is < 4g/L. | 0.4 to 0.6g/kg every four weeks (intravenous Ig [IVIg]) or 0.1 to 0.15g/kg every week (subcutaneous Ig [SCIg]), or more frequently, to achieve IgG trough level of at least the lower limit of the age-specific serum immunoglobulin G (IgG) reference range. More frequent dosing to achieve IgG trough level of up to 9g/L is permitted if chronic suppurative lung disease is not adequately controlled at an IgG trough level at the lower limit of the age-specific serum IgG reference range. A total dose of up to 1g/kg may be given over any four-week period. | 6 months, annually thereafter.  Cessation of treatment should be considered at 12 months. |
| **Possible CVID** | | |
| One dose of 0.4g/kg in the first month of therapy (in addition to the maintenance dose) is permitted if the serum IgG level is < 4g/L. | 0.4 to 0.6g/kg every four weeks (IVIg) or 0.1 to 0.15g/kg every week (SCIg), or more frequently, to achieve IgG trough level of at least the lower limit of the age-specific serum IgG reference range. More frequent dosing to achieve IgG trough level of up to 9g/L is permitted if chronic suppurative lung disease is not adequately controlled at an IgG trough level at the lower limit of the age-specific serum IgG reference range. A total dose of up to 1g/kg may be given over any four-week period. | 6 months, annually thereafter.  Cessation of treatment should be considered at 12 months. |
| **Transient hypogammaglobulinaemia of infancy (children aged less than 4 years)** | | |
| One dose of 0.4g/kg in the first month of therapy (in addition to the maintenance dose) is permitted if the serum IgG level is < 4g/L. | 0.4 to 0.6g/kg every four weeks (IVIg) or 0.1 to 0.15g/kg every week (SCIg), or more frequently, to achieve IgG trough level of at least the lower limit of the age-specific serum IgG reference range. More frequent dosing to achieve IgG trough level of up to 9g/L is permitted if chronic suppurative lung disease is not adequately controlled at an IgG trough level at the lower limit of the age-specific serum IgG reference range. A total dose of up to 1g/kg may be given over any four-week period. | 6 months, annually thereafter.  Cessation of treatment should be considered at 24 months. |
| **Primary immunodeficiency diseases for which immunoglobulin replacement is universally indicated** | | |
| One dose of 0.4g/kg in the first month of therapy (in addition to the maintenance dose) is permitted if the serum IgG level is < 4g/L. | 0.4g/kg every four weeks (IVIg) or 0.1 to 0.15g/kg every week (SCIg), or more frequently, to achieve IgG trough level of at least the lower limit of the age-specific serum IgG reference range. More frequent dosing to achieve IgG trough level of up to 9g/L is permitted if chronic suppurative lung disease is not adequately controlled at an IgG trough level at the lower limit of the age-specific serum IgG reference range. A total dose of up to 1g/kg may be given over any four-week period. | 6 months, annually thereafter**\*** |

**Abbreviations:** CVID: Common variable immunodeficiency; IgG: immunoglobulin G; IVIg: intravenous immunoglobulin G; SCIg: subcutaneous immunoglobulin G.

**Note:** Refer to the current product information sheet for further information on dose, administration and contraindications. **\***Patients generally require more than one authorisation for Ig therapy; however, the average duration of therapy is unknown given the vast number, and clinical variability, of conditions that comprise PID. An additional dose of 2g/kg is permitted at any stage to manage an enterovirus infection. As well as this, one dose of 0.4g/kg is permitted at any stage if the serum IgG level is less than 4g/L.

Delivery methods

Ig can be delivered in one of two ways; intravenously (IVIg) or via subcutaneous injection (SCIg). The main difference between the two delivery methods is that IVIg requires venous access, can deliver larger volumes (therefore fewer doses) and is carried out by skilled healthcare professionals in a hospital setting ([Ness, 2019](#_ENREF_60)). SCIg, which delivers smaller volumes, may be self-administered at home (following appropriate training by a registered nurse or technician) ([Ness, 2019](#_ENREF_60)).

IVIg may be associated with increased systemic adverse events (such as headache, flushing, chills, myalgia, wheezing, tachycardia, lower back pain, nausea and hypotension) compared with SCIg ([Ness, 2019](#_ENREF_60), [Palabrica et al., 2013](#_ENREF_67)). Because IVIg is administered under medical supervision its adverse events can usually be treated quickly and effectively ([Ness, 2019](#_ENREF_60)). SCIg requires more frequent dosages (due to smaller infusion volumes) via multiple injection sites around the body ([Ness, 2019](#_ENREF_60), [Palabrica et al., 2013](#_ENREF_67)). Adverse events for SCIg are typically localised to the injection site and smaller infusion volumes allow for steady absorption of Ig ([Ness, 2019](#_ENREF_60)). Serious adverse events of Ig therapy overall are rare and may include antibiotic allergy, anaphylaxis, veno-occlusive events and acute renal failure ([Ness, 2019](#_ENREF_60)).

### Marketing status of technology

All therapeutic products marketed in Australia require listing on the Australian Register of Therapeutic Goods (ARTG). MSAC will not consider a therapeutic product for reimbursement if it is not listed on the ARTG.

Ig products used for replacement therapy in PID are funded under the National Blood Authority. The NBA has contracts with suppliers to source products both domestically (from plasma collected by the Australian Red Cross Blood Service) and through a range of international suppliers.

The sixteen Ig items on the ARTG that are relevant to this application are shown in Table 6; those currently funded by the National Blood Authority (7 products) are highlighted in grey. It is important to note that the funded Ig products may change over time, dependent on agreements with suppliers.

Table 6 Ig products indicated for PID listed on the ARTG according to the Referral Form (Table 1; page 6)

| ARTG no. | Product name | Product description | Sponsor |
| --- | --- | --- | --- |
| IVIg | | | |
| 143803 (20g/400ml); 143802 (10g/200ml); 143801 (5g/100ml); 143800 (2.5g/50ml); 140602 (0.5g/10ml) | Flebogamma 5% | 5% DIF Human normal immunoglobulin intravenous use injection vial | Grifols Australia Pty Ltd |
| 182359 (20g/200ml); 182358 (10g/100ml); 184353 (5g/50ml) | Flebogamma 10% | 10% DIF Human normal immunoglobulin intravenous use injection vial | Grifols Australia Pty Ltd |
| 162489 (20g/200ml); 162488 (10g/100ml); 162487 (5g/50ml); 162486 (2.5g/25ml) | Intragam 10% | Normal immunoglobulin (human) solution for injection vial | CSL Behring Australia Pty Ltd |
| 164549 (10g/200ml); 164551 (5g/100ml); 164548 (2.5g/50ml); 164550 (1g/20ml) | Intratect 5% | 5% human normal immunoglobulin solution for intravenous infusion vial | Pfizer Australia Pty Ltd |
| 232085 (20g/200ml); 232084 (10g/100ml); 232078 (5g/50ml); 232077 (1g/10ml) | Intratect 10% | 10% human normal immunoglobulin solution for intravenous infusion vial | Pfizer Australia Pty Ltd |
| 113928 (10g/200ml); 113927 (5g/100ml); 113926 (2.5g/50ml); 113925 (1g/20ml) | Octagam 5% | Normal immunoglobulin (human) injection bottle | Octapharma Australia Pty Ltd |
| 155604 (20g/200ml); 155603 (10g/100ml); 155602 (5g/50ml); 155601 (2g/20ml) | Octagam 10% | Normal immunoglobulin (human) injection vial | Octapharma Australia Pty Ltd |
| 291644 (30g/300ml); 291646 (20g/200ml); 291648 (10g/100ml); 291647 (5g/50ml); 291740 (1g/10ml); 291645 (2.5g/25ml); | Panzyga 10% | Human normal immunoglobulin solution for intravenous infusion vial | Octapharma Australia Pty Ltd |
| 219160 (40g/400ml); 143368 (20g/200ml); 143337 (10g/100ml); 143273 (5g/50ml) | PriviIgen 10% | Normal immunoglobulin (human) (100g/L, 10%) solution for intravenous infusion | CSL Behring Australia Pty Ltd |
| SCIg | | | |
| 282579 | Cuvitru 20% | Normal immunoglobulin (human) infusion 20% for subcutaneous use in glass vial | Shire Australia Pty Ltd |
| AU 173315 (0.8g/5ml); 173323 (1.6g/10ml); 173324 (3.2g/20ml)  NZ 204954 (0.8g/5ml); 204955 (1.6g/10ml); 204956 (3.2g/20ml) | Evogam 16% | Normal immunoglobulin (human) 16% w/v, injection solution vial for subcutaneous use | CSL Behring Australia Pty Ltd |
| 128703 (1.65g/10ml); 128705 (3.3g/20ml) | Gammanorm 16.5% | Normal immunoglobulin (human) solution for intramuscular injection or subcutaneous infusion vial | Octapharma Australia Pty Ltd |
| 285344 (5ml syringe); 285345 (10ml syringe); 207386 (5ml vial); 207385 (10ml vial); 207383 (20ml vial); 207384 (50ml vial) | Hizentra 20% | Human Normal Immunoglobulin 20% Solution for Subcutaneous Injection 5-10ml pre-filled syringe OR 5-50ml vial | CSL Behring Australia Pty Ltd |
| 235178 | Hyqvia 10% | Normal Immunoglobulin Infusion 10% (Human) with Vorhyaluronidase alfa, Injection solution for subcutaneous use | Shire Australia Pty Ltd |
| IVIg and SCIg | | | |
| 116689 (1g/10ml); 117237 (2.5g/25ml); 117238 (5g/50ml); 117239 (10g/100ml); 117240 (20g/200ml) | Gamunex 10%\* | Normal immunoglobulin (Human) intravenous solution vial | Grifols Australia Pty Ltd |
| 198488 (30g/300ml); 131973 (20g/200ml); 131969 (10g/100ml); 131968 (5g/50ml); 131966 (2.5g/25ml); 131953 (1g/10ml) | Kiovig 10% | Normal immunoglobulin (human) solution for injection vial | Shire Australia Pty Ltd |

**Source:** Therapeutic Goods Administration, accessed 16 December 2019

**Abbreviations:** ARTG: Australian Register of Therapeutic Goods; IVIg: intravenous immunoglobulin; DIF: dual inactivation and filtration; IV: intravenous; SCIg: subcutaneous immunoglobulin; AU: Australia; NZ: New Zealand; SC: subcutaneous.

**Note:** All products were registered medicines. Those products highlighted in grey are currently funded by the National Blood Authority. It is important to note these may change over time depending on supplier agreements. **\***Gamunex 10% is funded by the National Blood Authority for *IVIg only*.

### Other Indications

Ig is currently used in the treatment and management of a range of clinical conditions in Australia. The top 10 medical conditions for which Ig was issued, according to the National Blood Authority’s 2017-18 *National Report on the Issue and Use of Immunoglobulin (Ig)* are reported in Table 7 ([NBA, 2017-18](#_ENREF_57)).

Table 7 Top 10 medical conditions for which Ig was issued in 2017-18([NBA, 2017-18](#_ENREF_57))

| Condition | Immunoglobulin issued (grams) | Percentage change 2016-17 to 2017-18 |
| --- | --- | --- |
| Acquired hypogammaglobulinaemia | 1,401,789 | 14.1 |
| Chronic inflammatory demyelinating polyneuropathy | 1,290,612 | 10.2 |
| Primary immunodeficiency diseases | 725,326 | 3.4 |
| Myasthenia gravis | 514,017 | 12.6 |
| Inflammatory myopathies | 377,479 | 14.7 |
| Multifocal motor neuropathy | 354,434 | 7.0 |
| Secondary hypogammaglobulinaemia | 222,136 | 22.8 |
| Immune thrombocytopenic purpuria (in adults) | 218,182 | 3.0 |
| Kidney transplantation | 126,587 | 2.9 |
| Guillain-Barré syndrome | 122,139 | 7.0 |

These 10 conditions accounted for approximately 88 per cent of all Ig issued in Australia ([NBA, 2017-18](#_ENREF_57)). In particular, PID with antibody deficiency accounted for approximately 12 per cent of total Ig use; this represents a 3.4 per cent increase in Ig use for this indication from 2016-17 to 2017-18 ([NBA, 2017-18](#_ENREF_57)).

### Current funding arrangements

In Australia, *the Criteria Version 3* describes for which conditions Ig is publicly funded under the National Blood Authority.

For PID these include:

* Severe combined immunodeficiency (SCID)
* Combined immunodeficiency (e.g. thymoma)
* Combined immunodeficiency with associated or syndromal features
* Common variable immunodeficiency (CVID)
* Possible CVID – below normal serum IgG but normal serum IgA
* Severe reduction in all Ig isotypes with decreased or absent B-cells
* Severe reduction in at least two Ig isotypes with low/normal B-cells (e.g. CVID)
* Severe reduction in serum IgG and IgA with normal/elevated IgM
* Transient hypogammaglobulinaemia of infancy
* Lymphoproliferative syndromes

Additional details for these conditions are reported in the ‘Population’ section of this Assessment.

Ig therapy may be delivered in an inpatient or outpatient setting, as a private or public patient, as well as in the patient’s own home in some cases (for SCIg only, following appropriate training by a qualified nurse or technician).

Access to Ig for patients who are not eligible under the National Blood Authority is possible though direct order arrangements. This may take place when the decision to prescribe Ig has been made by a hospital drug committee or similar. In this case, imported Ig products can be purchased directly from the supplier (for the same price negotiated by the National Blood Authority); however, full payment is required (from the patient or health service).

## Proposal for Public Funding

There are no proposed MBS items relevant to this Assessment.

## Population

Immunodeficiency disorders are characterised by an immune system defect that prevents a person’s body from fighting infections and diseases ([Healtline, 2019](#_ENREF_37)). People with immunodeficiency disorders are prone to infection (increased frequency and severity), abnormal inflammation, cancer and autoimmune diseases ([Immunodeficiency Australia, 2019](#_ENREF_44), [McCusker et al., 2018](#_ENREF_54)). There are two groups of immunodeficiency disorders; primary immunodeficiency diseases (PID) and secondary immunodeficiency diseases. PID are caused by inherited gene defects, often, but not always, present at birth or developed in the first few years of life ([Immunodeficiency Australia, 2019](#_ENREF_44)). Secondary immunodeficiency diseases are mostly caused by another disease, illness, injury or medication ([Immunodeficiency Australia, 2019](#_ENREF_44)). Secondary antibody deficiencies are covered by the categories of acquired and secondary hypogammaglobulinaemia in the *Criteria Version 3 and have been reviewed separately (refer to MSAC Reviews 1565 and 1591).*

PID refers to a large heterogeneous group of disorders where one or more components of the immune system is compromised, leading to absent or impaired immune function ([McCusker et al., 2018](#_ENREF_54)). PID are broadly separated as disorders of adaptive immunity or innate immunity. The focus of this Assessment is PID with antibody deficiency which are considered disorders of adaptive immunity. Specifically, defects relating to B-cell development and/or maturation result in B-cell disorders, or antibody deficiencies ([McCusker et al., 2018](#_ENREF_54)). Over 350 different PID disorders are recognised by the World Health Organization (WHO), with new ones continually being discovered ([IDF, 2020a](#_ENREF_40)). As such, the presentation of PID is highly variable.

PID are considered rare disorders; however, their true incidence and prevalence (individually or collectively) is unknown ([Joshi et al., 2009](#_ENREF_46)). Estimates of PID incidence and prevalence have been made based on registry data worldwide. The Australasian Society of Clinical Immunology and Allergy PID Register conducted a cumulative, cross-sectional survey of PID patients in Australia and New Zealand ([Kirkpatrick and Riminton, 2007b](#_ENREF_48)). A total of 1,209 patients across 88 centres and 56 PID syndromes responded to the voluntary questionnaire ([Kirkpatrick and Riminton, 2007b](#_ENREF_48)). Prevalence (cases per 100,000 population) was 5.6 for Australia and 4.9 for Australia and New Zealand combined. PID with antibody deficiency accounted for 77 per cent of patients ([Kirkpatrick and Riminton, 2007b](#_ENREF_48)).

The population described in the PICO Confirmation is patients with PID with antibody deficiency who are eligible for Ig treatment in Australia according to version 3.1 of *the Criteria Version 3* ([NBA, 2018](#_ENREF_58)). As previously mentioned, *the Criteria Version 3* is a framework where the medical conditions and specific circumstances eligible for publicly funded Ig treatment in Australia are outlined ([NBA, 2018](#_ENREF_58)).

The specific conditions (as diagnosed by an immunologist) described in *the Criteria Version 3* for patients with PID with antibody deficiency to be eligible for publicly funded Ig treatment in Australia are listed and briefly explained below:

* Severe combined immunodeficiency

Severe combined immunodeficiency (SCID) is generally considered the most serious of all PID as it is potentially fatal. There are at least 13 known genetic defects responsible for SCID which is characterised by the combined absence of both T- and B-lymphocyte function ([IDF, 2019](#_ENREF_39)). Despite this, 15 per cent of all infants with SCID have a gene defect of unknown origin ([NIAID, 2019](#_ENREF_61)). SCID is generally inherited in an autosomal recessive pattern, with more than 80 per cent of cases having no family history of the disease ([NIAID, 2019](#_ENREF_61)). The most common form of SCID is X-linked SCID (primarily affecting males) where white blood cells develop abnormally resulting in low T-cell and natural killer (NK) cell counts and B-cells that do not function ([NIAID, 2019](#_ENREF_61)).

* Combined immunodeficiency

Combined immunodeficiency (CID) is generally less profound than SCID due to hypomorphic (partial) gene mutations ([Su, 2014](#_ENREF_85)). As such, the two conditions differ in that SCID is characterised by no T-cell function and CID is characterised by low T-cell function. CID may be associated with thymoma, which is cancer of the thymus gland. The thymus is made up of lymphocytes and epithelial cells and plays a critical role in the production of immune cells in children ([Conrad-Stoppler, 2018](#_ENREF_24)).

* Combined immunodeficiency with associated or syndromal features

Two examples of CID with associated or syndromal features include Wiskott-Aldrich syndrome (WAS) and ataxia telangiectasia. WAS is a rare X-linked recessive disease characterised by eczema, thrombocytopenia (reduced number and size of platelets), immune deficiency and bloody diarrhoea (as a result of thrombocytopenia) ([Fernandez, 2019](#_ENREF_29)). WAS is caused by mutations in the gene which codes for the WAS protein which is a cytoplasmic protein essential for B- and T-cell signalling ([Fernandez, 2019](#_ENREF_29)). Typically, in people with WAS, IgM levels are reduced, IgA and Immunoglobulin E (IgE) levels are elevated and IgG levels can be normal, reduced or elevated ([Fernandez, 2019](#_ENREF_29)).

Ataxia telangiectasia, also known as Louis-Bar syndrome, is a rare disorder affecting the nervous system, immune system and other body systems; characterised by difficulty with control of movements ([NLM, 2019a](#_ENREF_62)). Ataxia telangiectasia is caused by mutations in the ATM gene, which assists in normal cell division and DNA repair ([NLM, 2019a](#_ENREF_62)). These mutations result in impaired or eliminated function of the ATM protein which causes cells to become unstable and die ([NLM, 2019a](#_ENREF_62)). Approximately half of all people with ataxia telangiectasia are immunodeficient ([Staples et al., 2008](#_ENREF_81)). When immunodeficiency is present, it typically presents as low IgG and IgA levels, as well as defective polysaccharide antibody responses and lymphopenia ([Staples et al., 2008](#_ENREF_81)). T-cell function is generally normal; therefore, opportunistic infections are rare ([Staples et al., 2008](#_ENREF_81)).

* Common variable immunodeficiency

Common variable immunodeficiency (CVID) is one of the most common PID; traditionally characterised by decreased IgG and IgA levels, with or without decreased IgM ([ASCIA, 2019a](#_ENREF_10)), as well as T-cell defects, namely reduced proliferative capacity ([Strober and Chua, 2000](#_ENREF_84)). Most people with CVID have normal B-cell levels that either do not mature correctly to produce effective antibodies or do not have the assistance of T-cells to carry out normal antibody responses ([ASCIA, 2019b](#_ENREF_11)). Unlike other PID, CVID may be diagnosed in adults; however, symptoms may start to appear in childhood ([ASCIA, 2019b](#_ENREF_11)). Approximately 10 per cent of cases of CVID have a known genetic cause ([NLM, 2020](#_ENREF_64)). The main symptoms of CVID are hypogammaglobinemia and recurrent infections (particularly in the lungs, sinuses and ears) ([NLM, 2020](#_ENREF_64)). Pneumonia is common in people with CVID, as well as infection or inflammation of the gastrointestinal tract, enlarged lymph nodes and spleen ([NLM, 2020](#_ENREF_64)). Possible CVID describes below normal serum IgG but normal serum IgA.

* Severe reduction in all Ig isotypes with decreased or absent B-cells

X-linked agammaglobulinaemia (XLA) is characterised by low or completely absent Ig in the bloodstream ([NLM, 2019b](#_ENREF_63)). XLA is present at birth, although symptoms generally do not develop until one to two months of age once the mother’s antibodies (acquired before birth) are depleted ([NLM, 2019b](#_ENREF_63)). People with XLA do not lack the genes required to produce Ig, rather the enzyme (Bruton’s agammaglobulinaemia tyrosine kinase) responsible for the maturation of B-cells. The lack, or insufficiency, of B-cells results in no, or low Ig levels in the bloodstream ([NLM, 2019b](#_ENREF_63)).

* Severe reduction in serum IgG and IgA with normal/elevated IgM

The above occurs in people with CD40 ligand (CD40L) deficiency. CD40L is a membrane bound protein which helps mediate the interaction between antigen presenting cells and lymphocytes. The absence of this protein results in defects in cellular and humoral immunity leading to recurrent infection ([Bishu et al., 2009](#_ENREF_21)). The survival rate of people with CD40L deficiency at 25 years is 20 per cent (when Ig therapy and best supportive care is used) ([Bishu et al., 2009](#_ENREF_21)).

* Transient hypogammaglobulinaemia of infancy

Transient hypogammaglobulinaemia of infancy (THI) is a relatively common PID in infants and young children characterised by reduced IgG with or without decreased IgA and IgM levels but with normal (or near-normal) antibody responses to protein immunisations ([Knutsen, 2019](#_ENREF_49)). Onset of THI generally occurs around 6 months of age, when the IgG acquired before birth are depleted. Symptoms may include recurrent infections of the upper and lower respiratory tract, allergic manifestations (such as asthma, eczema and food allergies) and gastrointestinal difficulties (such as chronic diarrhoea and persistent vomiting) ([IDF, 2020b](#_ENREF_41)). In most children, Ig levels normalise by 2 years of age (with some children taking up to age 6) ([Knutsen, 2019](#_ENREF_49)).

* Lymphoproliferative syndromes

Lymphoproliferative syndromes (LPS) are a heterogeneous group of diseases characterised by the uncontrolled production of T- and B-cells. The result of this is immunodeficiency, a dysfunctional immune system and lymphocyte dysregulation ([Angel A Justiz-Vaillant and Christopher M Stang, 2019](#_ENREF_9)). X-linked LPS (type 1 and 2) is a mutation of the X chromosome which predisposes NK cell and T-cell LPS ([Angel A Justiz-Vaillant and Christopher M Stang, 2019](#_ENREF_9)). CD27 deficiency is an autosomal recessive immunodeficiency disorder associated with LPS. CD27 is a molecule that regulates T-, NK-, B- and plasma cell function, survival and differentiation ([van Montfrans et al., 2012](#_ENREF_87)). In its absence, symptoms vary from asymptomatic borderline to low hypogammaglobulinaemia to symptomatic inflammatory response with life threatening complications, including haemophagocytic lymphohistiocytosis, LPS and malignant lymphoma ([Salzer et al., 2013](#_ENREF_75)). People with SCID, WAS, ataxia telangiectasia and CVID are also prone to LPS ([Angel A Justiz-Vaillant and Christopher M Stang, 2019](#_ENREF_9)).

Ig usage for PID conditions

Ig therapy, funded by the NBA, in 2018-19[[3]](#footnote-4) for the above conditions is described in Table 8 ([NBA, 2019](#_ENREF_59)). The total number of patients treated for that period was 2,292 (in 31,627 episodes), with the largest number of patients treated for CVID ([NBA, 2019](#_ENREF_59)).

Table 8 Ig usage, patient and episode numbers for PID with antibody deficiency in 2018-19 ([NBA, 2019](#_ENREF_59))

| Specific condition name | Ig usage (grams) | Patient count | Treatment episodes | | |
| --- | --- | --- | --- | --- | --- |
| **Total** | **Private** | **Public** |
| SCID | 10,496 | 42 | 550 | 86 | 464 |
| CID | 1,094 | 8 | 52 | 1 | 51 |
| Wiskott-Aldrich syndromeA | 845 | 5 | 52 | 13 | 39 |
| CVID | 639,109 | 1,847 | 26,590 | 5,740 | 20,850 |
| Possible CVID | 7,801 | 55 | 319 | 71 | 248 |
| Severe reduction in all Ig isotypes with decreased or absent B-cells | 826 | 5 | 33 | - | 33 |
| X-linked agammaglobulinaemiaB | 40,221 | 118 | 1,725 | 211 | 1,514 |
| Severe reduction in at least two Ig isotypes with low/normal B-cells | 9,560 | 67 | 504 | 68 | 436 |
| Severe reduction in serum IgG and IgA with normal/elevated IgM | 308 | 2 | 16 | 5 | 11 |
| Transient hypogammaglobulinaemia of infancy | 332 | 3 | 30 | 13 | 17 |
| Lymphoproliferative syndromes | 348 | 1 | 15 | - | 15 |
| Other PID | 35,377 | 139 | 1,741 | 267 | 1,474 |
| TOTAL | 746,316 | 2,292 | 31,627 | 6,475 | 25,152 |

**Source:** Personal Communication from National Blood Authority: Phase 2 HTA conditions, received January 2020.([NBA, 2019](#_ENREF_59))

**Abbreviations:** CID: combined immunodeficiency; CVID: Common variable immunodeficiency; Ig: immunoglobulin; Ig A: immunoglobulin A; IgG: immunoglobulin G; IgM: immunoglobulin M; SCID: severe combined immunodeficiency.

**Notes:** A = Wiskott-Aldrich syndrome is one example of CID with syndromal features. B = X-linked agammaglobulinaemia is one example of a PID where all Ig isotypes are reduced, and B-cells are decreased/absent.

Exclusion Criteria for Ig use in patients with PID

*The Criteria Version 3* outlines that PID patients with the following conditions are not eligible for Ig therapy under this indication (these may be eligible under other indications):

* Acquired hypogammaglobulinaemia secondary to haematological malignancy or post-haematopoietic stem cell transplantation
* Specific antibody deficiency
* IgG subclass deficiency
* Secondary hypogammaglobulinaemia (including iatrogenic immunodeficiency) ([NBA, 2018](#_ENREF_58)).

Other contraindications to Ig therapy may include allergies to human Ig or to a specific stabiliser or additive ingredient present in the Ig preparation (these vary from product to product).

## Comparator Details

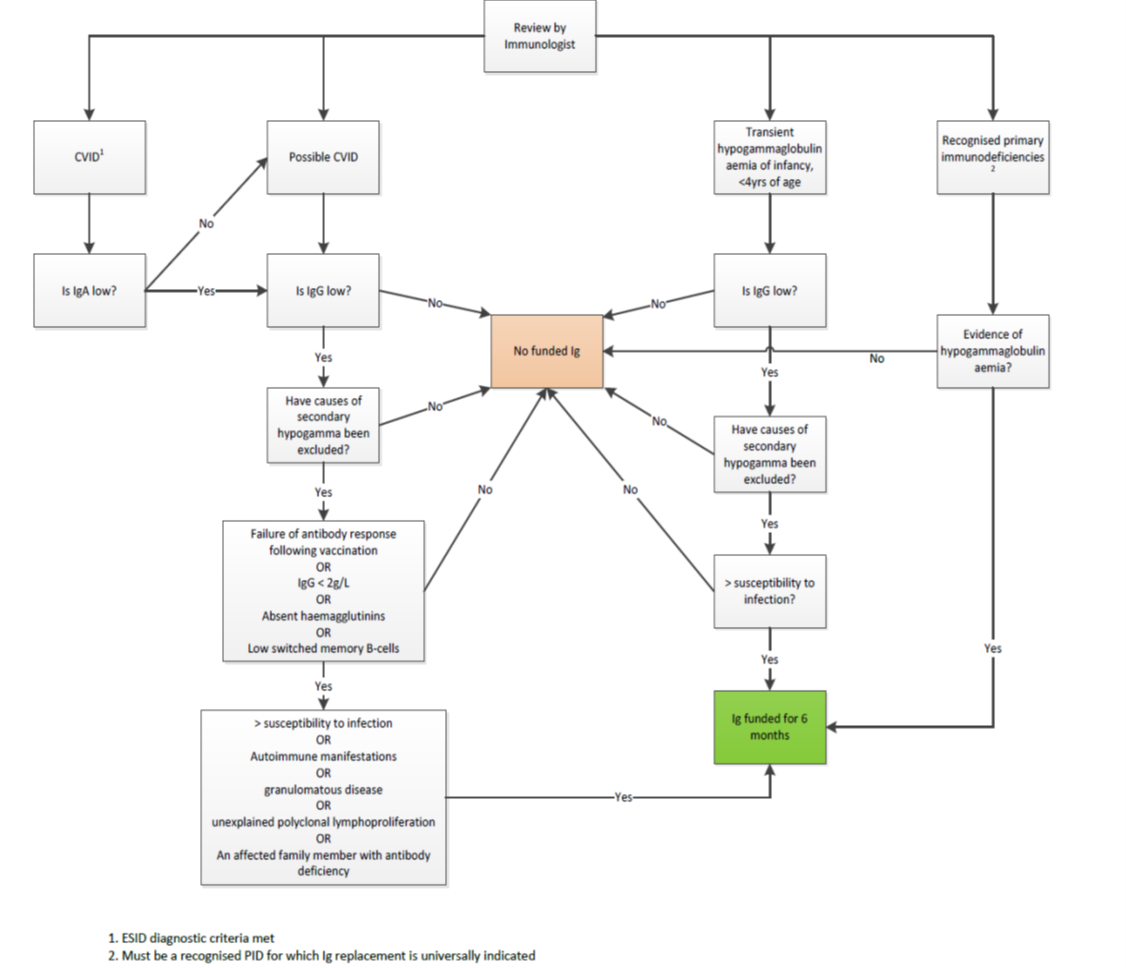
The comparator for Ig replacement therapy for the treatment of PID with antibody deficiency in this Assessment is no Ig (no active treatment). This may or may not include supportive care including antibiotic treatment, prophylactic antibiotics and antimicrobials.

Given the broad range of conditions that comprise PID and their clinical variations in presentation, there is no one standard of care treatment for PID ([Kirkpatrick and Riminton, 2007a](#_ENREF_47)). Standard therapies, other than Ig, may include haematopoietic stem cell transplant and/or gene therapy, splenectomy, thymectomy, chemotherapy, immunomodulation, antivirals, plasmapheresis, rituximab and cytokine inhibitors or supplements (Referral Form; page 22). This, together with the unlikely availability of comparative evidence for this patient population, supports the use of no Ig as an appropriate comparator for this Assessment.

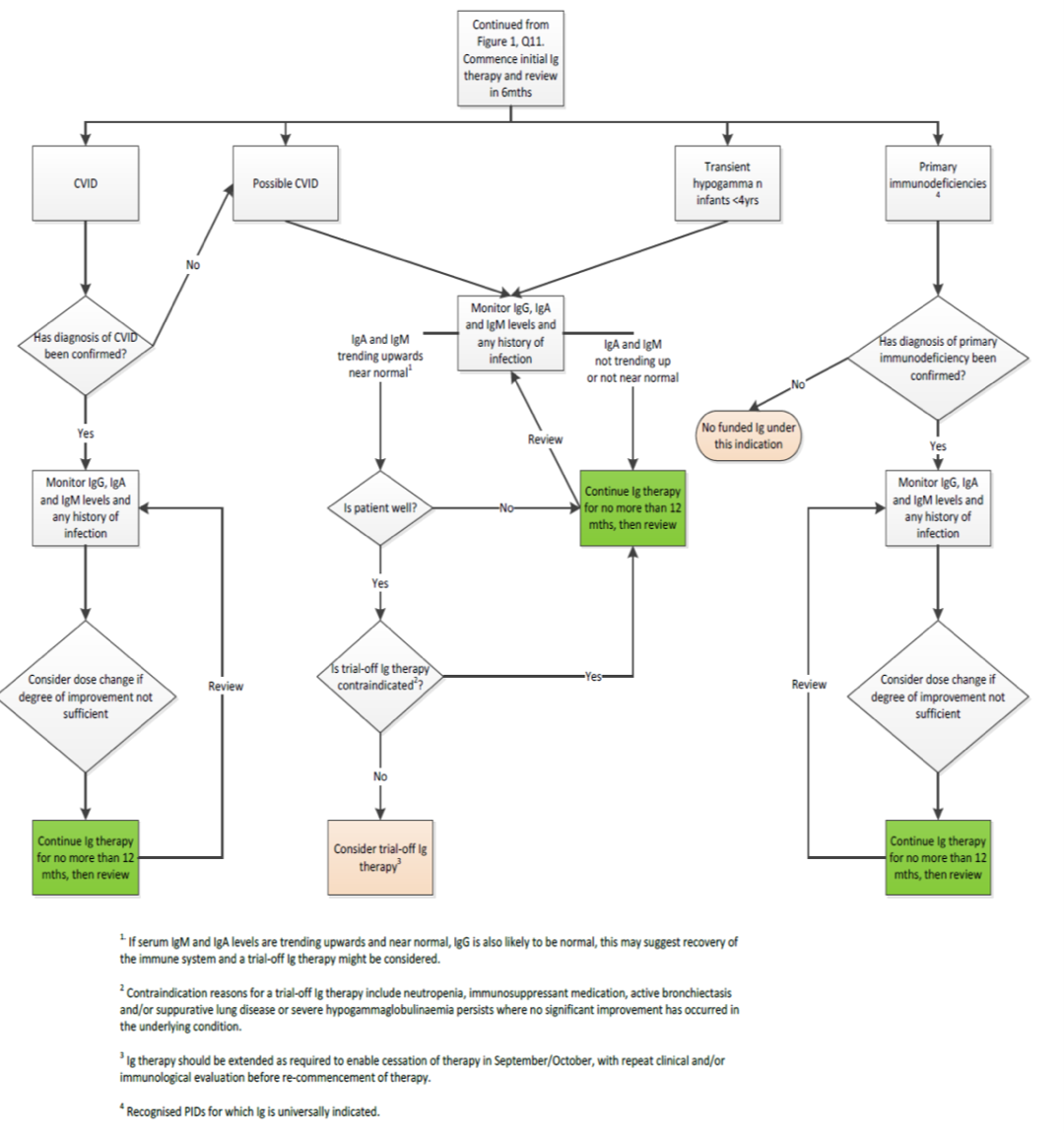
## Clinical management Algorithms

Figure 1 and Figure 2 describe the current management of patients with PID with antibody deficiency using IVIg, funded by the NBA (for initial access to Ig and continued access to Ig, respectively). It is important to note that these clinical management algorithms are a representation only as not all conditions are able to be captured in the flowchart.

Figure 3 describes the current management of patients with PID with antibody deficiency, where IVIg is not a treatment option. This is either due to contraindications or ineligibility according to *the Criteria Version 3* (including patients who were previously eligible for treatment under *the Criteria Version 3* but are no longer, for example, due to treatment failure).

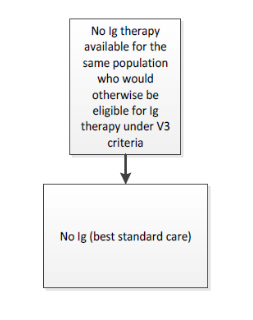
Figure 1 Clinical management algorithm for initial access to Ig for patients with PID with antibody deficiency.

**Source**: Reproduced from Figure 1, page 15 of the Referral Form. **Abbreviations**: CVID: Common variable immunodeficiency; ESID: European Society for Immunodeficiencies; Ig: Immunoglobulin; PID: Primary Immunodeficiency Diseases

Figure 2 Clinical management algorithm for continued access to Ig for patients with PID with antibody deficiency.

**Source:** Reproduced from Figure 2, page 21 of the Referral Form. **Abbreviations**: CVID: Common variable immunodeficiency; ESID: European Society for Immunodeficiencies; Ig: Immunoglobulin; PID: Primary Immunodeficiency Diseases

Figure 3 Clinical management for patients with PID with antibody deficiency in the absence (or failure) of Ig.



**Source:** Reproduced from Figure 3, page 24 of the Referral Form. **Abbreviations**: Ig: Immunoglobulin; PID: Primary Immunodeficiency Diseases

## Key Differences in the Delivery of the Proposed Medical Service and the Main Comparator

The main comparator for Ig therapy, for the purposes of this Assessment, is no Ig. The way in which Ig therapy is delivered has been described above. For the comparator (no Ig) standard of care may or may not include supportive treatment including antibiotics and antimicrobials.

## Clinical Claim

The following clinical claims have been made regarding Ig use for the treatment of PID with antibody deficiency:

* Ig has superior effectiveness and inferior safety compared to no Ig.

## Summary of the PICO

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

The Population, Intervention, Comparator and Outcomes (PICO) that were pre-specified to guide the systematic literature review are presented in Box 1 and Box 2.

Box 1 Criteria for identifying and selecting studies to determine the safety of Ig in patients with PID with antibody deficiency

|  |  |
| --- | --- |
| Selection criteria | Description |
| Population | Patients with primary immunodeficiency diseases (PID) with antibody deficiency |
| Intervention | Intravenous and/or subcutaneous immunoglobulin (IVIg and/or SCIg) |
| Comparator | No Ig |
| Outcomes | Critical for decision making: serious adverse events (e.g. antibiotic allergy, anaphylaxis, veno-occlusive events, acute renal failure/dysfunction), antibiotic resistance, blood-borne infections, thrombophlebitis.  Important, but not critical for decision making: short-lived, systemic adverse events (e.g. fevers, headaches, allergic reactions, hives, chills, arthralgia, nausea, vomiting, low blood pressure, moderate low back pain). |
| Systematic review question | What is the relative safety of Ig (IVIg and SCIg) for the treatment of PID with antibody deficiency? |

**Abbreviations:** Ig: immunoglobulin; IVIg: intravenous immunoglobulin; PID: primary immunodeficiency diseases; SCIg: subcutaneous immunoglobulin.

Box 2 Criteria for identifying and selecting studies to determine the effectiveness of Ig in patients with PID with antibody deficiency

|  |  |
| --- | --- |
| Selection criteria | Description |
| Population | Patients with primary immunodeficiency diseases (PID) with antibody deficiency |
| Intervention | Intravenous and subcutaneous immunoglobulin (IVIg and SCIg) |
| Comparator | No Ig |
| Outcomes | Critical for decision making: number of infections, number of antibiotic treatments, morbidity, quality of life, mortality, IgG trough levels, bronchiectasis. |
| **Systematic review question** | What is the relative effectiveness of Ig (IVIg and SCIg) for the treatment of PID with antibody deficiency? |

**Abbreviations:** Ig: immunoglobulin; IgG: immunoglobulin G; IVIg: intravenous immunoglobulin; PID: primary immunodeficiency diseases; SCIg: subcutaneous immunoglobulin.

## Consumer impact statement

The draft Referral Form was released for Targeted Consultation in August 2019 and the PICO Confirmation was released to Sponsor companies in December 2019. Four submissions were received; three from industry and one from a consumer group.

Overall, both industry and the consumer group were supportive of the use of Ig to treat PID as set out by *the Criteria Version 3* and depicted in the Referral Form. Industry discouraged further limitation to access of Ig in Australia and expressed concerns about the feasibility of conducting clinical comparisons across a highly heterogeneous population and the Assessment’s ability to draw meaningful conclusions. One sponsor provided feedback on the approach outline in the PICO Confirmation and was supportive of the approach noting that allogenic transplantations may be a relevant comparator to Ig and there were 26 such transplants performed in Australia in 2016.

The consumer representative was highly supportive of Ig therapy for PID; and provided personal examples of significant improvements in quality of life. Noted disadvantages included adverse events, regular attendance to hospital for Ig infusions, and time spent travelling and waiting due to delays in day units. However, consumers considered that the advantages of Ig therapy outweigh any potential disadvantages.

# Section B Clinical Evaluation

## Literature Sources and Search Strategies

The medical literature was searched on 20/11/2019 (PubMed) and 25/11/2019 (Embase) to identify relevant published studies and systematic reviews. Searches were conducted of the databases and sources described in Appendix B. Search terms are described in Table 9. After reviewing the list of references within systematic reviews selected during the drafting of this Assessment, additional relevant references and studies were included.

Table 9 Search terms used for the PubMed and Embase searches

| Element of clinical question | Search terms |
| --- | --- |
| **Population** | **MeSH words (PubMed)**  Combined immunodeficiency, x linked combined immunodeficiency, severe common variable immunodeficiency, Wiskott Aldrich syndrome, DiGeorge syndrome, ataxia telangiectasia, hyper IgM syndrome, lymphoproliferative disorder, X linked agammaglobulinemia. |
|  | **Subject headings (Embase)**  Combined immunodeficiency, common variable immunodeficiency, Wiskott-Aldrich syndrome, Di George syndrome, Ataxia telangiectasia, hyper IgM syndrome, lymphoproliferative disease, transient hypogammaglobulinemia, X linked agammaglobulinemia. |
|  | **Text words (PubMed and Embase)**  Primary hypogammaglobulinemia, primary immunodeficiencies, primary immunodeficiency, primary immune deficiency, PID and immune, combined immunodeficiency, combined immune deficiency, CVID and immune, SCID and immune, common variable immunodeficiency, common variable immune deficiency, CVID and immune, lymphoproliferative disease, lymphoproliferative syndrome, XLP and immune, Wiskott Aldrich syndrome, DiGeorge syndrome, Ataxia telangiectasia, X linked agammaglobulinemia, Bruton agammaglobulinemia, XLA and immune, Hype IgM syndrome, transient hypogammaglobulinemia, THI and immune, Good syndrome. |
| **Intervention** | **MeSH words (PubMed)**  Immunoglobulins. |
|  | **Subject headings (Embase)**  Immunoglobulin. |
|  | **Text words (PubMed and Embase)**  Immunoglobulin, Ig, IVIg, SCIg. |
| **Limits** | None used |

**Abbreviations:** CVID: common variable immunodeficiency; IgM: immunoglobulin M; IVIg: intravenous immunoglobulin; MeSH: medical subject headings; PID: primary immunodeficiency; SCID: severe combined immunodeficiency; SCIg: subcutaneous immunoglobulin; THI: transient hypogammaglobulinaemia of infancy; XLA: X-linked agammaglobulinaemia; XLP: X-linked lymphoproliferative disease.

## Results of Literature Search

A PRISMA flowchart (Figure 4) provides a graphic depiction of the results of the literature search and the application of the study selection criteria (listed in Box 1 and Box 2) (Liberati et al., 2009). Additional pre-specified criteria for study selection are reported in Table 10.

Table 10 Additional study selection criteria

| Study characteristic | Include | Exclude |
| --- | --- | --- |
| **Study type** | RCTs  Comparative studies  Case series studies (CVID only)A | Case reports (fewer than 10 patients)  Editorials  Narrative reviews  Conference abstracts |
| **Language** | English language | Non-English language studies |

**Abbreviations:** CVID: common variable immune deficiency; RCT: randomised controlled trial.

**Notes:** A: the decision to limit case series studies to only those on CVID was in accordance with the PICO confirmation.

From a total of 16,238 references, duplicates and foreign languages records (n = 3,973) were excluded. The remaining 12,265 references were screened by title and abstract by one of three reviewers, with 11,212 of these excluded due to wrong study type, wrong population, wrong intervention or non-English language.

Full text review of 1,053 citations was completed by two reviewers independently and disagreements regarding study selection were resolved with a third independent reviewer.

Studies that did not meet the inclusion criteria, or that met the inclusion criteria but contained insufficient or inadequate data for inclusion, are listed as Excluded Studies in Appendix D. All other studies meeting the inclusion criteria are listed in Appendix C.

Figure 4 Summary of the process used to identify and select studies for the assessment



**Abbreviations**: CVID: common variable immunodeficiency; Ig: immunoglobulin; PID: primary immunodeficiency.

### Study selection

The searches identified four comparative studies and 17 single arm studies providing pre- and post-Ig treatment data and/or Ig safety data.

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

Supplementary evidence is presented at the end of Section B.6. This evidence does not directly inform on the comparative safety and effectiveness of Ig compared to no treatment in patients with PID; however, it is evidence considered by the Assessment Group to provide additional context on the use of Ig to treat PID and which may be of interest to the Immunoglobulin Review Reference Group and MSAC. The supplementary evidence has not been assessed for risk of bias, and outcomes are not included in the GRADE quality appraisal presented in B.8.

### Clinical trials search

A search was conducted of ClinicalTrials.gov and the Australian and New Zealand Clinical Trials Registry to identify any upcoming evidence that may impact the results of this review. The details of the searches and identified trials are presented in Appendix F. While a large number of trials in patients with PID were identified; none of these trials is expected to provide comparative evidence relevant to this review.

### Appraisal of the evidence

Appraisal of the evidence was conducted in four stages:

Stage 1: Appraisal of the risk of bias within individual studies (or systematic reviews) included in the review (Section B.3).

Stage 2: Extraction of the pre-specified outcomes for this assessment, synthesising (meta-analysing or a narrative synthesis) to determine an estimate of effect per outcome and determining the assumed baseline risk.

Stage 3: Rating the overall quality of the evidence per outcome across studies, based on the study limitations (risk of bias), imprecision, inconsistency of results, indirectness of evidence, and the likelihood of publication bias. This was done to provide an indication of the confidence in the estimate of effect in the context of Australian clinical practice (Evidence profile tables, Appendix D).

Stage 4: Integration of this evidence for conclusions about the net clinical benefit of the intervention in the context of Australian clinical practice. (Sections B.6-8)

## Risk of Bias Assessment

A summary of the risk of bias tables are reported in Appendix C.

#### Comparative studies

Aghamohammadi et al. (2009) was assessed for risk of bias using the Cochrane ROBINS-1 tool ([Sterne et al., 2016](#_ENREF_82)). Overall, the study was judged to be at serious risk of bias. Key issues included the likely failure to adjust for all confounding issues, the potential that patients with a delayed diagnosis may have a different disease course than those diagnosed immediately, the selection of patients based on characteristics observed after starting the intervention, uncertainty into how many patients were eligible for the study but not enrolled, and uncertainty around how many patients had missing data or incomplete medical histories recorded.

The risk of bias for the three studies investigating IMIg has not been assessed and they are included as supplementary evidence only.

#### Case series

By nature, case series studies have an inherent risk of bias compared to randomised controlled trials (RCT). In the absence of comparative data, case series studies were used to inform the safety and effectiveness of Ig usage for CVID.

The Institute of Health Economics (IHE) quality appraisal checklist tool was used to appraise the quality of the selected case series (Table 37, Appendix C) ([IHE, 2012](#_ENREF_43)). Overall, the studies selected for this review have a high risk of bias. Most studies described the treatment, population characteristics and inclusion criteria appropriately, drew sound conclusions from the results presented, used appropriate statistical methods for the analysis of the results and presented data on random variability. Limitations of the case series studies were that most studies were retrospective, unblinded, conducted in single centres with non-consecutive recruitment, and most also failed to report their source of funding and conflicts of interest. Most studies failed to describe and assess co-interventions and confounding factors appropriately. Despite these limitations, no studies were excluded from this review due to an acceptably high risk of bias.

## Characteristics of the Evidence Base

Four non-randomised comparative studies ([Aghamohammadi et al., 2009b](#_ENREF_7), [Cunningham-Rundles, 1989](#_ENREF_25), [Gardulf et al., 1993](#_ENREF_32), [Waniewski et al., 1994](#_ENREF_89)) and seventeen case series studies were identified for inclusion in this Assessment ([Aghamohammadi et al., 2003](#_ENREF_3), [Aghamohammadi et al., 2008](#_ENREF_5), [Alkan et al., 2017](#_ENREF_8), [Baris et al., 2011](#_ENREF_15), [Bayrakci et al., 2005](#_ENREF_17), [Busse et al., 2002](#_ENREF_22), [de Gracia et al., 2004](#_ENREF_27), [Martinez Garcia et al., 2001](#_ENREF_53), [Pourpak et al., 2006](#_ENREF_70), [Quinti et al., 2008](#_ENREF_71), [Quinti et al., 2007](#_ENREF_72), [Salehzadeh et al., 2010](#_ENREF_74), [Singh et al., 1994](#_ENREF_80), [Aghamohammadi et al., 2004](#_ENREF_4), [Berger et al., 2007](#_ENREF_19), [Bichuetti-Silva et al., 2014](#_ENREF_20), [Dashti-Khavidaki et al., 2009](#_ENREF_26)). Details on the individual studies included in the evidence base are provided in Appendix C and discussed below.

The characteristics of the comparative studies are summarised in Appendix C and Table 13. Aghamohammadi et al. (2009) compared the effectiveness of IVIg to no treatment (due to delayed diagnosis) in patients with CVID. Three other studies were identified that included a very limited comparison between patients predominantly on IMIg before entering the study to patients who had not received treatment prior to study enrolment ([Cunningham-Rundles, 1989](#_ENREF_25), [Gardulf et al., 1993](#_ENREF_32), [Waniewski et al., 1994](#_ENREF_89)). In these three studies, this comparison was not the primary aim of the study and is based on data collected at the study baseline. The primary aim of these studies was to investigate the pre/post impact of SCIg treatment on patients.

The characteristics of the 17 single arm studies reporting pre/post data on the effect of Ig in patients with CVID is reported in Appendix C and summarised in Table 14 below.[[4]](#footnote-5) The studies included a total of 1,010 patients with CVID, with a slightly higher proportion of male patients overall (350 males, 312 females in studies reporting patient gender). Length of follow-up ranged from six months to eleven years with eleven studies reporting mean/medium follow-up of at least two years.

CVID was diagnosed according to the Pan-American Group for Immunodeficiency and the European Society for Immunodeficiencies (PAGID/ESID) criteria in ten studies, the WHO criteria in five studies, and two studies did not report which diagnostic criteria were used. *The Criteria Version 3* defines CVID as below normal serum IgG and IgA (with or without IgM decrease) and possible CVID as below normal serum IgG but normal serum IgA level. The included studies provide a definition most consistent with CVID, not possible CVID; therefore, the applicability of this evidence to patients with possible CVID as defined in *the Criteria Version 3* is not known.

The mean/median age of patients varied widely across studies and ranged from 1.8 to 45 years. Seven studies reported mean/median age range less than 18 years while five studies reported a mean/median age greater than 18 years. Only one study (Baris et al., 2011) restricted enrolment to paediatric patients. The mean/median diagnostic delay experienced by patients ranged from 3.25 to 8.9 years. Five studies did not report baseline demographics for CVID patients separately.

IVIg was used to treat patients in 15 of the studies, with doses typically delivered every three to four weeks ranging from 200 mg/kg to 800 mg/kg. Most studies used doses in the range of 300-500 mg/kg every three to four weeks. One study (de Garcia et al., 2004) used an initial loading dose of 200-300 mg/kg weekly for three weeks then 300 mg/kg once every three weeks.

Bayrakci et al. (2005) and Singh et al. (1994) reported that patients were treated with either IVIg or IMIg and did not report results for the two routes of administration separately.

Co-interventions included prophylactic antibiotics, chest therapy, inhaled corticosteroids and/or bronchodilators. In studies reporting their use, these interventions were usually targeted to patients with recurrent infections or patients with chronic pulmonary conditions. However, use of co-interventions was poorly reported with only five of seventeen studies commenting on their use. Advice from the Immunoglobulin Review Reference Group is that in Australia, co-interventions would typically include antibiotics and other antimicrobial agents (prophylactic, acute, and as rescue treatments), nebulised therapy (for example hypertonic saline), physiotherapy, nutritional support, treatment for autoimmune manifestations including immunosuppressive medications, cessation of smoking interventions, and support and bone marrow transplantation.

Several potential applicability issues were identified with the evidence base, which may limit the generalisability of the results to the Australian clinical context. These are summarised in Table 11.

Table 11 Potential applicability issues identified

| Potential applicability issue | Evidence base | Ig use in Australia | How has issue been addressed? |
| --- | --- | --- | --- |
| Population | Evidence only covers patients with CVID | *The Criteria Version 3* covers Ig use for other forms of PID. These conditions may have different outcomes than those reported for CVID. | The approach for the Assessment is in line with the PICO Confirmation and CVID is the PID for which Ig is most commonly funded in Australia (86% of Ig usage for PID in 2018/19 based on NBA data)A  Therefore, the evidence is applicable to most Ig use.  The applicability of the results to other PID conditions should be noted as an uncertainty. |
| Age of patients | Many studies weighted towards paediatric patients, with seven studies reporting average patient age <18 years. | From NBA data the average age of patients with CVID was 53 years | Subgroup of studies which report a mean/median patient age similar to the Australian data were investigated separately to see if any difference in trend was observed. |
| Diagnostic criteria used  See also Table 12 | PAGID/ESID 1999  WHO 1999 | *The Criteria Version 3* | See Table 12 for a breakdown of differences between the different diagnostic criteria.  While there are differences in the diagnostic criteria used in the evidence base and that required by *the Criteria Version 3*, these are considered unlikely to present a substantial applicability issue; however, this is noted as an uncertainty. |
| Ig dosages | Range 200-800 mg/kg 3-4 weekly, most studies 300-500 mg/kg 3-4 weekly | Maintenance Dose (IVIg) 400-600 mg/kg every 4 weeks or more frequently to achieve IgG trough levels at least at the lower limit of the age-specific IgG reference range.  Total dose 1000 mg/kg may be given in any 4-week period.  Loading dose: 400 mg/kg in first month (in addition to maintenance) if serum IgG < 4g/l  Median dose 340 mg/kg per episode | Most studies used IVIg doses which would be allowed under *The Criteria Version 3*.  This is noted as an uncertainty but evidence likely to be generalisable to Australian Context. |
| Ig administration method | Evidence in IVIg | Criteria allows SCIg and IVIg | Supplementary evidence included to investigate any differences in safety/effectiveness between IVIg and SCIg. |
|  | IMIg used in some (older studies) | Criteria does not allow IMIg | Supplementary evidence included to investigate any differences in safety/effectiveness between IVIg and IMIg. Advice from the Immunoglobulin Review Reference Group is that IMIg is no longer used ; therefore while this information may provide some information as to the effectiveness of Ig, the level of Ig may be subtherapeutic with IM administration and the associated response sub-optimal. |
| Impact of co-interventions | Poorly reported in most studies | Advice from the Immunoglobulin Review Reference Group is that in Australia, co-interventions including: prophylactic antibiotics, physiotherapy, hypertonic saline, nutritional supplementation, treatment of asthma, allergic rhinitis, sinus and middle ear surgery are the standard of care when patients are indicated. | This may represent a significant generalisability issue and may confound the results of the review.  Studies that report co-interventions and their effect separately have been investigated separately to attempt to quantify any confounding effect.  Advice from the Immunoglobulin Review Reference Group is that it is difficult to separate the effect of Ig and any co-interventions. |

**Abbreviations**: CVID: common variable immunodeficiency, IgG: immunoglobulin G, IMIg: intramuscular immunoglobulin, IVIg: intravenous immunoglobulin, NBA: National Blood Authority, PAGID/ESID: Pan-American Group for Immunodeficiency and European Society for Immunodeficiencies, PICO: population, intervention, comparator, outcomes, PID: primary immunodeficiency diseases, SCIg: subcutaneous immunoglobulin, WHO: World Health Organisation.

Note A: The percentage ultilisation of 86% of Ig usage for PID being attributable to patients with CVID is based data provided by the NBA for 2018-19 (summarised in Table 8, Section A.4. of this report) and only considers usage for CVID (not including possible CVID).

Table 12 Diagnostic criteria used in the studies

| Criteria | Serum Ig |
| --- | --- |
| WHO (1999) | Decreased serum IgG and IgA (not necessarily IgM)  Diagnosis based on inclusion of other known causes of humoral immune defects |
| PAGID/ESID 1999 | Marked decrease in IgG (at least 2 SD below mean for age) and a marked decrease in IgA or IgM  Onset > 2 years of age  Absent isohemagglutinins and/or poor response to vaccines  Defined causes of hypogammaglobulinemia have been excluded |
| *The Criteria Version 3* | Onset > 4 years  Marked decrease in IgG with marked decrease in IgA with or without low or IgM  Documented failure of serum antibody response after vaccination OR IgG < 2 g/L and delay providing Ig therapy would present a significant risk OR absent haemagglutinins (if blood group not AB) OR patient has low switched memory B-cells (< 70% age-related normal value)  Patient has increased susceptibility to infection OR patient has autoimmune manifestations, granulomatous disease, unexplained polyclonal lymphoproliferation or an affected family member with antibody deficiency  Initial review by an immunologist is required at 6 months and annually thereafter. Documentation of clinical effectiveness is required for continuation of Ig therapy. |
| **Key differences** | Age of onset > 2 years in the criteria used by the studies vs > 4 years in *The Criteria Version 3*.  *The Criteria Version 3* requires marked decrease in IgG and IgA (with or without IgM decrease) whereas other criteria require marked decrease in IgG with decrease in either IgA or IgM or both.  *The Criteria Version 3* requires a review by an immunologist after 6 months and documented clinical effectiveness is necessary for continuation of Ig therapy. The studies did not report whether an equivalent review was conducted; therefore, it is not clear how many patients in the included studies were not responding to Ig therapy and would have had therapy discontinued if this was required. No data was found investigating how many patients fail to respond to Ig therapy. Inclusion of patients who are not responding to therapy is likely to underestimate the effectiveness of Ig.  Advice from the Immunoglobulin Review Reference Group is that it is very unlikely a patient with CVID would cease Ig treatment and it is unlikely that any patients in the included studies would have remained on Ig treatment if they were not responding, therefore, this is unlikely to present a significant applicability issue. |

**Abbreviations**: IgA: immunoglobulin A, IgG: immunoglobulin G, IgM: immunoglobulin M, SD: standard deviation, WHO: World Health Organisation.

Table 13 Characteristics of the comparative studies

| Author (year)  Country | Study design  RoB | Duration of follow-up | Number of patients | Patient population  Diagnostic criteria | Patient baseline characteristics | Intervention | Comparator | Key outcome(s) |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Aghamohammadi et al. (2009)  Iran | Comp, Retro  SC  High | I: median 7 years (range 4-21)  C: median 5 years (range 1–15) | I: n = 23  C: n = 24 | CVID patients aged > 2 years referred to a medical centre between 1984–2009.  I: Patients diagnosed within 6 years of onset and received appropriate treatment for at least 5 years  C: Patients with a diagnostic delay > 6 years matched for age and gender with the I group  Criteria: PAGID/ESID | I group  M = 10, F = 13  Median age = 15.6 yrs (range 7-50)  Onset age: NR  Diagnostic delay: median 2.6 yrs (range 0.5-5)  C group  M = 12, F = 12  Median age = 14.6 yrs (range 8-42)  Onset age: NR  Diagnostic delay: median 8.4 yrs (range 6-32) | IVIg (400-600 mg/kg, every 3-4 weeks).  Prophylactic antibiotics, antibiotics at first sign of infection, regular outpatient visits. | No Ig or prophylactic treatment due to delayed diagnosis | Infections, hospital admissions, non-infectious complications, bronchiectasis, missed days from work or school, mortality |
| Cunningham-Rundles (1989)  USA | Comp, Retro  SC  NA | NR | I: n = 46  C: n = 57 | Consecutive CVID patients aged > 2 years  Criteria: March of Dimes Birth Defects Criteria | I + C combined  M = 51, F = 52  Age mean 29 yrs (range 3-71)  Onset age: mean 25 yrs  Diagnostic delay: mean 3 yrs | IMIg (dose NR) | No treatment | Trough IgG, IgA and IgM levels |
| Gardulf et al. (1993)  Sweden | Comp, Retro  MC  NA | NR | I: n = 15  C: n = 10 | Consecutive patients aged ≥ 18 years with CVID (n = 23), XLA (n = 1), thymoma with hypogammaglobulinemia (n = 1)  Criteria: NR | I + C combined  M = 12, F = 13  Age mean 43 yrs (SD 16)  Onset age: mean 25 yrs  Diagnostic delay: median 10 yrs (range 1-56) | IMIg (n = 13) or IVIg (n = 2) for mean of 78 months (dose NR) | No treatment | Functional status, Recreational activity, IgG trough levels |
| Waniewski et al. (1994)  Poland | Comp, Retro  SC  NA | NR | I: n = 17  C: n = 6 | Patients with CVID and increased infection rate aged ≥ 18 years  Criteria: WHO | I + C combined  M = 9, F = 14  Age, onset age and diagnostic delay NR | IMIg (dose NR) | No treatment | Serum IgG levels |

**Abbreviations:** C: comparator group;Comp: comparative study; Criteria: refers to the diagnostic criteria used to identify patients; CVID: common variable immunodeficiency, F: female patients, I: intervention group; Ig: immunoglobulin; IgA: immunoglobulin A; IgG: immunoglobulin G; IgM: immunoglobulin M; IMIg: intramuscular immunoglobulin; IVIg: intravenous immunoglobulin; M: male patients, MC: multicentre study, n: number of patients; NA: not assessed, NR: not reported; PAGID/ESID: Pan-American Group for Immunodeficiency and European Society for Immunodeficiencies, PID: Primary Immunodeficiency Disease; Retro: retrospective study; SC: single centre study, SCIg: subcutaneous immunoglobulin; SD: standard deviation,.XLA: X-linked agammaglobulinaemia.

Table 14 Characteristics of the single-arm studies of patients with CVID

| Author (year)  Country | Study design  RoB | Duration of follow-up | Number of patients CVID  Total | CVID patient population | Patients baseline characteristics | Intervention  Co-interventions | Key outcome(s) |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Aghamohammadi et al. (2003)  Iran | CS, Pros, SC  High | 36 months | 25  45 | CVID patients receiving IVIg at a single referral centre from 1997-2000  Criteria: WHO | M = 13, F = 12  Mean age = 15.8 yrs (SD 6.5)  Onset age, diagnostic delay, both NR | IVIg 400-500 mg/kg every 3-4 weeks  Co-interventions: NR | Trough IgG levels  AEs |
| Aghamohammadi et al. (2004)  Iran | CS, Retro, SC  High | NR data collected over 7 yrs | 31  71 | CVID patients receiving IVIg at a single referral centre from 1995-2002  Criteria: WHO | M = 51, F = 20  Mean age: 13.8 yrs (SD 5.5)  Onset age, diagnostic delay, both NR | IVIg 400-500 mg/kg every 3-4 weeks  Co-interventions: NR | AEs |
| Aghamohammadi et al. (2008)  Iran | CS, Retro, SC  High | Median 3 years (range 0.1-18) | 64  109 | CVID patients diagnosed and treated at a single referral centre from1980-2004  Criteria: PAGID/ESID | M = 33, F = 31  Median age 12.5 yrs (range 2.3-56)  Onset age: median 2 yrs (range 0.5-46)  Diagnostic delay median 3.25 yrs (range 0.5-39) | IVIg 400-500 mg/kg every 3-4 weeks  Co-interventions: NR | IgG serum level  Infection (otitis media and sinusitis) |
| Alkan et al. (2018)  Turkey | CS, Retro, SC  High | NR, data collected over 11 yrs | 12  12 | CVID patients diagnosed at a single centre from 2001-2012  Criteria: PAGID/ESID | M = 7, F = 5  Median age 11.6 (SD 3.7)  Onset age: median 7.2 yrs (SD 4.1)  Diagnostic delay: median 4.3 yrs (SD 2.6) | IVIg 500 mg/kg every 3 weeks  Co-interventions: NR | Infection (upper respiratory, lower respiratory)  Bronchiectasis (rates and prognosis) |
| Baris et al. (2011)  Turkey | CS, Retro, SC  High | Mean 5.6 yrs (SD 3.5, range 1.3-14)  Pre-Ig mean follow-up 1.1 yrs (SD 1.5) | 29  29 | Paediatric CVID patients diagnosed at a single centre and monitored for at least 12 months pre/post Ig treatment from 1994-2009  Criteria: PAGID/ESID | M = 22, F = 7  Mean age: 1.8 yrs (SD 6.1)  Onset age: mean 21 mo (SD 26.4)  Diagnostic delay: mean 3.9 yrs (SD 3.3) | IVIg 500 mg/kg every 3 weeks  Co-interventions: Antibacterial prophylaxis (patients with upper respiratory infections >1 per mo), daily chest therapy, inhaled corticosteroids, bronchodilators (patients with bronchiectasis) | Serum IgG levels  Infections (respiratory, gastrointestinal) Bronchiectasis (rates and prognosis)  Hospital stays (length and number)  Antibiotic usage  Growth |
| Bayrakci et al. (2005)  TurkeyA | CS, Retro, SC  High | Median 4.25 yrs (range 1.25-12.25) | 20  46 | CVID patients treated at a single centre from 1984-2000  Criteria: WHO | M = 20, F = 30  Median age: 13.8 yrs (range 7.8-22.3)  Onset age: median 1.8 yrs (range 0.1-5)  Diagnostic delay: median 4.5 yrs range 0.25-11.4) | IIVIg orIMIg median dose 370 mg/kg  Co-interventions: Antibacterial prophylaxis (patients with upper respiratory infections >1 per mo) | Trough Ig levels  Infection and hospitalisation rates  AEs |
| Berger et al. (2007)  USA/Canada | CS, Pros, MC  High | 0.5 yrs | 32 (ITT)  42 | Patients treated with stable IVIg therapy for > 6 mo at 11 sites in USA and 2 sites in Canada from 2004-2005  Criteria: PAGID/ESID | Baseline data for CVID patients NR | IVIg 200-800 mg/kg every 3-4 weeks  Co-interventions: NR | AEs |
| Bichuetti-Silva et al. (2014)  Brazil | CS, Pros, SC  High | 2 yrs | 50  117 | All patients with CVID who had received at least one dose of IVIg from August 2011-August 2013.  Criteria: PAGID/ESID | Baseline data for CVID patients NR | IVIg median dose 600 mg/kg every 3-4 weeks  Co-interventions: NR | AEs |
| Busse et al. (2002)  USA | CS, Retro, SC  High | Mean 6.6 yrs on IVIgB | 50  50 | Most recently referred patients with CVID  Criteria: PAGID/ESID | M = 20, F = 30  Mean age: 42.0 yrs (SD 16.3)  Age at onset, diagnostic delay NR | IVIg 300-400 m/kg every 3-4 weeks  Co-interventions: NR | Infection rates (pneumonia) |
| Dashti-Khavidaki et al. (2009)  Iran | CS, Retro, SC  High | NR data collected over 13 years | 54  99 | Patients with CVID on stable IVIg treatment who had received at least 4 infusions  Criteria: PAGID/ESID | Baseline data for CVID patients NR | IVIg 300-600 mg/kg every 3-4 weeks  Co-interventions: NR | AEs |
| De Garcia et al. (2004)  Spain | CS, Retro, SC  High | 2 yrs | 24  24 | Consecutive adult patients with CIVD diagnosed 1994-2001  Criteria: WHO | M = 10, F = 14  Mean age: 45 yrs (SD 18)  Onset age: NR  Diagnostic delay: NR | IVIg 200-300 mg/kg weekly for 3 weeks then every 3 weeks. Additional IVIg given if trough Ig levels < 600 mg/kg or if bacterial infections persisted  Co-interventions:  Postural drainage, chest percussion, bronchodilators, inhaled steroids and antibiotics considered if CPD present | IgG levels, Infection (serious and mild)  AEs |
| Martinez Garcia et al. (2001)  Spain | CS, Retro, SC  High | Mean 7.5 yrs | 19  19 | Patients diagnosed with CVID on Ig replacement therapy  Criteria: NR | M = 12, F = 7  Mean age: 33 yrs (SD 17.1)  Onset age: mean 14.7 yrs  Diagnostic delay: mean 8.5 yrs | IVIg 300-600 mg/kg every 3 weeks  Co-interventions: NR | Infection (upper respiratory, pneumonia, sinusitis, otitis media)  chronic pulmonary conditions (bronchiectasis, COPD, tuberculosis, asthma) |
| Pourpak et al. (2006)  Iran | CS, Retro SC  High | Mean 3.5 yrs (SD 2.95) | 26  26 | Patients diagnosed with CVID from 1999-2002 receiving IVIg who had been observed for at least 9 mo  Criteria: WHO | M = 14, F = 12  Mean age: 12.4 yrs (SD 5.6)  Onset age: mean 2.5 yrs (SD 3)  Diagnostic delay: mean 5.7 yrs (SD 3.9) | IVIg 400 mg/kg every 3-4 weeks  Co-interventions: NR | Infection (pneumonia)  Hospital admission  IgG levels |
| Quinti et al. (2008)  Italy | CS, Pros, MC  High | 1982 patient years | 262  262 | Patients diagnosed with CVID in the Italian Primary Immunodeficiency Network (26 centres) from 1999-2007  Criteria: PAGID/ESID | NR | IVIg 400 mg/kg 2-3 weekly  Co-interventions: antibiotic prophylaxis (11.6% of patients) | AEs |
| Quinti et al. (2007)  Italy | CS, Pros, MC  High | Mean 11.5 yrs (range 3-34) | 224  224 | Patients diagnosed with CVID in the Italian Primary Immunodeficiency Network (26 centres) from 1999-2007  Criteria: PAGID/ESID | M = 111, F = 113  Mean age: 26.6 yrs (range 2-73)  Onset age: mean 16.9 yrs (range 2-66)  Diagnostic delay: mean 8.9 yrs | IVIg 400 mg/kg 2-3 weekly  Co-interventions: antibiotic prophylaxis (11.6% of patients) | Serum IgG levels  Infection (prevalence) |
| Salehzadeh et al. (2010)  Iran | CS, Retro, SC  High | Mean 8 yrs (SD 4.6) | 24  24 | Patients aged >= 2 yrs with CVID diagnosed  Criteria: PAGID/ESID | M = 17, F = 7  Mean age 19.5 yrs (SD 12.6)  Onset age: NR  Diagnostic delay: median 5.3 yrs (0.25-39.75) | IVIg 300-600 mg/kg every 3-4 weeks  Co-interventions: NR | Serum IgG levels  Infection (prevalence)  Hospital admission rates |
| Singh et al. (1994)  India | CS, Retro, SC  High | NR | 14  14 | Patients with CVID  Criteria: NR | M = 10, F = 4  Age range 2-40 yrs  Onset age: NR  Diagnostic delay: NR | IVIg 10 ml/kg or IMIg 100 mg/kg at an interval to prevent diarrhoea and chest infections  Co-interventions: prophylactic antibiotics used | AEs |

**Abbreviations:** AEs: adverse events;CS: case series study; Consec: consecutive patients; COPD: chronic obstructive pulmonary disease; CPD: chronic pulmonary disease; CVID: common variable immunodeficiency; F: number of female patients; IgG: immunoglobulin G; IMIg: intramuscular immunoglobulin, IVIg: intravenous immunoglobulin; ITT: intention to treat population; M: number of male patients; MC: multicentre; Mo: months; NR: not reported, PAGID/ESID: Pan-American Group for Immunodeficiency and European Society for Immunodeficiencies, PP: per protocol population; Pros: prospective study design; Retro: retrospective study design; SC: single centre; SD: standard deviation), USA: United States of America, WHO: World Health Organisation, Yrs: years.

**Note:** A = Bayrakci et al. (2005) data was reported in trimesters, one trimester calculated to be 3 months based on total length of follow-up of 2733 months equating to 911 trimesters); B = Busse et al. (2002) note 3 patients began treatment on IMIg then switched to IVIg.

## Outcome Measures and Analysis

See Appendix C for details on the outcomes measured in the included studies, along with the statistical methods used to analyse the results.

No minimum clinically important difference (MCID) was defined for any outcome in the included studies. A targeted literature search also failed to identify any MCID. Advice from the Immunoglobulin Review Reference Group is that it is difficult to define an MCID for these outcomes as many variables need to be considered (including severity of infections, risks from infection, availability of hospital beds, time off work and school).

The following methods were used to measure each outcome:

**Adverse events** were assessed:

* during infusions by an immunologist and/or nurse and recorded on an a priori questionnaire (3 studies)
* during infusion by an immunologist and/or nurse and followed-up with a phone call to the patient 2-4 days post-infusion (1 study)
* during the infusion as observed by a clinician and reported by the patient at follow-up (1 study)

**IgG levels** were measured by nephrology. IgG levels are a surrogate outcome purported to be linked to patient-relevant outcomes (e.g. infection rate). The validity of IgG as a surrogate has been investigated for patients with CVID. Gathmann et al. (2014) analysed data on 2,212 CVID patients and found IgG levels were negatively associated with rate of pneumonia (p < 0.01). When patients were categorised into one of five trough IgG level groups (<4 g/l, 4-7 g/l, 7-10 g/l, 10-12 g/l and > 12 g/l) there was a significant inverse relationship between IgG level and serious infection. IgG was also inversely associated with days in hospital when comparing patients with IgG levels < 4 g/l to those with levels >4 g/l. No relationship for “days missed” or “infection episodes (any severity)” were observed ([Gathmann et al., 2014](#_ENREF_33)). Orange et al. (2010) investigated the impact of trough IgG levels on pneumonia incidence and found that pneumonia incidence declined by 21% for each 100 mg/dl increase in IgG (incidence ratio for CVID patients 0.785, 95% CI = 0.697, 0.885). Results from these studies indicate that it is relevant to report IgG levels and that higher levels may correspond to improved patient outcomes. A relevant clinically important trough level of IgG may be at a cut off of 4 g/l ([Orange et al., 2010](#_ENREF_66)).

A recent review investigated the impact of increasing IgG trough levels on infection rates in patients with PID and found that titrating IgG trough levels up to 9.9 g/l was associated with reduced rates of infections; however, titrating IgG beyond this level was not associated with increased benefit. The optimum IgG trough level for patients with PID is still unclear ([Lee et al., 2020](#_ENREF_50)). Advice from the Immunoglobulin Review Reference Group is that it is difficult to define a single value of IgG level that would represent a clinically meaningful response. The advice is that the aim of treatment is to normalise and reduce infection rather than achieve any one target IgG level.

**Infection** was measured:

* from patient record review; only those requiring treatment were included (2 studies)
* from a review of patient records (4 studies)
* from a medical history and physical exam (1 study)
* via 6 monthly patient-reported via questionnaire (1 study)
* via 12-monthly structured physician-completed questionnaire (2 studies)

Chart reviews and patient histories were supplemented by routine blood work (e.g. white cell counts), cultures and imaging. Due to the retrospective nature of many of the studies it is possible that infections, particularly those that did not require hospitalisation and/or treatment, may have been under-reported. However, patients with a diagnosis of PID are closely monitored and are likely to have had more accurate reporting of outcomes. Any under-reported infections are more likely to have occurred before diagnosis and this may underestimate the effectiveness of Ig treatment.

**Bronchiectasis** was defined by the presence of:

* Chronic productive cough combined with characteristic CT findings (1 study)
* Reduced pulmonary function combined with high resolution CT findings reviewed by two independent chest radiologists
* Findings on high resolution CT following blinded independent review by a radiologist and a pulmonologist

Due to the low quality of the evidence base and lack of comparative studies it was not deemed appropriate to pool any results. Therefore, the results in Section B.6 are described narratively.

## Results of the Systematic Literature review

## Is it safe?

Summary – What is the safety of Ig in patients with PID?

No comparative safety data was identified. Given the comparator is ‘no treatment’ there are not expected to be any safety issues relevant to the comparator.

Ig use was associated with mostly mild adverse events (chills, flushing, fever, nausea, headache, muscle ache, mild anxiety, pharyngolaryngeal pain, fatigue and hypotension) occurring in 14% to 67% of patients and 2% to 22% of infusions.

Moderate events (rash, severe headache abdominal pain, joint pain, chest tightness, vomiting, wheezing and mild dyspnoea) occurred in 6.7% to 24% of patients and 0.2% to 1.5% of infusions, and were resolved by slowing or stopping the infusions.

Severe events (severe chest pain, severe wheezing/breathlessness, severe headache, severe dizziness, tightness of the throat, sensation of pressure in the chest, collapse and moderate events that were persistent and could not be prevented by pre-infusion treatment with steroids and antihistamines) were rare, occurring in 0% to 5% of patients and 0% to 0.2% of infusions. These events required adrenaline, hospitalisation, withdrawal of treatment or changing to subcutaneous Ig administration.

No study assessed the comparative safety of Ig and no treatment (including placebo trials). In this section, the safety of Ig in this section was informed from single arm studies investigating the safety of Ig in patients with CVID.

Table 15 summarises adverse events from the ten single-arm studies reporting data on the safety of Ig therapy. Most studies reported adverse events across the entire PID population of the study rather than reporting outcomes for CVID separately. When all PID patients have been pooled this is reflected in the table.

Most adverse reactions experienced by the patients were mild and transient, occurring in 42% of patients overall (range per study 14% to 66.7%) and 8% of infusions overall (range per study 1.8% to 21.7%). Mild reactions included chills, flushing, fever, nausea, headache, muscle ache, mild anxiety, pharyngolaryngeal pain, fatigue and hypotension. These events were resolved by stopping or slowing the infusion rate. Discontinuation of Ig treatment was not required.

Moderate adverse events including rash, severe headache, abdominal pain, joint pain, chest tightness, vomiting, wheezing and mild dyspnoea, occurred in 6.7% to 24% of patients and 0.2% to 1.5% of infusions. These reactions led to slowing of the infusion, discontinuation of the infusion, and in some cases a change in Ig brand. Treatment included antihistamines, corticosteroids and/or anti-inflammatory agents.

Severe adverse events were rare, occurring in 0% to 5% of patients and 0% to 0.2% of infusions. Severe events included severe chest pain, severe wheezing/breathlessness, severe headache, severe dizziness, tightness of the throat, sensation of pressure in the chest and collapse. Moderate events that were persistent and could not be prevented by pre-infusion treatment with steroids and antihistamines were also included in this category. Treatment required adrenaline and in some cases hospitalisation. For at least some patients with severe reactions treatment was withdrawn or the patient was switch to subcutaneous Ig administration which was reportedly well tolerated (Quinti et al., 2008).

Three studies reported similar adverse event rates for CIVD and other PIDs (Bayrakci et al., 2005, Berger et al., 2007, Bicuuetti-Silva et al., 2014,), while, two studies reported that the adverse event rate was higher for patients with CVID (23% vs 12.4% and 8.5% vs 3.5% respectively) (Aghamohammadi et al., 2004 and Dashti-Khavidaki et al., 2009).

Berger et al. (2007) observed that the adverse event rate was highest for the first infusion compared to subsequent infusions (47.6% vs 22-38%).

Table 15 Summary of safety data

| Author (year)  Country | Number of patients  Duration of follow-up | Total AE rate  Per patient  Per infusion | Mild AEs  Per Patient  Per infusion | Moderate AEs  Per patient  Per infusion | Severe AEs  Per patient  Per infusion | Description of AEs and treatment |
| --- | --- | --- | --- | --- | --- | --- |
| Aghamohammadi et al. (2003)  Iran | 45 (all PID patients pooled)  3 yrs | PP: 25/45 (55.6%)  PI: 50/955 (5.2%) | PP: 22/45 (48.9%)  PI: 40/955 (4.2%) | PP: 3/45 (6.7%)  PI: 10/955 (1%) | PP: 0/45 (0%) | Mild: Chills, flushing, fever, nausea, headache  All subsided with slowed infusion rate  Moderate: Rash, severe headache, abdominal pain, joint pain, chest tightness  Treated with antihistamines and/or hydrocortisone |
| Aghamohammadi et al. (2004)  Iran | 71(all PID patients pooled)  NR data collected over 7 yrs | PP: 35/71 (49.3%)  PI: 152/1231 (12.4%) | PP: 33/71 (46.5%)  PI: 131/1231 (10.6%) | PP: 12/71 (16.9%)  PI: 19/1231 (1.5%) | PP: 2/71 (2.8%)  PI: 2/1231 (0.2%) | Mild: chills, fever, flushing, muscle aches, nausea, headache, anxiety  All subsided with slowed infusion rate  Moderate: vomiting, chest pain, wheezing  Treated with antihistamines and/or hydrocortisone  Severe: severe chest pain, severe wheezing, severe headache.  Treatment NR  Note: AE rate for CVID per infusion was higher than for the rate of all PID infusions pooled (23% vs 12.4%) |
| Bayrakci et al. (2005)  TurkeyB | 46 (all PID patients pooled)  Median 4.25 yrs (range 1.25-12.25 | PP: 3/46 (6.5%)  PI: NR | PP: NR  PI: NR  39 events total | PP: NR  PI: NR  12 events total | PP: NR  PI: NR  2 events total | Mild/Moderate: type NR, resolved by changing infusion rate or switching Ig brand  Severe: hospitalisation required for 2 patients  Note: no patient required therapy discontinuation  Note: AE rate for CVID patients was similar to the rate of all PID infusions pooled (5.5% vs 5.8%) |
| Berger et al. (2007)  USA/Canada | 42 (ITT, all PID patients pooled)  0.5 yrs | PP: 25/42 (60%)  PI: 100/314 (32%) | PP: 23/42 (54.8%)  PI: 69/42 (21.7%) | NR | PP: 0/42 (0%) | Mild: headache (59.5%), pharyngolaryngeal pain (38.1%), sinusitis (28.8%), diarrhoea (23.8%), fatigue (23.8%), nausea (23.8%), pyrexia (23.8%)  Moderate: mild dyspnoea resolved by stopping infusion  Note: AE rate for CVID patients was similar to the rate of all PID infusions pooled (62% vs 60%).  AE rates were higher for first infusion compared to subsequent ones (47.6% vs 22.2-37.5%)  AE rates higher with higher doses of Ig |
| Bichuetti-Silva et al. (2014)  Brazil | 117 (all PID patients pooled)  2 yrs | PP: 28/117 (23.9%)  PI: 38 /1765 (2.2%) | PP: NR  PI: 31/1765 (1.8%) | PP: NR  PI: 4/1765 (0.2%) | PP: NR  PI: 3/1765 (0.2%) | Mild: headache, fever, chills, nausea, emesis, hypotension, muscle cramps  Moderate: reactions necessitating discontinuation of infusion  Severe: moderate reactions that were persistent, tightness of throat, severe shaking, severe breathlessness or wheezing, severe dizziness, sensation of pressure in the chest, collapse. Severe reactions required adrenaline treatment.  Note: AE rate for CVID patients was similar to the rate of all PID infusions pooled (2.3% vs 2.2%) |
| Dashti-Khavidaki et al. (2009)  Iran | 99 (all PID patients pooled)  NR data collected over 13 years | PP: 66/99 (66.7%)  PI: 216/3004 (7.1%) | PP: 66/99 (66.7%)  PI: 172/3004 (5.7%) | PP: 24/99 (24%)  PI: 41/3004 (1.4%) | PP: 3/99 (3%)  PI: 3/3004 (0.1%) | Mild: chills, fever, cold feeling, backache, headache  Moderate: vomiting, chest pain, wheezing  Treatment: infusion stopped or rate reduced, antihistamines, anti-inflammatory agents and/or corticosteroids administered  Severe: severe chest pain, severe wheezing, severe headache  Note: AE rates per infusion varied depending on PID: e.g. CVID = 8.5%, XLA = 3.35%, Ataxia-telangiectasia = 3.8%, IgG subclass deficiency = 17.4% |
| De Garcia et al. (2004)  Spain | 24  24 mo | PP: NR  PI: 61/888 (6.8%) | NR | NR | NR | Type of AE NR  No AE required infusions to be discontinued |
| Martinez Garcia et al. (2001)  Spain | 19  Mean 7.5 yrs | NR | NR | NR | NR | Note: 1 patient withdrawn due to anaphylactic reaction |
| Quinti et al. (2008)  Italy | 262  Mean 7 years  1,982 patient years | NR | NR | NR | PP: 13/262 (5.0%)  PI: NR | Severe: Ig treatment withdrawn due to AE that could not be prevented with premedication (steroids, antihistamines) or switching Ig brand. Patients were started on SCIg which was well tolerated by most patients. |
| Singh et al. (1994)  India | 14  NR | PP: 2/14 (14%)  PI: NR | PP: 2/14 (14%)  PI: NR | None | None | Mild: nausea, joint pain, chills |

**Abbreviations**: AEs: adverse events, CVID: common variable immunodeficiency, PID: primary immunodeficiency diseases, Ig: immunoglobulin, IgG: immunoglobulin G, ITT: intention to treat, PI: per infusion, PP: per patient, NR: not reported, yrs: years.

## Is it effective?

Summary – What is the effectiveness of Ig in patients with PID?

One comparative study was identified that retrospectively compared a group of patients on Ig treatment to a group of patients not on Ig treatment due to delayed diagnosis. IVIg treatment was associated with improved patient outcomes, including lower infection rates, hospital admissions, bronchiectasis and mortality. This study was assessed as being at high risk of bias.

Data from single arm studies of patients with CVID comparing pre- and post-treatment outcomes, reported consistent findings. The post-Ig outcomes (infection rates, IgG levels and hospitalisation rates) were improved compared to those measured pre-Ig treatment.

Data from three studies reporting a mean age similar to that of Australian patients receiving NBA-funded Ig were consistent with the overall results of the Assessment. All three studies reported that Ig use was associated with reductions in infection rate compared to pre-treatment rates.

Key issues with the evidence base were identified, which may have a substantial impact on effectiveness results. Confounding factors and co-interventions were generally not reported and not investigated. It is unclear how these omissions influence results. Unadjusted co-intervention use may bias results in favour of Ig. Most studies were retrospective, and it was not clear if all patient information was captured consistently and comprehensively. It was also unclear if any eligible patients were excluded from analysis. The impact these issues may have on results is uncertain.

### Comparative effectiveness

No studies were identified comparing the effectiveness of immunoglobulins (IVIg or SCIg) to other treatments, or to a placebo, for patients with any form of PID.

Four studies were identified that compared—to varying degrees—the effectiveness of Ig treatment to no treatment.

Aghamohammadi et al (2009) compared a range of effectiveness outcomes between 24 untreated CVID patients and 23 CVID patients regularly treated with Ig therapy (400–600 mg/kg every three to four weeks). Untreated patients were those who had experienced long diagnostic delays (more than six years), thus long diagnostic delay was considered the equivalent of being untreated.

Table 16 shows the total number of infections, hospital admissions, bronchiectasis, missed days from work or school, and deaths. Untreated patients had significantly more infections, hospital admissions and bronchiectasis, and a significantly higher mortality rate compared with Ig-treated patients.

Table 16 Number of infections, hospital admissions, bronchiectasis, missed days from school or work and deaths in Ig-treated and untreated CVID patients

| Variable | Untreated patients (diagnostic delay)  N = 24  Total treatment follow-up = 256 patient years | Ig treated patients (diagnosed early)  N = 23  Total treatment follow-up = 207 patient years | p value |
| --- | --- | --- | --- |
| Total number of infections during study period | 500 | 75 | 0.048 (infection rate) |
| Total number of hospital admissions | 203 | 88 | 0.001 (hospitalisation rate) |
| Total number of non-infectious complications during study period | 85 | 39 | NR |
| Total number of infections that led to hospital admission | 105 | 62 | 0.001 |
| Hospital admissions due to other causes | 98 | 26 | NR |
| Bronchiectasis | 14/24 (58%) | 8/23 (34%) | 0.032 |
| Missed days from work or school | 1563 | 626 | NR |
| Death | 9/24 (40%) | 2/23 (8%) | 0.009 |

**Abbreviations**: NR: not reported

Complication rates for infectious and non-infectious conditions are described in detail in Table 17. For non-infectious complications, significantly higher rates were observed for obstructive lung disease, restrictive lung disease, hepato/splenomegaly and failure to thrive in the untreated patients compared with Ig treated patients. Rates of other non-infectious complications did not differ significantly between the untreated and Ig-treated patients. For infectious complications, significantly higher rates were observed in the untreated patients for all conditions except skin abscesses and mastoiditis. Probability of survival after CVID diagnosis (estimated from Kaplan-Meier life tables) showed that the mortality rate of untreated patients was significantly higher than that of Ig-treated patients (p = 0.005).

Table 17 Infectious and non-infectious complications among Ig-treated (early diagnosis) and untreated (delayed diagnosis) CVID patients

|  | Non-infectious complication rate (per patient per year) | | |
| --- | --- | --- | --- |
| Non-infectious complications | Ig treated patients (diagnosed early)  N = 23 | Untreated patients (diagnostic delay)  N = 24 | p value |
| Obstructive lung disease | 0 | 0.041 | 0.01 |
| Restrictive lung disease | 0 | 0.166 | 0.032 |
| Bronchiectasis | 0.391 | 0.54 | > 0.05 |
| Renal failure | 0.043 | 0.083 | > 0.05 |
| Cirrhosis | 0.347 | 0.291 | > 0.05 |
| Hepatitis | 0.043 | 0.208 | > 0.05 |
| Hepato/splenomegaly | 0.130 | 0.375 | 0.046 |
| Inflammatory bowel disease | 0 | 0.083 | > 0.05 |
| Lymphoid hyperplasia | 0.043 | 0.208 | > 0.05 |
| Deafness | 0.260 | 0.333 | > 0.05 |
| Failure to thrive | 0.130 | 0.666 | 0.043 |
| Immune thrombo-cytopenic purpura | 0.08 | 0.208 | > 0.05 |
| Autoimmune haemolytic anaemia | 0 | 0.083 | > 0.05 |
| Neutropenia | 0.043 | 0 | > 0.05 |
| Diabetes mellitus | 0 | 0.083 | > 0.05 |
|  | **Rate of infections, hospitalisations and missed work/school days (per patient per year)** | | |
| Infections | Ig treated patients (diagnosed early)  N = 23 | Untreated patients (diagnostic delay)  N = 24 | P value |
| Sinusitis/otitis media | 0.082 | 0.687 | 0.003 |
| Pneumonia | 0.103 | 0.382 | 0.001 |
| Septic meningitis | 0 | 0.041 | 0.034 |
| Encephalitis | 0 | 0.018 | 0.032 |
| Lung abcess | 0 | 0.090 | 0.01 |
| Septic arthritis | 0.002 | 0.058 | 0.027 |
| Reactive arthritis | 0.017 | 0.061 | 0.031 |
| Visceral abscess | 0 | 0.017 | 0.041 |
| Skin abscess | 0.012 | 0.023 | > 0.05 |
| Chronic diarrhea | 0.136 | 0.612 | 0.005 |
| Mastoiditis | 0.002 | 0.020 | > 0.05 |
| Liver diseases | 0.06 | 0.1 | 0.048 |
| Enteropathies | 0.13 | 0.699 | 0.012 |
| Hospitalisation | 0.430 | 0.996 | 0.001 |
| Missed days from work/school | 0.42 | 3.9 | 0.002 |

**Abbreviations**: Ig: immunoglobulin.

Three additional studies compared baseline data of CVID patients previously on IMIg to those with no previous Ig treatment. All three studies reported higher IgG levels in patients treated with IMIg compared to those receiving no treatment (statistical testing not performed). However, the applicability of the results is unclear as IMIg does not reflect current clinical practice in Australia.

### Case series pre/post effectiveness data

Eleven case series studies reported pre- and post-Ig effectiveness data for patients with CVID (summarised in Table 18).

Ten studies reported a change in infection-related outcomes pre- and post-Ig treatment. All reported that treatment with Ig lead to a reduction in the number of infections. Methodology and reporting varied between studies, with some studies reporting each infection separately and others reporting composite outcomes, e.g. serious infection (including pneumonia, sepsis, meningitis and pulmonary abscess). Similarly, some studies reported infection incidence (per patient per year) while others reported the percentage of patients who had at least one occurrence of the infection during the follow-up period.

Considering each infection type separately where possible:

* Incidence of lower respiratory infections (including pneumonia) was lower post-Ig treatment in all eight studies reporting this outcome ([Alkan et al., 2017](#_ENREF_8), [Baris et al., 2011](#_ENREF_15), [Busse et al., 2002](#_ENREF_22), [de Gracia et al., 2004](#_ENREF_27), [Martinez Garcia et al., 2001](#_ENREF_53), [Pourpak et al., 2006](#_ENREF_70), [Quinti et al., 2007](#_ENREF_72), [Salehzadeh et al., 2010](#_ENREF_74)). Pre-treatment incidence ranged from 0.28 to 2.04 infections per patient per year. Post treatment incidence ranged from 0.16 to 0.34 per patient per year.
* Otitis media, sinusitis and diarrhoea rates were generally lower post-Ig treatment ([Aghamohammadi et al., 2008](#_ENREF_5), [Baris et al., 2011](#_ENREF_15), [de Gracia et al., 2004](#_ENREF_27), [Quinti et al., 2007](#_ENREF_72), [Salehzadeh et al., 2010](#_ENREF_74)), although for Salehzadeh et al. (2010) this reduction was only statistically significant for recurrent infections (more than three infections per patient per year). Baris et al. (2011) reported no significant change in rates of diarrhoea pre- and post-treatment.

Seven studies reported change in IgG levels following Ig treatment. Baseline IgG levels ranged from 195 mg/dl (SD NR) to 416 mg/dl (SD 196). Post-Ig treatment levels ranged from 455 mg/dl (SD 200) to 891 mg/dl (SD 132). Four studies reported a statistically significant increase ([Aghamohammadi et al., 2003](#_ENREF_3), [Aghamohammadi et al., 2008](#_ENREF_5), [de Gracia et al., 2004](#_ENREF_27), [Pourpak et al., 2006](#_ENREF_70)) while three studies reported a numerical increase without commenting on the statistical significance of the results ([Baris et al., 2011](#_ENREF_15), [Quinti et al., 2007](#_ENREF_72), [Salehzadeh et al., 2010](#_ENREF_74)).

In four studies, Ig treatment was associated with a reduction in the number of required per patient per year. Pre-Ig treatment patients were hospitalised an average of 1.35 to 3.4 times per year. Patients receiving Ig required an average of 0.13 to 0.7 hospitalisations per year.

Two studies commented on the effect of Ig treatment on bronchiectasis. Bronchiectasis was associated with longer delays before diagnosis (Alkan et al., 2018, Baris et al. 2011) higher age at diagnosis, number of respiratory infections and frequency of antibiotic use (Baris et al., 2011).

One study (Baris et al., 2011) reported that Ig use was associated with a reduction in antibiotic use. Pre-Ig treatment patients received an average of 8.27 courses of antibiotic per year, which reduced to 2.5 course (p = 0.0001) after starting Ig therapy.

The only study (Baryakci et al., 2005) to investigate the impact of prophylactic antibiotics on outcomes, reported no change in infection frequency with antibiotic usage for patients with CVID. The impact of other co-interventions was not reported by any study.

Three studies (Busse et al., 2002, De Garcia et al., 2004, Martinez Garcia et al., 2001) included patients with a mean age of 42 years, 45 years and 33 years, respectively, the most similar in patient-age demographics to Australian patients receiving Ig (NBA data from 2018/19 reported an average patient age of 53 years for CVID). Results from these studies were consistent with the overall results of the Assessment. All three studies reported that Ig use was associated with reductions in infection rate compared to pre-treatment rates. No other outcomes were reported by these studies.

Table 18 Summary of effectiveness results

| Author (year)  Country | Number of patients  Duration of follow-up | IgG trough levels (mg/dl) | Infection rates (per patient per year) | Antibiotic usage (per patient per year) | PID-related hospitalisations (per patient per year) | Bronchiectasis | Other |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Aghamohammadi et al. (2003)  Iran | 35  3 yrs | Pre: 258.8 (SD 162.0)  Post: 657.5 (SD 262.6)  P < 0.001 | NR | NR | NR | NR | NR |
| Aghamohammadi et al. (2008)  Iran | 64  Median 3 yrs (range 0.1-18) | Pre: 195.1 (SD NR)  Post: 552.2 (SD NR)  P < 0.001 | Median (range)  Otitis media:  Pre: 0.73 (0-10)  Post: 0.12 (0-4)  P = 0.004  Sinusitis  Pre: 1.0 (0-30)  Post: 0.67 (0-6)  P = 0.018 | NR | NR | NR | NR |
| Alkan et al. (2018)  Turkey | 12  NR, data collected over 11 yrs | NR | Lower respiratory infection and gastroenteritis frequency significantly decreased at 1 year post-treatment  Upper respiratory infection significantly decreased at 5 years post-treatment | NR | NR | Bronchiectasis was associated with increased diagnostic delay and higher rates of lower respiratory infections | Pathological sounds of the lung improved in 3 patients with this symptom at diagnosis |
| Baris et al. (2011)  Turkey | 29  Mean 5.6 yrs (SD 3.5, range 1.3-14)  Pre-Ig mean follow-up 1.1 yrs (SD 1.5) | IgG serum levels  Pre: 416.1 (SD 195.5)  Post: 891.4 (SD 132.1) | Upper respiratory  Pre: 8.87 (SD NR)  Post: 2.04 (SD NR)  P = 0.0001  Lower respiratory  Pre: 2.23 (SD NR)  Post: 0.50 (SD NR)  P = 0.001 (SD NR)  Diarrhoea  Pre: 0.62 (SD NR)  Post: 0.38 (SD NR)  P > 0.05 (NS)  Serious infectionA  Pre: n = 7  Post: n = 0  P = NR | Pre: 8.27 (SD NR)  Post: 2.50 (SD NR)  P = 0.0001 | Pre: 1.35 (SD NR)  Post: 0.21 (SD NR)  P = 0.0001  Hospital stay was inversely correlated to IgG levels (r = -0.42m p = 0.03)  Length of stay (days)  Pre: 16.35 (SD NR)  Post: 6.33 (SD NR)  P = 0.04 | 12 cases detected before Ig therapy  During therapy, progression was marked in n= 5, regression observed in n = 4 and resolution in n = 3  No new cases during Ig therapy  Diagnostic delay, age at diagnosis, number of respiratory infections and frequency of antibiotic use were higher in patients with bronchiectasis | NR |
| Bayrakci et al. (2005)  TurkeyB | 20  Median 4.25 yrs (range 1.25-12.25) | NR | Significant reduction post-Ig (Data for CVID NR separately) | NR | Significant reduction post-Ig (Data for CVID NR separately) | NR | In patients with CVID prophylactic antibiotics did not change infection frequency (data NR) |
| Busse et al. (2002)  USA | 50  Mean 6.6 yrs on IVIgC | NR | Pneumonia prevalence (%)  Pre: 42/50 (84%)  Post: 11/50 (22%) | NR | NR | NR | NR |
| De Garcia et al. (2004)  Spain | 24  2 yrs | Pre: 239 (SD 138)  Post: 806 (SD 167)  P < 0.0001 | Serious infectionB  Pre: 0.48 (SD 0.45)  Post: 0.047 (SD 0.15)  P = 0.001  Mild infectionC  Pre: 4.9 (SD 4.1)  Post: (2.2 (SD 2.0)  P = 0.01 | NR | NR | NR | Pulmonary function No significant change in pulmonary function after 2 yrs Ig treatment |
| Martinez Garcia et al. (2001)  Spain | 19  Mean 7.5 yrs | NR | Lower respiratory tract  Pre: 0.28 (SD NR)  Post: 0.16 (SD NR)  P < 0.001 | NR | NR | Prevalence 11/19 (58%)  No data on impact of treatment | NR |
| Pourpak et al. (2006)  Iran | 26  Mean 3.5 yrs (SD 3.0) | Pre: 214.86 (SD 165.73)  Post: 616.37 (SD 287.38)  P = 0.001 | Pneumonia  Pre: 0.81 (SD NR)  Post: 0.34 (SD NR)  P = 0.0017 | NR | Pre: 3.4 (SD NR)  Post: 0.7 (SD NR)  P < 0.0005  Hospitalisation due to pneumonia:  Pre: 88.5% per year  Post: 46% per year  P = 0.0025 | NR | NR |
| Quinti et al. (2007)  Italy | 224  Mean 11.5 yrs (range 3-34) | Pre: 258.12 (SD NR)  Post: 579.49 (SD NR) | Significant reduction in pneumonia, otitis observed (p < 0.001, data NR)  Significant increase in sinusitis and chronic lung disease (p < 0.001, data NR) | NR | NR | NR | NR |
| Salehzadeh et al. (2010)  Iran | 24  Mean 8 yrs (SD 4.6) | Pre: 272.91 (SD 185.58)  Post: 455.29 (SD 200.23) | All % of patients with infection  RecurrentE Otitis media  Pre: 46%, Post: 4%,  P = 0.002  Recurrent Sinusitis  Pre 25%, post: 4%  P = 0.048  Recurrent pneumonia  Pre: 42%, post: 4%  P = 0.006  Recurrent diarrhoea  Pre: 50, post: 4  P = 0.001  Note: % patients with any otitis media, any sinusitis was not significantly different pre- and post- treatment | NR | Pre: 1.21 (SD NR)  Post: 0.125 (SD NR)  P 0.008 | Documented in 7 patients, effect of IG NR | NR |

**Abbreviations**: Ig: immunoglobulin, IgG: immunoglobulin G, NR: not reported, PID: primary immunodeficiency diseases, Pre: results from before immunoglobulin treatment, Post: results from after immunoglobulin treatment, SD: standard deviation.

**Notes**: A = all values are mean (standard deviation) unless specified. B = Baris et al. (2011) defined serious infection as cellulitis, meningitis, sepsis. C = De Garcia et al. (2004) defined serious infection as pneumonia, sepsis, meningitis and/or pulmonary abscess. D = De Garcia et al. (2004) defined mild infection as bronchitis, otitis, sinusitis or fever. E = Salehzadeh et al. (2010) defined recurrent as more than three episodes of infection.

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## Supplementary evidence: Studies comparing IVIg to IMIg or SCIg

Three randomised controlled trials were identified that compared administration route of Ig (IMIg or SCIg compared to IVIg) ([Chapel et al., 2000](#_ENREF_23), [Garbett et al., 1989](#_ENREF_31), [Nolte et al., 1979](#_ENREF_65)).

Advice from the Immunoglobulin Review Reference Group is that, IMIg is no longer used as an Ig administration method. Therefore, evidence comparing IMIg to IVIg is outside the scope of this review. The comparison has been retained here as supplementary evidence only.

Similarly, as the intervention is considered to be Ig (regardless of the route of administration), the comparison of SCIg to IVIg is outside the scope of this assessment and this comparison is presented as supplementary evidence only.

The Supplementary evidence is presented only to acknowledge that these issues have been investigated and do not form the basis of the findings of this review.

Chapel et al. (2000) randomised 30 patients to either IVIg or SCIg for 12 months. Patients were then crossed over to the alternate treatment for 12 months. A total of 22 patients completed the 24 months of the trial (four patients on SCIg therapy withdrew due to systemic reactions, pain at infection site, preferred intravenous administration or repeated local allergy). Four patients on or due to begin IVIg therapy withdrew due to product unavailability, fear of virus transmission or preferred SCIg therapy and refused intravenous administration.

There were no significant differences in the rate of infection between the two groups (mean 4.12 per patient per year for IVIg, mean 3.82 for SCIg, p = NR). Similarly, there were no significant differences in the length of infection (mean 87 days IVIg vs mean 73 days SCIg) or number of days missed work/school (mean 12 days for both IVIg and SCIg).

SCIg was associated with a higher number of adverse events overall (10.4% of infusions vs 5.5% for IVIg), however when pain or redness at infusion site was excluded the rate of systematic reactions for SCIg was 3.3%. Systematic adverse events included headache, fatigue rigors, hot flushes, urticaria/eczema, increased pulse, dizziness and nausea.

No differences in trough IgG serum levels were found between the two groups (IVIg median 7.8-8.4 g/l vs SCIg median 8.0-9.1 g/l). Patient preference varied, with 16 patients preferring IVIg, 10 patients preferring SCIg and four patients reporting no preference.

Two studies investigated the comparison between IMIg and IVIg, with both reporting better outcomes with IVIg ([Garbett et al., 1989](#_ENREF_31), [Nolte et al., 1979](#_ENREF_65)).

* Garbett et al. (1989) compared IMIg to IVIg in a RCT of 12 patients. Trough serum levels of IgG were higher with IVIg than IMIg (even higher with 3-weekly doses of IVIg than 4-weekly) (mean values not reported, p = 0.004 and p = 0.001, respectively). Patients reported significantly improved infection indices on IVIg compared to IMIg including fewer days feeling unwell (225 vs 407, p = 0.002), reduced antibiotic usage (296 vs 511, p = 0.03), fewer days with increased temperature (10 vs 30, p = not reported) and fewer days with acute respiratory tract symptoms (236 vs 388, p = 0.009). Further, these outcomes were significantly improved when using three-weekly IVIg dosing compared to four-weekly (p = 0.02).
* Nolte et al. (1979) randomised 20 patients to either IMIg or IVIg. Serum IgG levels increased from baseline by a higher proportion following IVIg treatment (248% increase vs 90%). Infection rates were lower in patients treated with IVIg (0.103 infections per patient per month vs 0.295).

## Supplementary evidence: What do existing systematic reviews say?

Five systematic reviews were identified investigating the effectiveness of Ig in patients with PID ([Abolhassani et al., 2012](#_ENREF_2), [Jones et al., 2018](#_ENREF_45), [Lingman-Framme and Fasth, 2013](#_ENREF_51), [Shabaninejad et al., 2016](#_ENREF_76), [Shrestha et al., 2019b](#_ENREF_79)). These reviews were pearled to ensure all relevant studies were captured in our review of primary evidence. The findings of these reviews are discussed below and summarised in Table 19.

The identified systematic reviews all compared IVIg to SCIg. Reviews were based on searches conducted between January 2012 and May 2018 and included patients with any type of PID. Results for each type of PID were analysed together.

IgG trough levels, infections rates and adverse events were the most commonly reported outcomes. The studies varied with respect to the comparison between SCIg and IVIg. Three reviews found IgG levels were higher with SCIg treatment than with IVIg ([Lingman-Framme and Fasth, 2013](#_ENREF_51), [Shabaninejad et al., 2016](#_ENREF_76), [Shrestha et al., 2019b](#_ENREF_79)), while Abolhassani et al. (2012) reported equivalent levels between the two administration routes.

All four reviews reporting comparative infection levels found no difference between the administration routes ([Abolhassani et al., 2012](#_ENREF_2), [Lingman-Framme and Fasth, 2013](#_ENREF_51), [Shabaninejad et al., 2016](#_ENREF_76), [Shrestha et al., 2019b](#_ENREF_79)).

Shabaninejad et al. (2016) reported no difference in systemic adverse events between IVIg and SCIg, conversely Abolhassani et al. (2012) reported SCIg was associated with lower adverse events. Lingman-Framme and Fasth (2013) noted that systemic events were rare and it was not possible to draw any conclusions as to the comparative safety of the two administration routes.

All reviews noted the low quality of the evidence base which limited the findings of the reviews. Calls for further research to be conducted were made by all reviews.

While some studies noted there may be benefits associated with SCIg use, no study found IVIg was associated with improved outcomes. Therefore, extrapolation of the results in Section B.6 to patients treated with SCIg is unlikely to overestimate the effectiveness of SCIg in the Australian clinical context.

Table 19 Characteristics of the systematic reviews

| Author (year) | Search date  Number of studies  Number of patients | Study characteristics | Purpose of the review | Patient characteristics | Key safety outcomes | Key effectiveness outcomes | Conclusions of the review |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Abolhassani et al. (2012) | January 2012  47  1,484 (1,028 unique patients) | 10 clinical trials, 17 prospective cohorts, 20 retrospective cohorts | Compare the safety and efficacy of SCIg to IVIg | Adult and paediatric patients with any form of PID | Decreased systemic events with SCIg (OR 0.09 (95% CI = 0.07, 0.11) | Trough IgG levels: comparable  Infection rate: no significant difference in odds of infection | SCIg may offer a benefit over IVIg  Results may be biased by lack of RCTs, and enrichment of patients who cannot tolerate IVIg |
| Jones et al. (2018) | August 2015  17  1,858 | 1 RCT, 7 prospective case series, 9 cross-sectional studies | To investigate the burden of Ig treatment in relation to administration route | Adult and paediatric patients with any form of PID | NR | Ig was not associated with high burden and patients were generally satisfied with either administration route  Patients preferred in-the-home delivery and generally patients preferred SCIg | Lack of control groups in most studies may have influenced results  PID patients satisfied with either treatment modality  More research required in this area |
| Lingman-Framme and Fasth (2013) | June 2012  19  284 | 2 RCTs, 17 observational studies | Compare the safety, efficacy, HRQoL and cost-effectiveness of SCIg to IVIg | NR | Serious adverse events: none reported for either group  Systemic events: rare, not possible to comment on comparative rates  Local events: higher for SCIg, mild | Trough IgG levels: higher for SCIg  Infection rate: no significant difference  HRQoL: improved with SCIg  Cost-effectiveness: SCIg more cost effective mostly due to reduced days of work/school lost | SCIg is safe and efficacious and at least non-inferior to IVIg.  Good quality studies are lacking. |
| Shabaninejad et al. (2016) | March 2015  24  945 | 6 clinical trials, 12 prospective studies, 6 retrospective studies | Compare the safety and efficacy of SCIg to IVIg | Adult and paediatric patients with any form of PID | No statistical difference in systemic adverse events (OR 0.497, 95% CI = 0.180, 1.371) | Trough IgG levels: higher in SCIg, mean 9.59 vs 8.54, SMD 0.339 (95% CI = 0.2, 0.47)  Infection: no difference in infection rate | Shifting from IVIg to SCIg can have clinical benefit for PID patients  More research in this area would be beneficial |
| Strestha et al. (2019) | May 2018  24 | 21 prospective studies, 2 ambispective, 2 retrospective studies | Investigate the relationship between IgG trough levels, route of administration and infection incidence. | Adult and paediatric patients with any form of PID  Mean patient age 23.8 yrs, majority male patients, predominantly CVID (> 80%) | NR | Trough IgG levels: higher for SCIg (MD 75.43, 95% CI 31.67, 119.19)  Infection: No difference in overall risk of infection (RD 1.58, 95% CI = 0.75, 3.33)  No difference in serious infection (OR 1.94, 95% CI = 0.59, 6.32) | SCig associate with higher IgG trough levels. Higher SCIg trough levels associate with reduced infection. For IVIg, no relationship between trough Ig and infection levels was found.  More RCTs required to investigate relationship between IgG levels and infection. |

**Abbreviations**: CI: confidence interval, HRQoL: health related quality of life, Ig: immunoglobulin, IgG: immunoglobulin G, IVIg: intravenous immunoglobulin, MD: mean difference, NR: not reported, OR: odds ratio, PID: primary immunodeficiency diseases, RCT: randomised controlled trials, RD: risk difference, SCIg: subcutaneous immunoglobulin, SMD: standard mean difference.

## Extended Assessment of Harms

The Database of Adverse Event Notification (DAEN) of the TGA was searched on 2 March 2020 for all medicines listed as “normal immunoglobulin” ([TGA, 2020](#_ENREF_86)).

A total of 2,035 cases of reaction were reported. The most common events (occurring in 100 or more patients) were:

* Chills (n = 403)
* Fever (n = 321)
* Headache (n = 305)
* Nausea (n = 223)
* Shortness of breath (n = 209)
* Tachycardia (n = 156)
* Hypertension (n = 153)
* Rash (n = 149)
* Urticaria (n = 129)
* Back pain (n = 125)
* Vomiting (n = 125)
* Pruritus (n = 109)
* Chest pain (n = 101)
* Hypotension (n = 101)
* Aseptic meningitis (n = 100)

These are consistent with the events reported in Section B.6, with the exception of aseptic meningitis which was not reported as an adverse event by any study (but may have been captured in effectiveness data in a single study).

Ig therapy is known to be associated with rare, but potentially serious adverse events including serious allergic reaction, thrombotic events (stroke and myocardial infarction), seizures, posterior reversible encephalopathy syndrome, renal impairment, haemolysis and neutropenia ([Guo et al., 2018](#_ENREF_35)).

Considering only these potentially serious events, the DAEN database reported the following number of these potentially serious rare events occurring with Ig use (for any indication):

* Anaphylaxis (n = 70)
* Thrombotic stroke (n = 4)
* Myocardial infarction (n = 10)
* Seizure (n = 18)
* Renal impairment (n = 12)
* Haemolysis (n = 54)
* Neutropenia (32)

The FDA has noted that immunoglobulins are associated with an increased risk of thrombosis and have issued a black box warning for all human immunoglobulins to reflect this ([IDF, 2013](#_ENREF_38)).

We note that these reports indicate that severe adverse events, although rare, can occur with Ig use. It is not clear to what extent these events occur in patients with PID.

## Interpretation of the Clinical Evidence

**On the basis of the evidence profile (summarised in Table 20), it is suggested that, relative to no treatment, Ig has inferior safety and may have superior effectiveness noting that there is only low to very low quality evidence available to support these conclusions.**

Ig is accepted as a safe therapy in Australia and is generally associated with mild adverse events. Severe events are rare and mostly resolved by treatment cessation. Overall it is estimated that approximately 44% of patients will experience an adverse event at some point during their treatment. Approximately 4% of patients are estimated to suffer a serious adverse event at some point during treatment.

Considering effectiveness, Ig is associated with lowered infection rates (including upper and lower respiratory tract infections, pneumonia, otitis media, sinusitis and diarrhoea), lower hospitalisation rates and higher IgG levels. However, these effectiveness results have been assessed as being low to very low quality due to the high risk of bias associated with the studies and the potential impact of confounding influencing the results (particularly the use of prophylactic antibiotic usage). Advice from the Immunoglobulin Review Reference Group is that it is difficult to separate the effect of Ig and any co-interventions.

On the other hand, for patients with CVID, *The Criteria Version 3* requires review by an immunologist after six months of therapy and documented evidence of clinical effectiveness is required to continue therapy. None of the studies reported whether such a review was undertaken for included patients. However, advice from the Immunoglobulin Review Reference Group is that it is unlikely that patients with CVID who start Ig therapy would cease the therapy due to absence of effect; therefore, this issue is considered unlikely to have impacted the results of this review substantially.

Generally, the patients included in the studies and the way Ig was used were considered applicable to the Australian context. Three further potential issues with the evidence base were identified:

* The findings of this review are limited to patients with CVID. The effectiveness of Ig in patients with another form of PID is not known. CVID does represent most Ig use in Australia for primary immunodeficiency conditions (86% according to NBA data); therefore, the findings of this review are applicable to the majority of patients on the proposed population.
* The average age of patients in the evidence base was lower than for patients receiving Ig treatment for CVID in Australia (average age 56 years in 2018/19, NBA data). A subgroup of three studies with similar patient demographic to the Australian data was assessed separately and no differences in results compared to the overall evidence base were identified. Therefore, the age discrepancy noted does not appear to impact the generalisability of this review to the Australian CVID population.
* The findings of this review are based on evidence conducted using IVIg as the treatment. One RCT and five systematic reviews of observational studies found SCIg was at least non-inferior to IVIg. SCIg may be associated with high rates of minor local adverse events at the infusion site but lower rates of systemic adverse events. Therefore, it is considered reasonable to extrapolate the results of this review to patients on SCIg therapy for CVID.

Despite the significant limitations associated with the evidence base, it is unlikely that higher quality studies will be forthcoming to investigate the comparative effectiveness of Ig therapy in patients with PID. No relevant upcoming clinical trials were identified, and due to the low incidence of PID, recruiting enough patients for a large prospective trial may not be feasible (for example, a Melbourne study[[5]](#footnote-6) included all patients with any form of PID treated over a period of 16 years and included 179 patients).

Further, based on the literature screening performed for this review, there does not appear to be any other treatment routinely available for patients with PID other than Ig therapy, therefore a trial comparing Ig to another active treatment for PID is unlikely to be feasible at this point in time. A trial comparing Ig treatment to no treatment/placebo may not be ethical given there is (limited, low quality) evidence that delaying Ig treatment may lead to worse outcomes for patients (for example a delay may increase the risk of bronchiectasis).

Table 20 Balance of clinical benefits and harms of intervention, relative to comparator, and as measured by the critical patient-relevant outcomes in the key studies

| Outcome  (units, follow-up) | No. of studies and study design | Risk of bias | Effect Ig | Effect no treatment | Quality | Importance |
| --- | --- | --- | --- | --- | --- | --- |
| Adverse events  follow up: range 1 years to 12 years (count) | 8 observational studies | Serious | 184/434 (42.4%) | NA | ⨁⨁⨁⨀  **Moderate quality** | Critical |
| Serious adverse events (count) | 5 observational studies | Serious | 20/519 (3.9%) | NA | ⨁⨁⨁⨀  **Moderate quality** | Critical |
| Lower respiratory infection rates (per patient per year) | 8 observational studies | Very serious | Range of means  0.16-0.34 | Range of means  0.28-2.04 | ⨁⨀⨀⨀  **Very low quality** | Critical |
| IgG trough levels (mg/dl) | 7 observational studies | Serious | Range of means  455-891 | Range of means  195-416 | ⨁⨁⨀⨀  **Low quality** | Critical |
| Hospitalisations (per patient per year) | 4 observational studies | Very serious | Range of means  0.13-0.7 | Range of means  1.35-3.4 | ⨁⨀⨀⨀  **Very low quality** | Critical |

**Abbreviations**: Ig: immunoglobulin, IgG: immunoglobulin G, NA: not applicable. **Source**: 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

With the agreement of the Immunoglobulin Review Reference Group, translation of the clinical evidence was not undertaken.

# Section D Review of Economic Evaluations

## Overview

To understand the cost-effectiveness profile of Ig replacement therapy for PID patients, a review of literature on published economic evaluations was conducted. Results of the literature review informed consideration of the feasibility of performing a model-based economic evaluation.

The literature searches and selection criteria resulted in the identification of 15 relevant studies. Six of these studies were model-based economic evaluations, six were cost analyses of disease burden and budgetary impact, and the remaining three were reviews of economic studies. None of the identified studies compared Ig use to non-Ig standard care for PID patients. All comparative studies were focused on how IVIg and SCIg compare in terms of clinical and economic outcomes. Despite the diversity in modelling approaches and evaluation results, there was a consistent finding across all studies: SCIg is likely to be substantially more cost-effective compared to IVIg.

Given the available evidence, it is unlikely to be feasible to conduct model-based economic evaluation to compare Ig and non-Ig standard of care due to the lack of data on the comparator. Ig use for patients with PID is routine and considered the standard clinical management strategy, particularly for patients with common subtypes of PID, including common variable immunodeficiency (CVID) and X-linked agammaglobulinemia (XLA).

## Existing evidence

### Literature search and selection

A targeted search was undertaken to identify existing economic evaluations of the cost-effectiveness of Ig therapy in PID. Keywords used in the search are provided in Appendix B. The search was designed to identify any economic evaluation involving the use of Ig in any form for patients with PID without limiting to any subtypes of PID. Further, the search did not limit specific types of economic evaluations. Literature reviews and health technology assessments with an economic evaluation component were also included for comprehensiveness. The search was performed in PubMed, and was limited to studies published in the last 10 years.

Literature screening and selection were conducted using the specific inclusion and exclusion criteria listed below (Table 21).

Table 21 Selection criteria for literature review

| Selection criteria |  |
| --- | --- |
| Inclusion criteria | * The investigation of Ig therapeutic use; * Treatment of primary immunodeficiency (PID), not limited to any subtypes;’ * Economic evaluation with or without using a modelled approach; * For studies using a modelled approach, any types of economic evaluation including CMA, CEA, CUA or CCA * Reviews of economic evaluations or HTAs with an economic evaluation component |
| Exclusion criteria | * Acquired immunodeficiency due to HIV or others; * Patients having secondary immunodeficiency; * Studies focused on the PID diagnosis instead of therapy; * Studies investigating non-human subjects; * Studies in foreign languages * Studies published over ten years |

**Abbreviations**: PID = primary immunodeficiency; CEA = cost-effectiveness analysis; CUA = cost-utility analysis; CMA = cost-minimisation analysis; CCA = cost-consequence analysis; HIV = human immunodeficiency virus;

The search yielded 83 potentially relevant studies and the application of the above selection criteria narrowed down the selection to 15 studies for review. Among the 15 studies, there were six modelled economic evaluations: one study conducted a cost-effectiveness analysis ([Shabaninejad et al., 2017](#_ENREF_77)), one study was a cost-utility analysis ([Windegger et al., 2020](#_ENREF_90)), and the other four studies were cost-minimisation analyses ([Beaute et al., 2010](#_ENREF_18), [Igarashi et al., 2014](#_ENREF_42), [Martin et al., 2013](#_ENREF_52), [Perraudin et al., 2016](#_ENREF_68)). A further six cost and budgetary impact analyses were identified in various settings and countries. All of them considered different Ig administration methods for PID patients in a specific health settings (e.g. the health system or a hospital) ([Fu et al., 2018](#_ENREF_30), [Menzin et al., 2014](#_ENREF_55), [Pollock and Meckley, 2018](#_ENREF_69), [Sadeghi et al., 2015](#_ENREF_73), [Gholami et al., 2017](#_ENREF_34), [Viti et al., 2018](#_ENREF_88)). Two of these studies examined the CVID subtype of PID ([Sadeghi et al., 2015](#_ENREF_73), [Viti et al., 2018](#_ENREF_88)).

Finally, three review-type studies were also identified and included. However, the scope of these reviews is larger than the current assessment. For example, one review of economic studies included both the treatment and (early) diagnosis of PID ([Elsink et al., 2020](#_ENREF_28)). All primary studies identified in that review were also identified and included by the current search. The second review was a comprehensive review of subcutaneous Ig only, and the investigated both primary and secondary immunodeficiencies ([Lingman-Framme and Fasth, 2013](#_ENREF_51)). As this review was published in 2013, it did capture economics studies which were outside the current inclusion limit of 10-years. The final review was an HTA conducted by Health Quality Ontario in Canada ([Health Quality Ontario, 2017](#_ENREF_36)). This study comprehensively analysed the clinical evidence comparing IVIg and SCIg, but only narratively reviewed the health economic literature identified.

It should be noted that, for all the studies identified above, none of the articles investigated the economic outcomes of comparing the use of Ig (IVIg or SCIg) against standard of care (without Ig). For most comparisons, the studies analysed economic outcomes comparing IVIg and SCIg; most using a cost minimisation analysis (CMA). All the CMAs assumed that clinically there was no significant difference in administration routes or settings: i.e., intravenous versus subcutaneous route; administration in hospital or at home. As this may lead to significant cost advantage of SCIg, they investigated whether the Ig administration in home setting via subcutaneous route could be cost-saving. No cost-consequence analyses were identified.

While the current evidence base does not directly address the question of the cost-effectiveness between Ig and non-Ig standard care, information presented in these included studies could still be relevant. Therefore, relevant information such as study settings, costs and evaluation approaches as well as evaluation methodologies have been extracted and appraised. The applicability of the published information to the Australian context has also been explored.

### Key characteristics of the costing studies included

To provide a clear profile of the evidence base currently available, key study information was categorised from the three types of economics studies included in the current review: 1) studies with economic modelling approaches (n = 6), 2) costing studies on budgetary impact (n = 6), and 3) review studies (n = 3).

#### Model-based economic evaluations

There are in total of six model-based studies. As previously described, most were cost-minimisation analyses due to the presumed clinical equivalency between IVIg and SCIg. It was understood that SCIg, which was administered at a home setting with a potential better safety profile, may have cost advantages over the conventional hospital administered IVIg. The cost benefits are primarily attributable to savings around reduced requirements for professional care (e.g. nurses) and avoidance of potential adverse events associated with intravenous infusions. Key study characteristics, methodologies and evaluation results are shown in Table 22 below. It should be highlighted that the studies included in this review were comparing IVIg and SCIg, hence do not directly inform the comparative cost-effectiveness of Ig against no Ig and BSC.

Table 22 The key characteristics and evidence profile presented in the included model-based studies

| Author  Publish year  Country | Model settings  Data sources | Population  Comparison  Economic Outcome | Modelling approach  Sensitivity analysis | Results and  Conclusion |
| --- | --- | --- | --- | --- |
| Shabaninejad et al  2017  Iran | Healthcare payer perspective  Iran health administration data | PID patients NOS  IVIg in hospitals and SCIg at home  Incremental costs per 1% increase in Ig serum level and reduction in adverse events | **CEA** via decision tree, with 1-year TH  DSA variables tested: Ig cost, infusion period, hospital, material and personnel costs | Incremental costs per 1% increase in Ig serum level with SCIg compared to IVIg = -$4,348  Incremental costs per 1% reduction in adverse events with SCIg compared IVIg = $2,939  SCIg is more cost effective than IVIg |
| Windegger et al.  2020  Australia | Australian healthcare system perspective  Data from Sunshine Coast Hospital and Health Services | PID patients NOS  IVIg in hospitals and SCIg at home  Incremental costs per QALY gained | **CUA** via Markov cohort transition model with six health states with 10-year TH and weekly cycle;  Both DSA and PSA to identify key drivers of the model | Incremental cost = $45,835;  Incremental QALY = -0.021;  SCIG dominant |
| Perraudin et al.  2016  Switzerland | Healthcare provider perspective  Pharmaceutical companies and Government statistics | PID patients NOS  IVIg in hospitals and SCIg at home  Cost differences | **CMA** via decision tree with 3-year TH  DSA only on uncertain cost items; the main drivers were all related to Ig dosage and frequency of administrations | SCIg = $36,595 in the 1st year and $30,309 in subsequent years;  IVIg = $35,370 per year  Cost saving = $9,828 over 3 years |
| Igarashi et al.  2014  Japan | Societal perspective  Only included non-medical costs by assuming equivalent medical expense | PID patients NOS  IVIg in hospitals and SCIg at home  Life quality index (LQI) score, productivity loss and hospital-related absenteeism | **CMA was indicated but method not reported in detail;**  No sensitivity analysis | SCIg demonstrated  Higher LQI  60% reduction in productivity loss, saving about JPY 10,875  Less hospital-related absenteeism for patients and carers |
| Martin et al.  2012  Canada | Canadian healthcare perspective  St Paul’s Hospital, Vancouver, Canada | PID patients NOS  IVIg in hospitals and SCIg at home  Cost differences per patient and to overall national health budget | **CMA** via decision tree with 3-year TH, also a budgetary impact analysis (BIA) model  DSA on numbers of hospital visits for IVIg and scenario of SCIg switching in both CMA and BIA | Cost reduction of $5,736 per patient over 3 years by CMA model  Cost saving of 1.308 million (37%) in the first 3 years from the national health budget |
| Beaute et al.  2010  France | French social insurance perspective  Specific source of data used not provided, but verified by field data through questionnaires | PID patients with subtypes of agammaglobulinemia or hyper-IgM syndrome.  IVIg in hospitals or home and SCIg at home  Cost differences | CMA, 1-year TH  DSA on infusion period, nurse costs and related medical equipment and material | SCIg was 25% less expensive based on field data analysis due to lower dose |

**Abbreviations**: PID = primary immunodeficiency; NOS = no otherwise specified; IVIg = intravenous immunoglobulin; SCIg = subcutaneous immunoglobulin; CEA = cost-effectiveness analysis; CUA = cost-utility analysis DSA = deterministic sensitivity analysis; TH = time horizon; JPY = Japanese Yin

The six model-based health economic evaluations demonstrated a consistent cost advantage of SCIg over IVIg. All of the four-cost minimisation analysis presented the cost-saving result in the base-case scenario, where the other two studies also showed that SCIg is more cost-effective than IVIg. In the CMA, the main driver of the economic evaluation outcomes seems to be the cost of Ig administration where the saving was due to the avoidance of hospital-related costs.

Due to the nature of these evaluations, the time horizons in these studies are very short. The only long-term studies were the cost-utility analysis by Windegger et al. (2020). This cost-utility model extrapolated the evaluation to 10-years, and also showed the SCIg being dominant over IVIg due to reduced costs. From the included CMA studies, costs incurred by IVIg within the hospital setting were relatively stable over time, and additional costs associated with SCIg, such as medical equipment and training, tended to only occur in initial years. Regular costs of SCIg in the longer-term were also relatively stable. Therefore, although few studies looked at the long-term economic outcome of different forms of administration for Ig, the evaluation results in the studies with short time horizons may also be applicable to a longer time horison. This should be however, established on the premise of patients using SCIg and IVIg having similar clinical characteristics.

#### Budgetary impact analysis

Various costing studies were also identified and included in the current assessment. Although they are not comparative in nature, they provide valuable information regarding PID prevalence, clinical management strategies, and the cost burden of disease. On the other hand, the information presented in this type of study is diverse due to significant differences in health system across countries and settings. Also, the methodologies used across the modelling and non-modelling studies were highly variable. To ensure the extraction of useful information, only high-level data extractions were undertaken focusing on key data from the studies. The key information is tabulated below in Table 23.

Table 23 Key study characteristics for budgetary analysis for PID patients

| Author  Publish year  Country | -Population  -Prevalence  -% treated by Ig  -IVIg and SCIg split | Costs involved  -direct costs  -indirect costs | -Estimating approach  -Sensitivity analysis | Results and  Conclusion |
| --- | --- | --- | --- | --- |
| Viti et al.  2018  Italy | PID with CVID and XLA subtype  CVID = 3.17 per 100k,  XLA = 0.22 per 100k  CVID = 85%,  XLA = 91.5%  CVID: 69.5% vs. 30.5%;  XLA: 66.5% vs. 33.5% | Direct costs including Ig drugs, personnel, pre-medications, adverse events, administration and diagnosis;  Indirect costs including productive loss and absenteeism due to IVIg (all estimated) | Combination of epidemiological and market share approach  PSA on all population related variables | Population size: CVID = 1,885 and XLA = 133;  Total annual estimated costs = € 42.68 million |
| Pollock and Meckley  2018  Switzerland | PID NOS  Population size: PID = 338, 42.1% treated with Ig | Ig use,  Healthcare professional (HCP) costs  Ancillary usage (pump etc.) | Combination of epidemiological and market share approach  DSA on Ig dosage, frequency, PID prevalence, HCP involvement and Ig administration splits | 142 treated with Ig  With SCIg (Ig20Gly), 11.151 million CHF by year 3;  Without SCIg (Ig20Gly), 11.163 million by year 3 |
| Fu et al.  2018  Canada | PID with CVID and XLA subtype, subtype specific detail not reported  IVIg and SCIg split = 30:27 | Ig use  Physician visits  Hospital costs | Observational study at a hospital level  Sensitivity analysis not performed | Unadjusted average total costs for SCIg ($1,836) is significantly lower than IVIg ($4,187) at hospital level (diff = $2,351)  Adjusted (for age, sex, weight and comorbidities) the incremental difference at hospital level is $2,103. |
| Gholami et al.  2017  Iran | Paediatric PID patients with 10 subtypes based on the ICD-10 codes, including CVID and XLA | All direct costs around hospital admission, medical equipment and tests plus interventional procedures including surgery or bronchoscopy | Observational study at one specific local hospital in Iran  Sensitivity analyses not performed, but uncertainty ranges were estimated and provided | Mean admission cost = $7,090 per patients, costs for specific medication categories (e.g. anti-infective drugs) also reported, which accounted 4.6% to 28.1% of all costs |
| Sadeghi et al.  2015  Iran | PID with CVID subtype  Epidemiological data used for cost modelling via the PID registry, but no detail reported. | Direct costs = physicians and ambulatory care, hospital admission, medications (including Ig and others), outpatient care, laboratory tests and ambulatory transport are included;  Indirect costs = loss of productivity and premature death | Cost modelling using hidden Markov model  PSA performed on all variables included | Cost of diagnoses per patients = $6,500, the cost of hospital admission = $25,000, and medication costs = $40,600  Total annual costs per patient = $274,200 |
| Menzin et al.  2014  The US | PID NOS  Epidemiological data not relevant | All direct costs including hospitalisation, ER visits, outpatient visits, allied healthcare professionals | Retrospective observational study using market share approach  Sensitivity not performed, but uncertainty ranges estimated and reported. | Infection was the most expensive resource used, and costed $11,925 on average per patients over the 7 months period;  Hospitalised patients due to infection cost significantly more, around $38,574 per patients |

**Abbreviations**: PID = primary immunodeficiency; XLA = X-linked agammaglobulinemia; NOS = no otherwise specified; IVIg = intravenous immunoglobulin; SCIg = subcutaneous immunoglobulin; CEA = cost-effectiveness analysis; CUA = cost-utility analysis DSA = deterministic sensitivity analysis; TH = time horizon; JPY = Japanese Yin

Three studies reviewed the budgetary impact or cost burden at a national level ([Viti et al., 2018](#_ENREF_88), [Pollock and Meckley, 2018](#_ENREF_69), [Sadeghi et al., 2015](#_ENREF_73)), and the other three examined the cost burden at a local level ([Fu et al., 2018](#_ENREF_30), [Gholami et al., 2017](#_ENREF_34), [Menzin et al., 2014](#_ENREF_55)). The observation shared across all the included studies is that Ig replacement therapy for PID is expensive but there is room to gain more efficiency in its administration. Studies which evaluated cost burden at national levels were difficult to compare due to differences in health systems and diversity in how health services and goods were costed. In contrast, for the costing studies at local levels, it appears that Ig treatment is a significant cost burden. A common finding shared across all studies was that, in the absence of Ig treatment, increased infection rates leading to hospitalisations will lead to increased costs.

Four of the six budgetary impact studies discussed specific subtypes of PIDs in their publication ([Viti et al., 2018](#_ENREF_88), [Fu et al., 2018](#_ENREF_30), [Gholami et al., 2017](#_ENREF_34), [Sadeghi et al., 2015](#_ENREF_73)), and three of these were limited to specific PID subtypes of CVID and XLA ([Viti et al., 2018](#_ENREF_88), [Fu et al., 2018](#_ENREF_30), [Sadeghi et al., 2015](#_ENREF_73)). The remaining two budgetary impact studies reported the coverage rate of Ig as a therapy options for patients with any form of PID ([Viti et al., 2018](#_ENREF_88), [Pollock and Meckley, 2018](#_ENREF_69)). There was some variation as to how PID patients were managed using Ig due to the inclusion of different PID subtypes. The coverage rate ranged from very high (91.5% of XLA patients in Italy treated with Ig) ([Viti et al., 2018](#_ENREF_88)) to less than half (42.1% of the PID patients in Switzerland) ([Pollock and Meckley, 2018](#_ENREF_69)). The low coverage rate reported by the Swiss study was not explained in their report, and the percentage figure was referenced from an external study. When the original study was examined, it appeared the common types of PIDs, including CVID and XLA, had high coverage rates ([Ballow et al., 2009](#_ENREF_14)). Therefore, the reported low rate in the Swiss study seemed to be an overall average figure.

#### Reviews and HTA

Three reviews were identified. Due to the diversity in the review scope, key evidence has been summarised narratively rather than tabulated.

A very recent comprehensive review of economic studies by Elsink et al. (2020) examined all studies reporting economic outcomes relevant to the diagnosis and treatment of PID ([Elsink et al., 2020](#_ENREF_28)). The review found that patients with CVID and XLA were most commonly treated with Ig replacement therapy, in form of either IVIg or SCIg. However, due to some of the included studies not specifying PID subtypes in their investigated population, a consistent result was difficult to find. Further, the review found that the economic consequences of Ig treatment are heavily reliant on disease duration and treatment time span. Therefore, the review recommended interpreting the economic evaluation outcomes with caution.

The assessment by Health Quality Ontario conducted a review of economic literature as a part of their comprehensive HTA, similar to the current assessment. The HTA review included a smaller number of studies (n = 3), and it addressed the comparison between IVIg and SCIg ([Health Quality Ontario, 2017](#_ENREF_36)). Therefore, the information available in the publication was of limited relevance to this Assessment (comparing Ig to no Ig treatment). Nevertheless, the HTA found that SCIg was associated with substantial cost-savings compared to IVIg due to the reduction in nursing care required. This is consistent with the findings described above.

The 2013 review by Lingman et al. reviewed both clinical and economic aspects of Ig use via the either intravenous or subcutaneous route ([Lingman-Framme and Fasth, 2013](#_ENREF_51)). The review found that published studies up to the end of 2012 demonstrated the SCIg could introduce substantial cost savings to patients compared to IVIg while sharing similar safety and effectiveness profile. However, this cost-saving was primarily derived from societal benefits such as the avoidance of unnecessary productivity loss.

### Applicability to the Australian clinical context

As described above, none of the included economic studies is directly relevant to the main question of the current report, regarding the relative cost, effectiveness, and cost-effectiveness of Ig use compared with non-Ig use in patients with PID. Consequently, it is not possible to draw any conclusions from the economic literature regarding the cost-effectiveness of Ig: the incremental cost-effectiveness of Ig versus no Ig can neither be confirmed nor dismissed. Based on the clinical and economic studies discussed herein, it is possible to infer that Ig (especially SCIg) may be cost-effective for the management of PID.

Consequently, the potential cost-effectiveness of Ig in PID has been explored using three indirect approaches. These three approaches are discussed in more detail below. It should be noted that, in the absence of detailed modelling work, the analyses below are exploratory, and the cost-effectiveness of Ig compared to no Ig in PID remains uncertain.

#### Impact of Ig on serious infections and bronchiectasis

From the clinical evaluation in Section B, it is apparent that Ig is effective in improving patient outcomes such as reducing infections, controlling the onset of bronchiectasis, and avoiding general hospital admissions (noting the low-quality evidence to support these conclusions). The cost-utility analysis by Windegger et al. showed that the costs of bronchiectasis and infections were the two greatest drivers of their model ([Windegger et al., 2020](#_ENREF_90)). This finding provides strong support for the use of Ig from an economic perspective: in the absence of Ig therapy, patients may experience significantly higher rates of infections and/or exacerbated bronchiectasis. These conditions are potentially expensive to treat, and they are likely to remain as long-term issues. Therefore, any Ig-related reduction in PID-associated disease burden is likely to have cost benefits, which may in the long-term, partially offset Ig treatment costs.

#### Adverse events associated with Ig

One of the concerns regarding Ig use for PID is the potential for Ig-related adverse events. Adverse events by route of Ig administration were not considered as a part of the modelling work in most of the economic studies above. Windegger et al. did not include costs of adverse event management and acknowledged that some mild adverse events due to IVIg such as headaches, muscle aches, and itching or pain were mitigated or managed preventatively by appropriate OTC drugs, and no serious adverse events requiring hospital admissions were reported ([Windegger et al., 2020](#_ENREF_90)). Although the study in Iran by Shabaninejad et al. reported the incremental cost reduction ($2,939) per percentage reduction in adverse events when using SCIg compared to IVIg, the study did not provide any specific details of theses adverse events ([Shabaninejad et al., 2017](#_ENREF_77)). None of the four cost minimisation analyses included any costs of adverse event management due to Ig use. Two of the analyses commented that Ig-related adverse events were rare and negligible, and the use of SCIg would further reduce the chances of adverse reactions due to the avoidance of intravenous infusion ([Beaute et al., 2010](#_ENREF_18), [Igarashi et al., 2014](#_ENREF_42)). These findings are consistent with the safety data presented in Section B. Therefore, it is assumed that adverse events associated with Ig use are unlikely to be an issue from either a clinical or economic perspective.

#### Current Ig treatment for PID

It is clear, especially for PID patients with common subtypes of CVID or XLA, that Ig replacement therapy is a standard treatment in Australia. The lack of data for PID patients *not* on Ig replacement therapy poses significant challenges when populating a cost-effectiveness model (as noted above, given the limited data available for PID in general and for CVID in particular, it was the view of the Assessment Group and the Immunoglobulin Review Refernece Group that there is likely to be little value developing a comparative cost-effectiveness analysis).

Further, clinical management changes are happening around how Ig could be safely and more conveniently administered. As SCIg has been proven to be an attractive option for patients and providers, the paradigm in Ig replacement therapy is experiencing a shift from IVIg to SCIg. Due to the cost benefits likely to be realised with SCIg, the overall economic profile of Ig replacement therapy for PID may be significantly reduced in the future.

### Feasibility of conducting model-based economic evaluation

To directly answer the question of how cost-effective Ig replacement therapy is compared to non-Ig therapy for PID patients, a model-based health economic evaluation would be required. General model design and structure could be informed by existing evaluations such as the study by Windegger et al. (2020). From this perspective, it is feasible to conduct the model.

However, from an execution perspective, the proposed model may encounter substantial difficulties. Based on the review and evidence available in the published literature so far, the lack of reliable model input parameters for PID patients on non-Ig therapy would make the model unreliable. Finally, the model-based evaluation would require assumptions to be made on how IVIg and SCIg are used currently and how this may change in the future. Due to the significant difference in cost between IVIg and SCIg, an unreliable estimate in future split between these administration routes will introduce significant uncertainty to the model.

Whether or not the results derived from such an economic model would be sufficiently reliable to inform funding decision is highly uncertain. Therefore, a comparative economic evaluation to compare Ig and non-Ig standard care for PID patients is not recommended.

Due to the lack of available clinical information and the high level of uncertainty surrounding the currently available data, a cost-consequences analysis was proposed to evaluate the incremental costs and outcomes of Ig for PID. This cost consequence analysis takes a one-year time horizon. This is justified as the Ig therapy is likely to follow a routine for PID patients, and it is unlikely to significantly change over time. Therefore, all costs presented in the cost-consequence analysis are annual costs.

## Variables used in the cost consequence analysis

### The cost of Ig and its administration

The cost of Ig therapy mainly involves two categories of cost: the acquisition of Ig product and the costs associated with its administration. These two categories of cost are calculated separately at an individual patient level, and the results are presented in the cost consequence analysis.

#### The unit cost of Ig product

The acquisition cost of Ig depends on the Ig unit cost as well as the dosage when applied to patients. Although Ig can be sourced either domestically or from the overseas, and the administration method can be either from intravenous (IVIg) or subcutaneous (SCIg) pathways, the unit cost of Ig (i.e. cost per gram) is under a fix-price schedule provided by the NBA. 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 in all the pilot Ig reviews. The base case cost/gram was 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. Additional estimates are presented assuming:

* The highest cost of Ig (i.e. domestic IVIg, including the cost of plasma collection and 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

While there are slight variations between the prices per gram used in the DCAR to that published on the NBA website in 2020, as all costs above (including that of plasma fractionation) could be sourced from the same year and for consistency these prices have been used in all of the pilot Ig reviews.

#### The Ig dosage

The Ig dosage is determined by patients’ body weight. Heavier patients would receive higher doses to ensure treatment effectiveness. However, due to the lack of data on patient characteristics, the Ig dosage information is not estimated based on the treatment regimen but derived from the usage data provided by the NBA. The NBA BloodSTAR data documented the total annual quantity of Ig used in 2018 to 2019 financial year, as well as the number of patients, who received the therapy during this period of time. The per patient dosage is hence derived and presented below in **Error! Reference source not found.**. The per patient dosages derived here are the mean value across all PID patients in Australia. The uncertainty measures (e.g. confidence intervals) of these point estimates over the entire PID population in Australia were not estimated based on population characteristics but assumed with 10% upper and lower thresholds for sensitivity analyses.

Table D.2. 1 Ig dosage calculation based on NBA data

| **Row** | **2018 – 2019 Data** | **Domestic IVIg** | **Imported IVIg** | **Domestic SCIg** | **Imported SCIg** | **Source or calculation** |
| --- | --- | --- | --- | --- | --- | --- |
| **1** | **Total annual usage (gram)** | 546,781 | 41,647 | 46,426 | 111,451 | NBA |
| **2** | **Annual patient count** | 1,738 | 131 | 207 | 384 | NBA |
| **3** | **Per patient dosage (gram per patient)** | 315 | 318 | 224 | 290 | Row 1 ÷ Row 2 |

**Abbreviations**: PID = primary immunodeficiency; NBA = National Blood Authority; IVIg = intravenous immunoglobulin; SCIg = subcutaneous immunoglobulin;

As Ig is sourced and delivered differently in Australia, the NBA data are used to derive a global weighting on how different Ig therapies are sourced and administered at the population level. Based on the data available from BloodSTAR, the IVIg and SCIg split for PID in 2018-2019 financial year was 76% and 24%, respectively. For IVIg, approximately 97% of Ig was produced domestically whereas only 3% were imported from overseas. In contrast, more than half of the SCIg were imported (65%) compared to the domestically produced counterpart (35%). Combining the Ig sources and administration pathways, the global weights for Ig use are derived, and its proportional distribution is tabulated below in Table D.2. 2. The more detailed calculations can also be found in the Excel spreadsheet for cost consequence analysis.

Table D.2. 2 Ig use by its source and administration method

|  |  |  |
| --- | --- | --- |
|  | **Source: domestic** | **Source: imported** |
| **IVIg** | 70.68% | 5.32% |
| **SCIg** | 8.40% | 15.60% |

**Abbreviations**: PID = primary immunodeficiency; IVIg = intravenous immunoglobulin; SCIg = subcutaneous immunoglobulin;

The calculation below is presented to estimate the annual patient cost of Ig product by itself.

Table D.2. 3 Annual Ig dosage and cost estimation.

| **Row** | **2018 – 2019 Data** | **Domestic IVIg** | **Imported IVIg** | **Domestic SCIg** | **Imported SCIg** | **Source or calculation** |
| --- | --- | --- | --- | --- | --- | --- |
| **1** | **Per patient dosage (gram per patient)** | 315 | 318 | 224 | 290 | **Error! Reference source not found.** |
| **2** | **Unit cost of Ig ($)** | 60.41 | 60.41 | 60.41 | 60.41 | NBA |
| **3** | **Global weighting** | 70.68% | 5.32% | 8.40% | 15.60% | Derived via NBA data |
| **4** | **Weighted dosage (gram per patient)** | 222.36 | 16.91 | 18.84 | 45.28 | Row 2 × Row 3 |
| **5** | **Annual dosage** |  | 303.39 | gram / patient |  | Sum of Row 4 |
| **6** | **Total cost per patient** |  |  | $18,327.88 |  | Row 5 × $60.41 |

**Abbreviations**: PID = primary immunodeficiency; NBA = National Blood Authority; IVIg = intravenous immunoglobulin; SCIg = subcutaneous immunoglobulin;

Based on the calculation above, the weighted average quantity of Ig at an individual patient level is 303.39 gram per patient annually. Using the base case fixed price of Ig at $60.41, the annual cost of Ig product is estimated at $18,327.88per patient.

#### The cost of Ig administration

Healthcare resource utilisation and procedures involved in delivering Ig therapy via the intravenous or the subcutaneous pathways are different. Therefore, the cost of Ig administration varies as well. IVIg delivery involves a more consistent regimen due to the product being administered in a hospital setting. In comparison, SCIg has a two-step arrangement to firstly allow patients to receive some training and education for several months with help from professional medical staff, then to self-administer the medicine at home. Also, the SCIg involves the purchase of pump and various consumables suitable for the home-setting administration. Therefore, the cost of Ig delivery needs to be calculated separately for the IVIg and SCIg.

The administration cost of IVIg is tabulated below in **Error! Reference source not found.**. It should be noted that the cost of IVIg delivery is calculated as the annual cost at the individual patient level. Also, the healthcare resource use is collected at the wider Australia health system perspective, which involves PBS, MBS and state hospital costs.

Table D.2. 4 Ig administration costs (annually per patient)

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Costing Items** | **Provider** | **Price per unit** | **Per year** | **% of Patients** | **Total cost** | **Costs to the Australian health system (%)** | **Costs to the Australian health system**  **($)** | **Source** |
| Antihistamine, Cetirizine hydrochloride 10mg tablet, | PBS | $0.90 | 13.2 | 10% | $1.20 | 100% | $1.20 | PBS website. Pack cost divided by 30 |
| Immunologists Specialist Consultations. | MBS | $267.90 | 1 | 100% | $267.90 | 75% | $200.90 | MBS 132. Professional attendance |
| Immunologist Follow-up Consultations. | MBS | $136.30 | 1 | 100% | $136.30 | 75% | $102.20 | MBS 133. Professional attendance |
| Consumables (syringes, needles and lines etc.), IVIg | State hospital | $4.94 | 52 | 76% | $195.23 | 100% | $195.23 | Windegger et al. (2020) |
| Consumables (syringes, needles and lines etc.) SCIg | State hospital | $20.88 | 52 | 24% | $260.58 | 100% | $260.58 | Windegger et al. (2020) |
| Pump for SCIg | State hospital | $1.29 | 52 | 24% | $16.10 | 100% | $16.10 | Windegger et al. (2020) |
| Ward costs (IVIg) | State hospital | $46.33 | 52 | 76% | $1,830.96 | 100% | $1,830.96 | Windegger et al. (2020) |
| Ward costs (SCIg) | State hospital | $23.16 | 52 | 24% | $289.04 | 100% | $289.04 | Windegger et al. (2020) |
| **Total** |  |  |  |  |  |  | **$2,896.21** |  |

**Abbreviations**: PID = primary immunodeficiency; IVIg = intravenous immunoglobulin; SCIg = subcutaneous immunoglobulin;

### The cost of Management of PID Related conditions

The management of PID related illness could be broadly grouped into two categories:

1) management and treatment of serious infections; and

2) the management of bronchiectasis; and

#### Cost for infection-related conditions

Infections due to PID can include conditions with different origins including bacterial, viral or fungal infections ([Menzin et al., 2014](#_ENREF_55)). Different medications with various regimens will be used to treat these infections, depending on the origin and the severity of the disease. The current consideration of infections in the cost consequence analysis only accounts for patients to have severe symptoms which need medical attention by hospitalisation.

A broad range of information source was searched to identify relevant information on the rate of infection due to PID, as well as the associated costs. Information on these parameters is scarce with significant limitations. Therefore, there might be significant uncertainties and applicability issues surrounding these estimates. The sources of information on infections rates and the associated costs were tabulated below.

Table D.2. 5 Probability of infections and associated costs

|  |  |  |
| --- | --- | --- |
|  | **Aghamohammadi et al (2009)** | **Windegger et al. (2020)** |
| **Infection under IVIg** | Infection rate: 62/207 = 0.30  Converted to the annual probability = 0.259 | Probability of infection (weekly): 0.054  Estimated infection cost per hospitalisation episode: $7910.10 |
| **Infection under SCIg** |  | Probability of infection (weekly): 0.039  Estimated infection cost per hospitalisation episode: $6732.00 |
| **Infection under no Ig** | Infection rate: 105/256 = 0.41  Converted to annual probability = 0.336 | Not applicable |

**Abbreviations**: PID = primary immunodeficiency; IVIg = intravenous immunoglobulin; SCIg = subcutaneous immunoglobulin;

The likelihood of infection among PID patients was reported in one comparative study, and the results were extracted and summarised in Section B.6 with more detail. However, the data is significantly limited for calculating the cost due to the variability of how infections were defined and the lack of specific detail regarding the severity leading to hospitalisation. The cost-utility analysis performed in the study by Windegger et al. (2020) provided the (transition) probabilities of infection for one week as well as the estimated costs under a local hospital perspective. However, as the study was comparing IVIg and SCIg, the probability of infection under no Ig treatment was not relevant to the study. Further, the weekly probability needs to be converted to the annual value for the current cost consequence analysis, yet this conversion would not be appropriate to use in the absence of information on the duration of the infection management.

Therefore, a basic weighted cost for both IVIg and SCIg on infection requiring hospitalisation was derived as a weekly cost, then multiplied by 52 to estimate the annual cost. Then the weighted average cost for Ig is compared against no Ig using infection rates reported by Aghamohammadi et al. (2009). An alternative cost estimate on infection treatment is also sourced from a parallel HTA of Ig (MSAC 1565) for acquired hypogammaglobulinemia. Although the HTA is investigating a different immunodeficiency disease, the management of common infection due to immunodeficiency was considered relevant. The cost calculation procedures are summarised below in Table D.2. 6 below.

Table D.2. 6 Estimates of incremental costs for infection management

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Windegger et al. (2020)** | **Aghamohammadi et al (2009), base case** | **Infection cost variation** |
| **Cost and rate** | IVIg = 0.054 × $7910.10= $427.14  SCIg = 0.039 × $6732.00 = $262.55  Weighted weekly cost = $689.69  Annual cost = $689.69 × 52 = $35,863.78 | Infection with Ig = 0.259  Infection with no Ig = 0.336 | Serious infection episode cost = $12,852 |
| **Infection cost with Ig** |  | 0.259 × $35,863.78  = $9,282.47 | 0.259 × $12,852 = $3,326.40 |
| **Infection cost with no Ig** |  | 0.336 × $35,863.78  $12,066.59 | 0.336 × $12,852 = $4,324.10 |
| **Incremental** |  | -$2,784.11 | -$997.70 |

**Abbreviations**: PID = primary immunodeficiency; IVIg = intravenous immunoglobulin; SCIg = subcutaneous immunoglobulin; CEA = cost-effectiveness analysis;

Based on the calculations, in the base case the incremental cost for serious infection management by hospitalisation for Ig compared to no Ig treatment is estimated as a cost-saving of $2,784.11 per year. The result from the alternative scenario estimated using cost data from the HTA (for acquired hypogammaglobulinemia) is lower than the base case, yielding at a difference of $997.70 in costs saved. As the alternative cost for infection is the per episode cost, the annual total cost may be subject to underestimation due to the possibility of patients suffering multiple episodes of infection within one calendar year.

#### Cost of management of bronchiectasis

Bronchiectasis is the permanent enlargement of the airway in the lung. The expansion in the air passage could lead to symptoms such as chronic coughing, shortness of breath and potential chest pain. Also, bronchiectasis is susceptible to a range of acute and chronic infections. Among many infections, patients are particularly at risk of suffering from chronic P*. aeruginosa* infection.

The key role of Ig relevant to bronchiectasis is to prevent infections in the lung. However, Aghamohammadi and colleagues pointed out that a small proportion of patients would still develop chronic conditions in the lung, including bronchiectasis, despite being treated with Ig ([Aghamohammadi et al., 2009a](#_ENREF_6)). The comparative data between Ig and no Ig treatment on the rate of bronchiectasis due to PID is very limited. In Section B, the comparative rate of bronchiectasis without infection was extracted from the study by Aghamohammadi et al. (2009). The reported prevalence data have been converted to annual probabilities to derive the cost of bronchiectasis management and monitoring. The result of the converted probabilities is tabulated below in Table D.2. 7. Here it should be acknowledged that the bronchiectasis rate is for CVID patients, and while this is a large subgroup of the general PID population, there is still uncertainty regarding the estimation of rates and costs for this outcome.

There is a routine but limited treatment for bronchiectasis. The cost of bronchiectasis ongoing monitoring and management include regular clinic visits, respiratory function test, imaging tests for the lung plus some other routine consultations with haematologists to monitor the Ig level on a regular basis.([Aghamohammadi et al., 2009a](#_ENREF_6), [Windegger et al., 2020](#_ENREF_90)) The cost of bronchiectasis were estimated in the study by Windegger et al. (2020) for the comparison of IVIg and SCIg.([Windegger et al., 2020](#_ENREF_90)) The study provided the delineated costs for bronchiectasis with or without common infections, as well as with or without *p. aeruginosa* infection specifically. For simplicity, the CCA only considers patients with simple bronchiectasis without any infection, as the non-infectious bronchiectasis rates are the only available data. For IVIg and SCIg, it appears the ongoing management of bronchiectasis was estimated using similar methods in the study by Windegger et al. (2020).([Windegger et al., 2020](#_ENREF_90)). In the current analysis, the weekly cost of managing bronchiectasis was estimated at $32.65, yielding an annual cost is $1,697.80. Similar to infections, Windegger and colleagues only considered patients receiving Ig, hence the cost of ongoing bronchiectasis for non-Ig recipients were not provided. It is reasonable to assume the basic ongoing monitoring and management strategy for bronchiectasis would be similar, if not the same for the Ig patients compared non-Ig patients. Therefore, the total cost of managing bronchiectasis for non-Ig (?) patients experiencing this outcome is also assumed to be $1697.80.

Table D.2. 7 Cost of management for bronchiectasis

|  |  |  |  |
| --- | --- | --- | --- |
| **PID infections** | **Rate from literature data** | **Windegger et al. (2020)** | **Cost estimate** |
| **Infection under no Ig** | Estimated prevalence = 0.54  Annual probability = 0.417 | Estimated cost for ongoing management: $32.65 per week The annual cost is $1,697.80 | 0.417 × 1,697.80 = $708.41 |
| **Infection under Ig (IVIg or SCIg)** | Estimated prevalence = 0.391  Annual probability = 0.324 | Not applicable | 0.324 × 1,697.80 = $549.44 |
| **Incremental** |  |  | **- $158.97** |

**Abbreviations**: PID = primary immunodeficiency; IVIg = intravenous immunoglobulin; SCIg = subcutaneous immunoglobulin; CEA = cost-effectiveness analysis;

## Results of the cost consequence analysis

### Cost consequence analysis

The cost consequence analysis comparing the total annual cost of Ig versus no Ig per PID patient is summarised below in Table D.3. 1. The reduction in PID associated illnesses (summarised in the table below) was derived from literuature where calculation was described in detail in the previous section. The reduction in probabilities between the two arms were calculated to produce the incremental differences. The cost included the Ig acquisition cost with the associated delivery and management costs, plus the costs of managing PID related infections and bronchiectasis. The incremental cost between the Ig versus no Ig treatment regimen is estimated to be $18,281.01 per patient per year, and the greatest contributor of this cost difference is the Ig product cost, which is estimated at around $18,327.88 per patient per year. In this analysis, the additional cost of Ig administration is partially offset by cost savings gained through better infection control as well as treatment and management of bronchiectasis.

Table D.3. 1 Result of the cost consequence analysis (base case)

| **PID outcomes** | **The intervention arm**  **Ig therapy** | **The comparator arm**  **No Ig treatment** | **Incremental effectiveness or costs** |
| --- | --- | --- | --- |
| **Effectiveness** |  |  |  |
| Annual probability of serious infections and the number of patients estimated\* | 0.259  637 per year | 0.336  828 per year | 190 avoided |
| Annual probability of bronchiectasis and the number of patients estimated\* | 0.324  796 per year | 0.417  1,026 per year | 230 avoided |
| **Costs** |  |  |  |
| Cost of product (Ig cost alone) | $18,327.88 | - | $18,327.88 |
| Cost of Ig administration | $2,896.21 | - | $2,896.21 |
| Hospitalisation due to infection | $9,282.47 | $12,066.59 | -$2,784.11 |
| Treatment and management of bronchiectasis | $549.44 | $708.41 | -$158.97 |
| **Total annual incremental cost** |  |  | **$18,281.01** |

**Abbreviations**: PID = primary immunodeficiency;

**Note**: The calculation of the number of patients avoiding associated illnesses was based on the estimate annual PID patient number of **2,460** (Table D.2. 1). However, these numbers have NOT been directly used as the basis of calculating Ig product cost

### Sensitivity analyses on the cost consequence analysis

A range of sensitivity analyses were performed over the base case of the cost consequence analysis to capture some of the uncertainties of the evaluation. Firstly, the Ig product cost are tested sensitivity analysed using the Reference Group agreed unit cost. The one-way sensitivity analyses were undertaken, and the result is presented below. A standard 10% increase or decrease in values for (non-Ig) costs or probabilities has been undertaken and the results are compared to the base case. Finally, when alternative scenarios are available, the results from the alternative scenarios are also evaluated and presented below in Table D.3. 3. It should be noted that the sensitivity was only performed on the cost of severe infection needing hospitalisation and the ongoing monitoring and management of bronchiectasis.

Table D.3. 2 One-way sensitivity analysis on Ig product unit cost

|  | **Intervention**  **Ig therapy** | **Comparator**  **No Ig therapy** | **Incremental cost** |
| --- | --- | --- | --- |
| **Cost breakdown** |  |  |  |
| Base case ($60.41) | $18,327.88 | - | $18,327.88 |
| High Ig unit cost ($140.18) | $42,529.41 | - | $42,529.41 |
| Low Ig unit cost ($44.94) | $13,634.41 | - | $13,634.41 |
| Weighted Ig unit cost ($94.51) | $28,673.52 | - | $28,673.52 |
| Cost of Ig administration | $2,896.21 | - | $2,896.21 |
| Hospitalisation due to infection | $9,282.47 | $12,066.59 | -$2,784.11 |
| Treatment and management of bronchiectasis | $549.44 | $708.41 | -$158.97 |
| **Total annual incremental cost (by different Ig unit cost scenarios)** |  |  |  |
| **Base case Ig unit cost** |  |  | **$18,281.01** |
| High Ig unit cost ($140.18) |  |  | $42,482.54 |
| Low Ig unit cost ($44.94) |  |  | $13,587.54 |
| Weighted Ig unit cost ($94.51) |  |  | $28,626.65 |

As shown in the table above, the incremental cost between Ig and no Ig is very sensitive to the Ig product cost. With the higher Ig product costs, the incremental cost has increased by more than two-fold, and such increase is directly translated from the similar two-fold increase in the Ig unit cost. This observation highlights that the incremental cost of Ig therapy is essentially the direct cost Ig product since the administration costs are mostly offset by the reduction in serious infections and bronchiectasis.

Table D.3. 3 Sensitivity analysis on generic variations and alternative scenarios

|  |  | **Outcome specific** |  |  | **Total** |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Incremental base case** | **10% increase** | **10% decrease** | **Incremental base case** | **10% increase** | **10% decrease** |
| **Infections requiring hospitalisation** |  |  |  |  |  |  |
| Rate of hospitalisation due to infection | -$2,784.11 | -$3,368.78 | -$2,255.13 | $18,281.01 | $17,696.35 | $18,809.99 |
| Cost of infection in general | -$2,784.11 | -$2,505.70 | -$3,062.52 | $18,281.01 | $18,002.60 | $18,559.42 |
| Alternative scenario: Lower cost of infection | -$2,784.11 | -$997.70 |  | $18,281.01 | $20,067.43 |  |
| **Bronchiectasis** |  |  |  |  |  |  |
| Rate of bronchiectasis without infection | -$158.97 | -$166.94 | -$149.86 | $18,281.01 | $18,273.04 | $18,290.12 |

As shown in the table above, uncertainties over the rate and the cost of infection and bronchiectasis are tested via one-way sensitivity analyses. Due to the relatively low proportion of costs contributed by the infection and bronchiectasis to the overall cost-consequence outcome, the impact of these uncertainties is relatively limited. Between the infection and bronchiectasis, the impact of uncertain infection rate seems to be larger. This is reasonable due to the relatively higher costs associated with the serious infections requiring hospital care. Also, the lower cost scenario of infection also has a relatively larger impact to the overall cost-consequence outcome. The smaller offset in costs of treating infection leads to an overall higher incremental cost between the Ig and no Ig arm. Therefore, the overall incremental cost is relatively more susceptible to the uncertainties around infection rates and costs.

# Section E Financial Implications

## E.1 Justification of the Selection of Sources of Data

This section of the report provides an evidence-based projection of the financial implications of the use of Ig for PID from 2021 to 2025. These estimates are primarily based on the Ig usage figures from the past two financial years (2017 to 2019) provided by the NBA, as well as externally sourced epidemiological studies conducted in Australia. Version 3 of the Criteria was introduced in October 2018. It is not clear how Ig usage will change under Version 3 as only a single year of data is available; therefore, the projections of future usage are uncertain.

Two studies were identified through a targeted literature search, which were published ten years apart. The study by Baumgart and colleagues in 1997 estimated that in Australia the prevalence of PID was 2.1 per 100,000 population with uncertain range of 1.18 to 4.57 per 100,000 population ([Baumgart et al., 1997](#_ENREF_16)). Approximately ten years later the publication by Kirkpatrick and colleagues estimated that PID prevalence was around 5.6 per 100,000, and the study also claimed that the adjusted prevalence estimates were much higher, ranging between 13.2 to 14.5 per 100,000 ([Kirkpatrick and Riminton, 2007a](#_ENREF_47)). Using the PID data provided by the NBA based on Ig use, the prevalence of PID was approximately 9.09 per 100,000 population in 2018-2019 financial year. These changes to the population prevalence estimates over the past 20 years may be due to various reasons including increasing diagnostic capabilities, changes in disease definitions, improved access to treatments and improved study performance in relation to patient recruitment. It is important to note that the NBA provided data in financial year figures on Ig use for PID. PID patients (diagnosed or otherwise) who are not on Ig therapy are not included in the NBA data calculation. Therefore, the 9.09 per 100,000 population treated prevalence rate is likely to be less than the true population prevalence for PID.

For the purpose of estimating the financial implications of Ig use for PID patients, the data provided by the NBA are considered the primary source. While Australian population based PID epidemiological studies are not available, the PID patient number ascertained through a therapeutic channel (i.e. Ig usage) are considered the most relevant. Historical studies can be used to safeguard the estimation through sensitivity analyses. Further, the administration of Ig is a personalised dosage scheme determined by patients’ body weight and other factors (e.g. height, gender, general health status, as well as treatment frequencies),([National Blood Authority](#_ENREF_56)) hence patients will receive different dosages adjusted to their personal circumstances. Administration method of Ig also includes intravenous or subcutaneous administration, and dosage and costs associated with these two routes of administration are different. As the NBA provided the Ig usage data, the annual Ig consumption will also be used as an alternative method to project costs.

The financial implications of Ig use for PID patients in this section will include the cost of Ig itself and costs associated with Ig delivery, particularly around intravenous delivery. The unit cost of intravenous Ig (IVIg) and subcutaneous Ig (SCIg) are both priced at $60.41 per gram as the base cost. This cost per gram of Ig was provided by the Applicant and accepted by the Immunoglobulin Review Reference Group to be used in the base case across each of the Ig Reviews.

It should be noted that due to the limitation in the clinical data; the financial estimates do not take into account any costs associated with other PID treatment requirements, including hospitalisations due to infection. The financial estimates also have not considered costs associated with adverse events arising from Ig usage as rates and consequences of these are uncertain for the PID population but estimated to be of minor consequence in our review of safety data and in other identified economic analyses.

## E.2 Use and cost of Ig for PID

### E.2.1 Number of patients with the medical condition

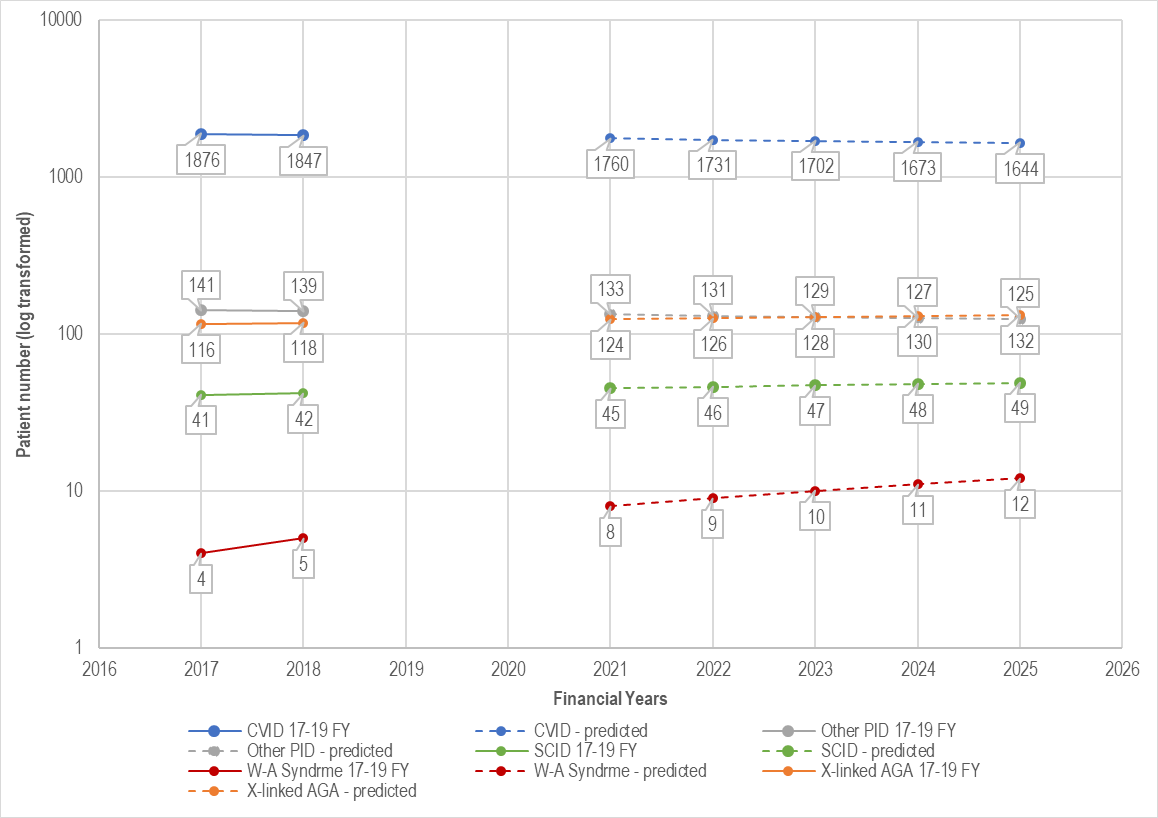
The PID patient numbers in the 2017-18 and 2018-19 financial years (FY) were provided by the NBA. Specific disease subtypes were also provided to stratify the total PID numbers further. A total of six subtypes of PID were reported in the 2017-2018 FY while twelve subtypes (inclusive of the previous six) were reported in 2018-19. Therefore, the cross-FY comparisons were made only among the reported PID disease subtypes.

As the two years’ of PID patient counts are the only data available, the projection on patient numbers is likely to be very uncertain. Four methods are used to estimate how many patients are likely to be diagnosed with PID from 2021 to 2025. These estimates were generated to cross-validate the projection and provide the best and worst-case scenarios.

1. PID subtypes (based on the six reported ones) are analysed where their trends are derived to predict patient numbers at the subtype level. For disease subtypes which were not reported from the first FY, the patient counts were carried forward (Last Observation Carry Forward, LOCF) assuming no change. The six reported PID subtypes and associated predictions were plotted in Figure 5, with the detailed calculation provided in the Excel file. It is not clear whether the reduction in patient number is due to changes in eligibility criteria, and whether this trend will continue over time. Therefore, this method was not used as the base case.
2. The annual change in PID patient counts was derived based on each of the PID subtypes. The same assumption regarding LOCF in the above scenario is also used here. Based on the data provided, the most significant decline was seen for the common variable immunodeficiency disease (CVID) subtype with a 29-patient drop. Only three disease subtypes were increasing in the second FY compared to the previous one, and the maximum increase was the X-linked agammaglobulinemia with two more patients counted over the year. This resulted in an averaged reduction of 2.58 patients annually. Results of this projection were reported in Table 24.
3. A naïve patient number change was observed comparing the 2018 FY and the 2019 FY with an increase of 107 patients. This was also applied to derive the projection, and the estimated patient counts are provided in Table 24.
4. Based on the data provided, the use of Ig at the population level was also calculated. It was estimated that approximately 9.09 per 100,000 Australians would receive Ig therapy due to PID. Assuming this prevalence is not going to change substantially, the PID patient projection was then based on the Australia population, which is experiencing approximately 1.5% growth annually. The estimated population and PID patient numbers are also provided in Table 24. This is considered to be the most stable estimates for PID numbers, and hence is used as the base case for budgetary projection in this section.

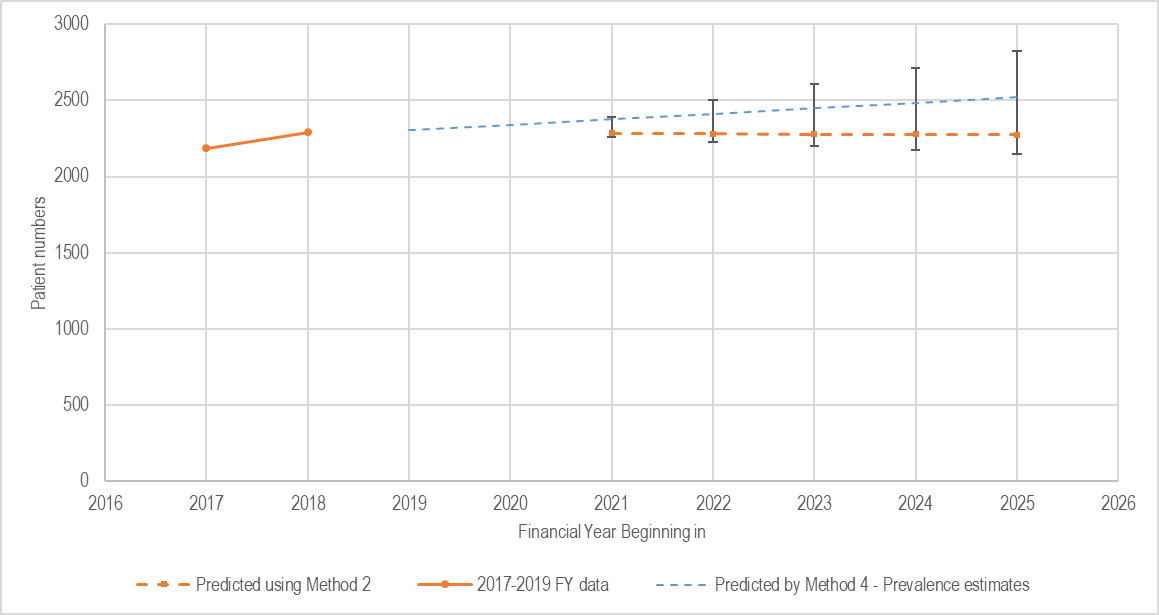
It is clear that all the methods above are associated with some uncertainty. To illustrate this, results of projection from all the four methods were plotted in the same graph (Figure 6). Among the four methods used, Method 2 (average reduction of 2.58 patients annually) seems reasonable, and Method 4 was also considered appropriate. Methods 1 and 3 were considered as the lower and upper boundaries of the estimates, which are represented by error bars.

Figure 5 PID patient numbers projected by specific PID subtypes



**Abbreviations**: CVID = Common variable immunodeficiency disease; PID = Primary immunodeficiency diseases; SCID = Severe combined immunodeficiency; W-A = Wiskott–Aldrich; AGA = agammaglobulinemia; FY = financial year

Figure 6 Total PID patient projection via different methods



**Abbreviations**: FY = financial year

Based on the four methods described above, the patient number projection from 2021 to 2025 is tabulated below in Table 24. The results from Method 4 are considered most likely and were chosen to be the base case scenario; advice from the Immunoglobulin Review Reference Group is that the choice of method for the base case is appropriate (Immunoglobulin Review Reference Group Meeting 25 March 2020). Estimates from Method 2 are considered as an alternative scenario for sensitivity analyses, plus further sensitivity analyses on Method 1 and 3 are presented as the best- and worst-case scenarios.

Table 24 PID population projected via different methods

| Year | 2021 | 2022 | 2023 | 2024 | 2025 | Source |
| --- | --- | --- | --- | --- | --- | --- |
| Australian population | 26,130,936 | 26,522,900 | 26,920,744 | 27,324,555 | 27,734,423 | ABS ([Australian Bureau of Statistics, 2019](#_ENREF_13)) |
| PID estimates via pure changes in counts | 2613 | 2720 | 2827 | 2934 | 3041 | 107 more cases each year  Method 3 |
| **PID estimates via Ig use (Base case)** | **2375** | **2411** | **2447** | **2484** | **2521** | **9.09 per 100K Aus. Population,**  **Method 4** |
| PID estimates via average changes | 2284 | 2282 | 2279 | 2277 | 2274 | 2.58 case reduction per year,  Method 2 |
| PID estimates via trends in subtypes | 2208 | 2181 | 2154 | 2127 | 2100 | Extrapolation and LOCF,  Method 1 |

**Abbreviations**: PID = primary immunodeficiency diseases; Ig = immunoglobulin; ABS = Australian Bureau of Statistics, LOCF = last-observation-carry-forward

The Ig use to treat PID varies based on its administration route, intravenous or subcutaneous, and is either collected from Australian blood sources such as domestic volunteer donors or imported from other countries. Variations regarding the Ig administration methods and product sources exist in Australia. However, due to applying a consistent unit cost on Ig regardless, these variations are not going to affect the financial estimates. The Ig use split regarding the source and administration methods are provided below for demonstration only (Table 25).

Table 25 Ig usage split for PID patients

| Ig usage split | IVIg | SCIg | Source |
| --- | --- | --- | --- |
| Administration route split | 76% | 24% | NBA 2018-2019 FY data |
| Domestic sourced | 93% | 35% |  |
| Imported | 7% | 65% |  |

Abbreviations: PID = primary immunodeficiency diseases; IVIg = intravenous immunoglobulin; SCIg = subcutaneous immunoglobulin; FY = financial year

The average dosage per person was derived from the 2018-2019 FY data provided by the NBA. As the use of Ig for PID is a weight-based scheme, to use the average dose at the population level is a crude approximation. The approximation was considered appropriate under the assumption that:

* there would be no significant or foreseeable changes in how Ig would be used across PID patients,
* patient demographics will remain relatively stable.

Based on how patients are diagnosed and managed, these two assumptions are likely to be reasonable in the short term.

On the other hand, the use of average dosage at the population level does not account for wastage. Wastage is likely to occur when a patient does not exhaust the entire Ig vial based on their weighted dose, and a certain volume of Ig is discarded. Given the various vial sizes available for Ig (ranged from 0.5g to 20g), wastage may or may not be a significant issue. Also, at the time of requesting Ig in BloodSTAR, there is scope to make adjustment between patients’ weight and vial size, hence there should be very little to no wastage.

Average dosages in gram per person stratified by administration routes and sources are Table 26 below. These values are used in the calculation of Ig cost projections. It should be noted that this is not going to affect the financial estimates due to the same unit cost of Ig across different sources and administration methods.

Table 26 Average dosage per person of Ig by sources and types

| Average dosage in gram per person | IVIg | SCIg | Source |
| --- | --- | --- | --- |
| Domestic sourced | 315g/pp | 224g/pp | NBA 2018-2019 FY data |
| Imported | 318g/pp | 290g/pp |  |

**Abbreviations**: PID = primary immunodeficiency diseases; IVIg = intravenous immunoglobulin; SCIg = subcutaneous immunoglobulin; FY = financial year

**Notes**: The dosage was estimated at the population level using the NBA data provided;

The cost of Ig was informed by the NBA and agreed with the Ig Review Reference Group to be $60.41 per gram as a base case regardless of its administration routes or sources (domestically sourced or imported). It was acknowledged that the cost of Ig might vary depending on a range of factors such as manufacturers, administration methods and sources and the allocation of domestic and imported product to each medical condition changes frequently. Therefore, the base case price of $60.41 is considered the most appropriate price to use for consistency across each of the Ig Reviews. Alternative pricing arrangements have been tested in sensitivity analyses.

Table 27 Unit cost of Ig by sources and types

| Unit cost (per gram) | IVIg | SCIg | Source |
| --- | --- | --- | --- |
| Domestic sourced | $60.41 | $60.41 | NBA |
| Imported | $60.41 | $60.41 |  |

**Abbreviations**: PID = primary immunodeficiency diseases; IVIg = intravenous immunoglobulin; SCIg = subcutaneous immunoglobulin;

**Notes**: This pricing is provided by the NBA.

With the information obtained above, cost projection of Ig for PID can be calculated. The total cost projection of Ig use was evaluated separately by the intravenous (i.e. IVIg) and the subcutaneous (SCIg) pathways, then combined. The calculating procedures and results are presented in Table 28 to Table 30.

The model predicts that the cost of Ig use in treatment of PID patients starts from $43.8 million in 2021, rising to $46.2 million in 2025 with about 1.5% growth annually.

Table 28 Cost projection of IVIg for PID from 2021 to 2025

| FY | 2021 | 2022 | 2023 | 2024 | 2025 | Source | Calculation reference |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Total PID estimates | 2375 | 2411 | 2447 | 2484 | 2521 | 9.09 per 100K | A |
| IVIg patient numbers | 1805 | 1832 | 1860 | 1888 | 1916 | Table 25 | B = A × 0.76 |
| IVIg domestic | 1679 | 1704 | 1730 | 1756 | 1782 | Table 25 | C1 = B × 0.93 |
| IVIg Imported | 126 | 128 | 130 | 132 | 134 | Table 25 | C2 = B × 0.07 |
| Domestic IVIg consumption | 528842 | 536775 | 544826 | 552999 | 561294 | Table 26 | D1 = C1 × 315 |
| Imported IVIg consumption | 40184 | 40787 | 41399 | 42020 | 42650 | Table 26 | D2 = C2 × 318 |
| Cost of IVIg domestic | $31,947,346 | $32,426,556 | $32,912,954 | $33,406,648 | $33,907,748 | Table 27 | E1 = D1 × 60.41 |
| Cost of IVIg imported | $2,427,540 | $2,463,953 | $2,500,913 | $2,538,426 | $2,576,503 | Table 27 | E2 = D2 × 60.41 |
| **Total cost of IVIg** | **$34,374,886** | **$34,890,509** | **$35,413,867** | **$35,945,075** | **$36,484,251** |  | F = E1 + E2 |

**Abbreviations**: PID = primary immunodeficiency diseases; IVIg = intravenous immunoglobulin; FY = financial year

Table 29 Cost projection of SCIg for PID from 2021 to 2025

| FY | 2021 | 2022 | 2023 | 2024 | 2025 | Source | Calculation reference |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Total PID estimates | 2375 | 2411 | 2447 | 2484 | 2521 | 9.09 per 100K | A |
| SCIg patient numbers | 570 | 579 | 587 | 596 | 605 | 24% use SC route | B = A × 0.76 |
| SCIg domestic | 200 | 203 | 206 | 209 | 212 | 35% domestic | C1 = B × 0.35 |
| SCIg Imported | 371 | 376 | 382 | 388 | 393 | 65% imported | C2 = B × 0.65 |
| Domestic SCIg consumption | 44688 | 45365 | 46043 | 46739 | 47435 | Table 26 | D1 = C1 × 224 |
| Imported SCIg consumption | 107445 | 109074 | 110702 | 112376 | 114050 | Table 26 | D2 = C2 × 290 |
| Cost of SCIg domestic | $2,699,602 | $2,740,522 | $2,781,443 | $2,823,500 | $2,865,557 | Table 27 | E1 = D1 × 60.41 |
| Cost of SCIg imported | $6,490,752 | $6,589,139 | $6,687,525 | $6,788,644 | $6,889,763 | Table 27 | E2 = D2 × 60.41 |
| **Total cost of SCIg** | **$9,190,355** | **$9,329,661** | **$9,468,967** | **$9,612,143** | **$9,755,319** |  | F = E1 + E2 |

**Abbreviations**: PID = primary immunodeficiency diseases; SCIg = subcutaneous immunoglobulin; FY = financial year

Table 30 Total Ig cost projection from 2021 to 2025

| FY | 2021 | 2022 | 2023 | 2024 | 2025 | Source | Calculation reference |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Total cost of IVIg | $34,374,886 | $34,890,509 | $35,413,867 | $35,945,075 | $36,484,251 | Row F in Table 28 | A |
| Total cost of SCIg | $9,190,355 | $9,329,661 | $9,468,967 | $9,612,143 | $9,755,319 | Row F in Table 29 | B |
| **Total Ig cost** | **$43,566,409** | **$44,219,905** | **$44,883,204** | **$45,556,452** | **$46,239,799** |  | **A + B** |

**Abbreviations**: PID = primary immunodeficiency diseases; IVIg = intravenous immunoglobulin; SCIg = subcutaneous immunoglobulin; FY = financial year

### E.2.2 Costs of Ig delivery

Ig delivery is via the intravenous or subcutaneous route. Both of these administration pathways will incur some costs due to the utilisation of therapeutic goods or services. These associated costs are mostly covered by MBS, PBS or state governments, and they form the totality of the Ig therapy for PID patients. Costs associated with Ig use are extracted and tabulated below in Table 31**Error! Reference source not found.**. Some of these costs are incurred for generic Ig usage, which is non-specific to PID patients. Also, the inclusion of these costs is considered conservative. In the absence of expert advice regarding the inclusion/exclusion of the use of specialised drugs use or services for PID treatment option, these associated costs are likely to be underestimated.

Table 31 Costs associated with Ig delivery via the intravenous route (IVIg)

| Costing Items | Provider | Price per unit | Per year | % of Patients | Total cost | % cost incurred | Costs to the Australian health system | Source |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Antihistamine, Cetirizine hydrochloride 10mg tablet | PBS | $0.9 | 13.2 | 10% | $1.2 | 100% | $1.2 | PBS website. Pack cost divided by 30 |
| Immunologists Specialist Consultations. | MBS | $267.9 | 1.0 | 100% | $267.9 | 75% | $200.9 | MBS 132. Professional attendance |
| Immunologist Follow-up Consultations. | MBS | $136.3 | 1.0 | 100% | $136.3 | 75% | $102.2 | MBS 133. Professional attendance |
| Consumables (syringes, needles and lines etc.) | State hospitals | IVIg = $4.94;  SCIg = $20.88  per week | 52 | IVIg = 76%  SCIg = 24% |  | 100% | IVIg = $195.23  SCIg = $260.58  Total = $455.81 | Windegger et al. (2020) |
| Pump for SCIg | State hospitals | $1.29  SCIg only  per week | 52 | SCIg only, 24% |  | 100% | $16.10 | Windegger et al. (2020) |
| Ward costs | State hospitals | IVIg = $46.33  SCIg = $23.16  per week | 52 | IVIg = 76%  SCIg = 24% |  | 100% | IVIg = $1,830.96  SCIg = $289.04  Total = $2120.00 | Windegger et al. (2020) |
| **Total** |  |  |  |  |  |  | **$2,896.21** |  |

**Abbreviations**: PID = primary immunodeficiency diseases; IVIg = intravenous immunoglobulin; PBS = pharmaceutical benefit scheme; MBS = medical benefit scheme; IV = intravenous

The costs for IVIg delivery was estimated at $5,202 per patient per year, whereas SCIg delivery incurred much lower costs at $1,404.20. It should be noted that the annual cost of SCIg administration was derived with the exclusion of the initial training of new patients. As the current PID patient numbers were prevalence estimates, it was not clear how many patients were new to Ig use due to new diagnoses and how many patients were off Ig. Therefore, excluding initial training costs was to reduce this uncertainty, and this could be considered as a conservative approach, and likely to result in a low level of underestimation. The annual costs of Ig delivery were then calculated, and the results are presented in Table 32.

Table 32 Total Ig costs including delivery

| FY | 2021 | 2022 | 2023 | 2024 | 2025 | Source | Calculation reference |
| --- | --- | --- | --- | --- | --- | --- | --- |
| IVIg number | 1805 | 1832 | 1860 | 1888 | 1916 | Table 25 | A |
| SCIg number | 570 | 579 | 587 | 596 | 605 | Table 25 | B |
| **Total cost of Ig delivery** | $6,879,371 | $6,982,561 | $7,087,300 | $7,193,609 | $7,301,513 | **Calculated** | **C** |
| Ig product costs | $43,566,409 | $44,219,905 | $44,883,204 | $45,556,452 | $46,239,799 | Table 30 | D |
| **Grand total of Ig for PID patients** | **$50,445,780** | **$51,202,467** | **$51,970,504** | **$52,750,061** | **$53,541,312** | **Calculated** | **E = C + D** |
| *% of delivery from the total* | 13.64% | 13.64% | 13.64% | 13.64% | 13.64% | *Calculated* | *F = C ÷ E* |

**Abbreviations:** PID = primary immunodeficiency diseases; IVIg = intravenous immunoglobulin; SCIg = subcutaneous immunoglobulin; FY = financial year

The total Ig cost, including delivery, was estimated at $66.7 million in 2021 and increasing to $70.7 million in 2025. The delivery cost of Ig for PID patients accounted for approximately 13.64% of the total costs, and this proportion was stable over the five projected years.

## E.3 Sensitivity analyses

Due to the uncertainty in PID patient number estimates and how Ig is used, the projected costs from 2021 to 2025 are likely to also be uncertain. A range of sensitivity analyses were performed to test several assumptions and elicit the impact of these uncertainties. Variables tested by sensitivity analyses include:

* Patient number estimates from 2021 to 2025 via different methods:

Method 2 was used to provide alternative scenarios for PID patient number estimates. In contrast, the other two methods were used to provide the lower and upper limits for the best- and worst-case scenarios.

* Price of Ig for PID treatment using other agreed values:

Three alternative Ig unit costs were provided besides the agreed base-case value of $60.41. The highest cost of Ig is $140.18 per gram, and the the lowest possible Ig is at $44.94 per gram. Also, a weighted average cost of Ig across all indications was estimated at $94.51 per gram. These alternative values were estimated by the Applicant, and the calculation was based on the 2017/18 National Report on the issues and use of Ig in Australia. Detailed derivation of these Ig unit costs was discussed in Section D.3. These costs are used to estimate the budgetary impact for sensitivity analyses.

* Ig dosage increase or decrease by 10% at the population level:

As the Ig dosage was estimated at a population level, it could be subject to high levels of uncertainty, attributable to patient weights, personal circumstance and potential wastage. Therefore a 10% variation was tested in sensitivity analysis.

Results of the sensitivity analyses are provided below in Table 33. It appears the greatest impact was the unit cost of Ig; the $140.18 per gram pricing arrangement increases costs significantly.

Table 33 Sensitivity analyses considering only Ig costs (not delivery)

| Year | 2021 | 2022 | 2023 | 2024 | 2025 |
| --- | --- | --- | --- | --- | --- |
| Base case  Ig cost alone | $43,566,409 | $44,219,905 | $44,883,204 | $45,556,452 | $46,239,799 |
| ***Ig cost alone***  ***Sensitivity analysis*** |  |  |  |  |  |
| PID patients via Method 2  *Uncertainty range by Method 1 and Method 3* | $41,896,385  ($40.5m, $47.9m) | $41,849,003  ($40.0m, $49.9m) | $41,801,621  ($39.5m, $51.9m) | $41,754,239  ($39.1m, $53.8m) | $41,706,857  ($38.5m, $55.8m) |
| Price of Ig at lowest cost ($44.94) | $32,409,774 | $32,895,920 | $33,389,359 | $33,890,200 | $34,398,553 |
| Price of Ig at highest ($140.18) | $101,094,839 | $102,611,262 | $104,150,431 | $105,712,687 | $107,298,378 |
| Price of Ig at weighted average ($94.51) | $68,158,605 | $69,180,984 | $70,218,699 | $71,271,980 | $72,341,059 |
| 10% increase in dosage | $47,923,050 | $48,641,896 | $49,371,524 | $50,112,097 | $50,863,779 |
| 10% decrease in dosage | $39,209,768 | $39,797,915 | $40,394,884 | $41,000,807 | $41,615,819 |

**Abbreviations:** PID = primary immunodeficiency diseases; IVIg = intravenous immunoglobulin; SCIg = subcutaneous immunoglobulin; FY = financial year

# Section F Other relevant considerations

The Assessment group has identified the following areas for potential future research on PID in Australia:

* Currently, most evidence considers all forms of PID together, having studies that report data separately for each subtype would be informative. This may be difficult due to the rare nature of these conditions.
* From a clinical effectiveness point of view, research into the impact of co-interventions on outcomes would be helpful to resolve the confounding issues identified in the evidence base.
* More broadly, it may be useful to establish a registry or database for PID patients and document the treatment(s) they are receiving. This would be helpful to understand Ig therapy coverage and true population prevalence in Australia.
* It would be beneficial to have more granular information on how Ig is used for PID in Australia. Ideally, future research would focus on each PID subgroup separately and be aimed to answer the questions such as:
  + Is there any difference is usage patterns for children compared to adults?
  + Does severity of disease impact Ig usage?
  + Which patients are trialling periods of Ig and which of these patients are able to successful stop or reduce Ig usage?
  + Is the pattern of Ig usage consistent over time for each PID subtype?

**Appendix A Clinical Experts and Assessment Group**

## Assessment group

**RACS Research and Evaluation (ASERNIP-S)**

Name Position

David Tivey Manager

Joanna Duncan Team Leader

Ning Ma Team Leader

Deanne Forel Senior Research Officer

Virginie Gaget Research Officer

Meegan Vandepeer Research Officer

**Noted conflicts of interest**

There were no conflicts of interest.

# Appendix B Search strategies

## Bibliographic databases

|  |  |
| --- | --- |
| Electronic database | Time period searched |
| Embase | Inception to 25/11/2019 |
| PubMed | Inception to 20/11/2019 |

Notes: It is worth noting that two subject headings in Embase, namely “combined immunodeficiency” and “lymphoproliferative disease”, provided a very high number of hits compared to the Pubmed search (i.e. 161,859 vs 3,928 hits for combined immunodeficiency and 427,086 vs 349,407 hits for lymphoproliferative disease). In the light of these results, the assessors opted to eliminate these two subject headings but added these two terms as text words in the search. The Pubmed and Embase searches returned a similar number of hits with 7,234 and 8,461 references respectively. When combining the two libraries, 462 references were accidentally added in duplicate (verified posteriori), which provided an original database of 16,157 references to screen. Duplicates and foreign languages records (n = 3,973) were excluded to obtain 12,200 references, which were then screened by title and abstract by three reviewers.

## Additional sources of literature

| Source | Location |
| --- | --- |
| Australian and New Zealand Clinical Trials Registry | https://www.anzctr.org.au/ |
| Clinical Trials | https://clinicaltrials.gov/ |

## Search Terms Used in Economic Review

|  |  |  |
| --- | --- | --- |
| **Search** | **Query** | **Items found** |
| #25 | ((((((((immunoglobulins[MeSH Terms]) OR (((ig[Title/Abstract]) OR ivig[Title/Abstract]) OR scig[Title/Abstract])) OR immunoglobulin\*[Title/Abstract])) AND (((((immunologic deficiency syndrome[MeSH Terms]) OR (((PID[Title/Abstract]) OR CVID[Title/Abstract]) OR SCID[Title/Abstract])) OR ((primary[Title/Abstract]) AND immunodeficienc\*)) OR (((primary[Title/Abstract]) AND immune[Title/Abstract]) AND deficienc\*[Title/Abstract])) OR ((((combine\*[Title/Abstract]) OR (common[Title/Abstract] AND variable[Title/Abstract]))) AND ((((immune[Title/Abstract]) AND deficienc\*[Title/Abstract])) OR immunodeficienc\*[Title/Abstract]))))) NOT (HIV[Title/Abstract] OR AIDS[Title/Abstract]))) AND (((((economic[Title/Abstract]) AND (model\*[Title/Abstract] OR evaluat\*[Title/Abstract]))) OR ((((((utility[Title/Abstract]) OR consequence[Title/Abstract]) OR effectiveness[Title/Abstract]) OR (minimization[Title/Abstract] OR minimisation[Title/Abstract]))) AND cost[Title/Abstract])) OR (((benefit and cost[MeSH Terms])) OR cost benefit analysis[MeSH Terms])) | 83 |
| #24 | ((((economic[Title/Abstract]) AND (model\*[Title/Abstract] OR evaluat\*[Title/Abstract]))) OR ((((((utility[Title/Abstract]) OR consequence[Title/Abstract]) OR effectiveness[Title/Abstract]) OR (minimization[Title/Abstract] OR minimisation[Title/Abstract]))) AND cost[Title/Abstract])) OR (((benefit and cost[MeSH Terms])) OR cost benefit analysis[MeSH Terms]) | 203182 |
| #23 | (economic[Title/Abstract]) AND (model\*[Title/Abstract] OR evaluat\*[Title/Abstract]) | 79165 |
| #22 | (((((utility[Title/Abstract]) OR consequence[Title/Abstract]) OR effectiveness[Title/Abstract]) OR (minimization[Title/Abstract] OR minimisation[Title/Abstract]))) AND cost[Title/Abstract] | 88166 |
| #21 | (((utility[Title/Abstract]) OR consequence[Title/Abstract]) OR effectiveness[Title/Abstract]) OR (minimization[Title/Abstract] OR minimisation[Title/Abstract]) | 797308 |
| #20 | ((benefit and cost[MeSH Terms])) OR cost benefit analysis[MeSH Terms] | 88900 |
| #19 | ((((((immunoglobulins[MeSH Terms]) OR (((ig[Title/Abstract]) OR ivig[Title/Abstract]) OR scig[Title/Abstract])) OR immunoglobulin\*[Title/Abstract])) AND (((((immunologic deficiency syndrome[MeSH Terms]) OR (((PID[Title/Abstract]) OR CVID[Title/Abstract]) OR SCID[Title/Abstract])) OR ((primary[Title/Abstract]) AND immunodeficienc\*)) OR (((primary[Title/Abstract]) AND immune[Title/Abstract]) AND deficienc\*[Title/Abstract])) OR ((((combine\*[Title/Abstract]) OR (common[Title/Abstract] AND variable[Title/Abstract]))) AND ((((immune[Title/Abstract]) AND deficienc\*[Title/Abstract])) OR immunodeficienc\*[Title/Abstract]))))) NOT (HIV[Title/Abstract] OR AIDS[Title/Abstract]) | 19905 |
| #18 | (((((benefits and costs[MeSH Terms])) OR cost[Title/Abstract]) OR economic[Title/Abstract])) AND (((((immunoglobulins[MeSH Terms]) OR (((ig[Title/Abstract]) OR ivig[Title/Abstract]) OR scig[Title/Abstract])) OR immunoglobulin\*[Title/Abstract])) AND (((((immunologic deficiency syndrome[MeSH Terms]) OR (((PID[Title/Abstract]) OR CVID[Title/Abstract]) OR SCID[Title/Abstract])) OR ((primary[Title/Abstract]) AND immunodeficienc\*)) OR (((primary[Title/Abstract]) AND immune[Title/Abstract]) AND deficienc\*[Title/Abstract])) OR ((((combine\*[Title/Abstract]) OR (common[Title/Abstract] AND variable[Title/Abstract]))) AND ((((immune[Title/Abstract]) AND deficienc\*[Title/Abstract])) OR immunodeficienc\*[Title/Abstract])))) | 543 |
| #17 | (((benefits and costs[MeSH Terms])) OR cost[Title/Abstract]) OR economic[Title/Abstract] | 621000 |
| #16 | ((((immunoglobulins[MeSH Terms]) OR (((ig[Title/Abstract]) OR ivig[Title/Abstract]) OR scig[Title/Abstract])) OR immunoglobulin\*[Title/Abstract])) AND (((((immunologic deficiency syndrome[MeSH Terms]) OR (((PID[Title/Abstract]) OR CVID[Title/Abstract]) OR SCID[Title/Abstract])) OR ((primary[Title/Abstract]) AND immunodeficienc\*)) OR (((primary[Title/Abstract]) AND immune[Title/Abstract]) AND deficienc\*[Title/Abstract])) OR ((((combine\*[Title/Abstract]) OR (common[Title/Abstract] AND variable[Title/Abstract]))) AND ((((immune[Title/Abstract]) AND deficienc\*[Title/Abstract])) OR immunodeficienc\*[Title/Abstract]))) | 36346 |
| #15 | ((immunoglobulins[MeSH Terms]) OR (((ig[Title/Abstract]) OR ivig[Title/Abstract]) OR scig[Title/Abstract])) OR immunoglobulin\*[Title/Abstract] | 945020 |
| #14 | immunoglobulin\*[Title/Abstract] | 154329 |
| #13 | ((((immunologic deficiency syndrome[MeSH Terms]) OR (((PID[Title/Abstract]) OR CVID[Title/Abstract]) OR SCID[Title/Abstract])) OR ((primary[Title/Abstract]) AND immunodeficienc\*)) OR (((primary[Title/Abstract]) AND immune[Title/Abstract]) AND deficienc\*[Title/Abstract])) OR ((((combine\*[Title/Abstract]) OR (common[Title/Abstract] AND variable[Title/Abstract]))) AND ((((immune[Title/Abstract]) AND deficienc\*[Title/Abstract])) OR immunodeficienc\*[Title/Abstract])) | 359999 |
| #12 | (((combine\*[Title/Abstract]) OR (common[Title/Abstract] AND variable[Title/Abstract]))) AND ((((immune[Title/Abstract]) AND deficienc\*[Title/Abstract])) OR immunodeficienc\*[Title/Abstract]) | 14063 |
| #11 | (combine\*[Title/Abstract]) OR (common[Title/Abstract] AND variable[Title/Abstract]) | 889168 |
| #10 | (((immune[Title/Abstract]) AND deficienc\*[Title/Abstract])) OR immunodeficienc\*[Title/Abstract] | 154117 |
| #9 | (immune[Title/Abstract]) AND deficienc\*[Title/Abstract] | 28111 |
| #8 | immunodeficienc\*[Title/Abstract] | 131589 |
| #7 | ((primary[Title/Abstract]) AND immune[Title/Abstract]) AND deficienc\*[Title/Abstract] | 3425 |
| #6 | (primary[Title/Abstract]) AND immunodeficienc\* | 20039 |
| #5 | ((PID[Title/Abstract]) OR CVID[Title/Abstract]) OR SCID[Title/Abstract] | 24651 |
| #4 | immunologic deficiency syndrome[MeSH Terms] | 326964 |
| #3 | ((((ig[Title/Abstract]) OR ivig[Title/Abstract]) OR scig[Title/Abstract])) OR immunoglobulins[MeSH Terms] | 898214 |
| #2 | ((ig[Title/Abstract]) OR ivig[Title/Abstract]) OR scig[Title/Abstract] | 43432 |
| #1 | immunoglobulins[MeSH Terms] | 881128 |

# 

# Appendix C Studies included in the Systematic Review

Table 34 Profiles of comparative studies on Ig replacement therapy in patients with PID included in the systematic literature review

| Author (year)  Country | Study design  RoB | Duration of follow-up | Number of patients | Patient population  Diagnostic criteria | Patient baseline characteristics | Intervention | Comparator | Key outcome(s) | Measurement of outcomes and analysis |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Aghamohammadi et al. (2009)  Iran | Comp, Retro  SC  High | I: median 7 years (range 4-21)  C: median 5 years (range 1–15) | I: n = 23  C: n = 24 | CVID patients aged > 2 years referred to a medical centre between 1984–2009.  I: Patients diagnosed within 6 years of onset and received appropriate treatment for at least 5 years  C: Patients with a diagnostic delay > 6 years matched for age and gender with the I group  Criteria: ESID/.PAGID | I group  M = 10, F = 13  Median age = 15.6 yrs (range 7-50)  Onset age: NR  Diagnostic delay: median 2.6 yrs (range 0.5-5)  C group  M = 12, F = 12  Median age = 14.6 yrs (range 8-42)  Onset age: NR  Diagnostic delay: median 8.4 yrs (range 6-32) | IVIg (400-600 mg/kg, every 3-4 weeks).  Prophylactic antibiotics, antibiotics at first sign of infection, regular outpatient visits. | No Ig or prophylactic treatment due to delayed diagnosis | Infections, hospital admissions, non-infectious complications, bronchiectasis, missed days from work or school, mortality | Data was obtained by reviewing patients’ hospital records and interviewing.  Survival was estimated from Kaplan-Meier life tables. |
| Cunningham-Rundles (1989)  USA | Comp, Retro  SC  NA | NR | I: n = 46  C: n = 57 | Consecutive CVID patients aged > 2 years  Criteria: March of Dimes Birth Defects Criteria | I + C combined  M = 51, F = 52  Age mean 29 yrs (range 3-71)  Onset age: mean 25 yrs  Diagnostic delay: mean 3 yrs | IMIg (dose NR) | No treatment | Trough IgG, IgA and IgM levels | Radial immunodiffusion was used to quantify serum Ig levels were quantitated by radial immunodiffusion. The serum Ig were also examined for monoclonal proteins using an immunoelectrophoresis approach.  To analyse immunologic parameters a χ2 test and a test of correlation were applied to the data obtained (Pearson). |
| Gardulf et al. (1993)  Sweden | Comp, Retro  MC  NA | NR | I: n = 15  C: n = 10 | Consecutive patients aged ≥ 18 years with CVID (n = 23), XLA (n = 1), thymoma with hypogammaglobulinemia (n = 1)  Criteria: NR | I + C combined  M = 12, F = 13  Age mean 43 yrs (SD 16)  Onset age: mean 25 yrs  Diagnostic delay: median 10 yrs (range 1-56) | IMIg (n = 13) or IVIg (n = 2) for mean of 78 months (dose NR) | No treatment | Functional status, Recreational activity, IgG trough levels | Questionnaire based.  Non-parametric statistical methods applied.  A Wilcoxon-Mann-Whitney test was used to determine the difference between groups.  A Spearm rank-order approach was used to express the relations between variables in correlation coefficients.  Fisher’s exact test was applied to treat nominal data. |
| Waniewski et al. (1994)  Poland | Comp, Retro  SC  NA | NR | I: n = 17  C: n = 6 | Patients with CVID and increased infection rate aged ≥ 18 years  Criteria: WHO | I + C combined  M = 9, F = 14  Age, onset age and diagnostic delay NR | IMIg (dose NR) | No treatment | Serum IgG levels | IgG levels from the time of diagnosis were obtained from patients’medical reports.  Blood samples were collected at follow-up for analysis.  Results were summarized using descriptive statistics. Two non-parametric tests, namely the Kruskall-Wallis test and the Mann-Whitney test, were used to compare different patient groups. To compare IgG levels across time and groups, the paired t test was applied to the data obtained. |

**Abbreviations:** C: comparator group;Comp: comparative study; Criteria: refers to the diagnostic criteria used to identify patients; CVID: common variable immunodeficiency, F: female patients, I: intervention group; Ig: immunoglobulin; IgA: immunoglobulin A; IgG: immunoglobulin G; IgM: immunoglobulin M; IMIg: intramuscular immunoglobulin; IVIg: intravenous immunoglobulin; M: male patients, MC: multicentre study, n: number of patients; NA: not assessed, NR: not reported; PAGID/ESID: Pan-American Group for Immunodeficiency and European Society for Immunodeficiencies, PID: Primary Immunodeficiency Disease; Retro: retrospective study; SC: single centre study, SCIg: subcutaneous immunoglobulin; SD: standard deviation,.XLA: X-linked agammaglobulinaemia.

Table 35 Profiles of single arm cohort studies assessing the safety and effectiveness of Ig replacement therapy for patients diagnosed with CVID

| Author (year)  Country | Study design  RoB | Duration of follow-up | Number of patients CVID  Total | CVID patient population | Patients baseline characteristics | Intervention  Co-interventions | Key outcome(s) |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Aghamohammadi et al. (2003)  Iran | CS, Pros, SC  High | 36 months | 25  45 | CVID patients receiving IVIg at a single referral centre from 1997-2000  Criteria: WHO | M = 13, F = 12  Mean age = 15.8 yrs (SD 6.5)  Onset age, diagnostic delay, both NR | IVIg 400-500 mg/kg every 3-4 weeks  Co-interventions: NR | Trough IgG levels  AEs |
| Aghamohammadi et al. (2004)  Iran | CS, Retro, SC  High | NR data collected over 7 yrs | 31  71 | CVID patients receiving IVIg at a single referral centre from 1995-2002  Criteria: WHO | M = 51, F = 20  Mean age: 13.8 yrs (SD 5.5)  Onset age, diagnostic delay, both NR | IVIg 400-500 mg/kg every 3-4 weeks  Co-interventions: NR | AEs |
| Aghamohammadi et al. (2008)  Iran | CS, Retro, SC  High | Median 3 years (range 0.1-18) | 64  109 | CVID patients diagnosed and treated at a single referral centre from1980-2004  Criteria: PAGID/ESID | M = 33, F = 31  Median age 12.5 yrs (range 2.3-56)  Onset age: median 2 yrs (range 0.5-46)  Diagnostic delay median 3.25 yrs (range 0.5-39) | IVIg 400-500 mg/kg every 3-4 weeks  Co-interventions: NR | IgG serum level  Infection (otitis media and sinusitis) |
| Alkan et al. (2018)  Turkey | CS, Retro, SC  High | NR, data collected over 11 yrs | 12  12 | CVID patients diagnosed at a single centre from 2001-2012  Criteria: PAGID/ESID | M = 7, F = 5  Median age 11.6 (SD 3.7)  Onset age: median 7.2 yrs (SD 4.1)  Diagnostic delay: median 4.3 yrs (SD 2.6) | IVIg 500 mg/kg every 3 weeks  Co-interventions: NR | Infection (upper respiratory, lower respiratory)  Bronchiectasis (rates and prognosis) |
| Baris et al. (2011)  Turkey | CS, Retro, SC  High | Mean 5.6 yrs (SD 3.5, range 1.3-14)  Pre-Ig mean follow-up 1.1 yrs (SD 1.5) | 29  29 | Paediatric CVID patients diagnosed at a single centre and monitored for at least 12 months pre/post Ig treatment from 1994-2009  Criteria: PAGID/ESID | M = 22, F = 7  Mean age: 1.8 yrs (SD 6.1)  Onset age: mean 21 mo (SD 26.4)  Diagnostic delay: mean 3.9 yrs (SD 3.3) | IVIg 500 mg/kg every 3 weeks  Co-interventions: Antibacterial prophylaxis (patients with upper respiratory infections >1 per mo), daily chest therapy, inhaled corticosteroids, bronchodilators (patients with bronchiectasis) | Serum IgG levels  Infections (respiratory, gastrointestinal) Bronchiectasis (rates and prognosis)  Hospital stays (length and number)  Antibiotic usage  Growth |
| Bayrakci et al. (2005)  TurkeyA | CS, Retro, SC  High | Median 4.25 yrs (range 1.25-12.25) | 20  46 | CVID patients treated at a single centre from 1984-2000  Criteria: WHO | M = 20, F = 30  Median age: 13.8 yrs (range 7.8-22.3)  Onset age: median 1.8 yrs (range 0.1-5)  Diagnostic delay: median 4.5 yrs range 0.25-11.4) | IIVIg orIMIg median dose 370 mg/kg  Co-interventions: Antibacterial prophylaxis (patients with upper respiratory infections >1 per mo) | Trough Ig levels  Infection and hospitalisation rates  AEs |
| Berger et al. (2007)  USA/Canada | CS, Pros, MC  High | 0.5 yrs | 32 (ITT)  42 | Patients treated with stable IVIg therapy for > 6 mo at 11 sites in USA and 2 sites in Canada from 2004-2005  Criteria: PAGID/ESID | Baseline data for CVID patients NR | IVIg 200-800 mg/kg every 3-4 weeks  Co-interventions: NR | AEs |
| Bichuetti-Silva et al. (2014)  Brazil | CS, Pros, SC  High | 2 yrs | 50  117 | All patients with CVID who had received at least one dose of IVIg from August 2011-August 2013.  Criteria: PAGID/ESID | Baseline data for CVID patients NR | IVIg median dose 600 mg/kg every 3-4 weeks  Co-interventions: NR | AEs |
| Busse et al. (2002)  USA | CS, Retro, SC  High | Mean 6.6 yrs on IVIgB | 50  50 | Most recently referred patients with CVID  Criteria: PAGID/ESID | M = 20, F = 30  Mean age: 42.0 yrs (SD 16.3)  Age at onset, diagnostic delay NR | IVIg 300-400 m/kg every 3-4 weeks  Co-interventions: NR | Infection rates (pneumonia) |
| Dashti-Khavidaki et al. (2009)  Iran | CS, Retro, SC  High | NR data collected over 13 years | 54  99 | Patients with CVID on stable IVIg treatment who had received at least 4 infusions  Criteria: PAGID/ESID | Baseline data for CVID patients NR | IVIg 300-600 mg/kg every 3-4 weeks  Co-interventions: NR | AEs |
| De Garcia et al. (2004)  Spain | CS, Retro, SC  High | 2 yrs | 24  24 | Consecutive adult patients with CIVD diagnosed 1994-2001  Criteria: WHO | M = 10, F = 14  Mean age: 45 yrs (SD 18)  Onset age: NR  Diagnostic delay: NR | IVIg 200-300 mg/kg weekly for 3 weeks then every 3 weeks. Additional IVIg given if trough Ig levels < 600 mg/kg or if bacterial infections persisted  Co-interventions:  Postural drainage, chest percussion, bronchodilators, inhaled steroids and antibiotics considered if CPD present | IgG levels, Infection (serious and mild)  AEs |
| Martinez Garcia et al. (2001)  Spain | CS, Retro, SC  High | Mean 7.5 yrs | 19  19 | Patients diagnosed with CVID on Ig replacement therapy  Criteria: NR | M = 12, F = 7  Mean age: 33 yrs (SD 17.1)  Onset age: mean 14.7 yrs  Diagnostic delay: mean 8.5 yrs | IVIg 300-600 mg/kg every 3 weeks  Co-interventions: NR | Infection (upper respiratory, pneumonia, sinusitis, otitis media)  chronic pulmonary conditions (bronchiectasis, COPD, tuberculosis, asthma) |
| Pourpak et al. (2006)  Iran | CS, Retro SC  High | Mean 3.5 yrs (SD 2.95) | 26  26 | Patients diagnosed with CVID from 1999-2002 receiving IVIg who had been observed for at least 9 mo  Criteria: WHO | M = 14, F = 12  Mean age: 12.4 yrs (SD 5.6)  Onset age: mean 2.5 yrs (SD 3)  Diagnostic delay: mean 5.7 yrs (SD 3.9) | IVIg 400 mg/kg every 3-4 weeks  Co-interventions: NR | Infection (pneumonia)  Hospital admission  IgG levels |
| Quinti et al. (2008)  Italy | CS, Pros, MC  High | 1982 patient years | 262  262 | Patients diagnosed with CVID in the Italian Primary Immunodeficiency Network (26 centres) from 1999-2007  Criteria: PAGID/ESID | NR | IVIg 400 mg/kg 2-3 weekly  Co-interventions: antibiotic prophylaxis (11.6% of patients) | AEs |
| Quinti et al. (2007)  Italy | CS, Pros, MC  High | Mean 11.5 yrs (range 3-34) | 224  224 | Patients diagnosed with CVID in the Italian Primary Immunodeficiency Network (26 centres) from 1999-2007  Criteria: PAGID/ESID | M = 111, F = 113  Mean age: 26.6 yrs (range 2-73)  Onset age: mean 16.9 yrs (range 2-66)  Diagnostic delay: mean 8.9 yrs | IVIg 400 mg/kg 2-3 weekly  Co-interventions: antibiotic prophylaxis (11.6% of patients) | Serum IgG levels  Infection (prevalence) |
| Salehzadeh et al. (2010)  Iran | CS, Retro, SC  High | Mean 8 yrs (SD 4.6) | 24  24 | Patients aged >= 2 yrs with CVID diagnosed  Criteria: PAGID/ESID | M = 17, F = 7  Mean age 19.5 yrs (SD 12.6)  Onset age: NR  Diagnostic delay: median 5.3 yrs (0.25-39.75) | IVIg 300-600 mg/kg every 3-4 weeks  Co-interventions: NR | Serum IgG levels  Infection (prevalence)  Hospital admission rates |
| Singh et al. (1994)  India | CS, Retro, SC  High | NR | 14  14 | Patients with CVID  Criteria: NR | M = 10, F = 4  Age range 2-40 yrs  Onset age: NR  Diagnostic delay: NR | IVIg 10 ml/kg or IMIg 100 mg/kg at an interval to prevent diarrhoea and chest infections  Co-interventions: prophylactic antibiotics used | AEs |

**Abbreviations:** AEs: adverse events;CS: case series study; Consec: consecutive patients; COPD: chronic obstructive pulmonary disease; CPD: chronic pulmonary disease; CVID: common variable immunodeficiency; F: number of female patients; IgG: immunoglobulin G; IMIg: intramuscular immunoglobulin, IVIg: intravenous immunoglobulin; ITT: intention to treat population; M: number of male patients; MC: multicentre; Mo: months; NR: not reported, PAGID/ESID: Pan-American Group for Immunodeficiency and European Society for Immunodeficiencies, PP: per protocol population; Pros: prospective study design; Retro: retrospective study design; SC: single centre; SD: standard deviation), USA: United States of America, WHO: World Health Organisation, Yrs: years.

**Note:** A = Bayrakci et al. (2005) data was reported in trimesters, one trimester calculated to be 3 months based on total length of follow-up of 2733 months equating to 911 trimesters); B = Busse et al. (2002) note 3 patients began treatment on IMIg then switched to IVIg

Table 36 Risk of bias of the comparative study Aghamohammadi et al. (2009) using the ROBINS-1 tool ([Sterne et al., 2016](#_ENREF_82)):

| Domain | Risk of bias | Reasons |
| --- | --- | --- |
| Bias due to confounding | Serious | Study did not report or consider disease severity or co-interventions as potential confounds. This may favour either the intervention or the control. |
| Bias in selection of participants into the study | Serious | Patients were potentially selected based on characteristics observed after start of the intervention. Selection bias was not adjusted for. This may favour either the intervention or the control. |
| Bias in classification of interventions | Low |  |
| Bias due to deviations from intended interventions | Moderate | Treatment adherence was not reported. This may favour comparator. |
| Bias due to missing data | Serious | It was not clear if data was missing and if patients were excluded due to missing data. This may favour either the intervention or the control. |
| Bias in measurement of outcomes | Moderate | It was not clear that data were collected in a consistent way for all patients. Due to retrospective study design some elements of patient history may be missing. This may favour either the intervention or the control. |
| Bias in selection of the reported result | Low |  |
| Overall risk of bias | Serious | It is not clear whether the predicted bias will favour the intervention or control overall. |

Table 37 Quality appraisal of the selected case series studies using the IHE assessment tool.

|  | Aghamohammadi et al. (2003) | Aghomahammadi et al. (2004) | Aghomahammadi et al. (2008) | Alkan et al. (2018) | Baris et al. (2011) | Bayrakci et al. (2005) | Berger et al. (2007) | Bichuetti-silva et al. (2014) | Busse et al. (2002) | Dashti-Khavidaki et al. (2009) | De Garcia et al. (2004) | Martinez Garcia et al. (2001) | Pourpak et al. (2006) | Quinti et al. (2008) | Quinti et al. (2007) | Salehzadeh et al. (2010) | Singh et al. (1994) |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study objective |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 1. Objective clearly stated | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Study design |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 2. Prospective | Y | N | N | N | N | N | Y | Y | N | N | N | N | N | Y | Y | N | N |
| 3. Multicentre | N | N | N | N | N | N | Y | N | N | N | N | N | N | Y | Y | N | N |
| 4. Consecutive recruitment | N | N | N | N | N | N | N | Y | Y | N | Y | N | N | N | N | N | N |
| Study population |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 5. Were patient characteristics included? | P | P | Y | Y | Y | Y | N | N | P | N | P | Y | Y | N | Y | Y | P |
| 6. Eligibility criteria clearly stated | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| 7. Did patient enter the study at a similar point in the disease | ? | ? | ? | ? | ? | ? | ? | ? | ? | ? | ? | ? | ? | ? | ? | ? | ? |
| Intervention and co-intervention |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 8. Was the intervention of interest clearly described? | Y | Y | I | Y | Y | P | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | P |
| 9. Were additional interventions clearly described? | N | N | N | N | Y | Y | N | N | N | N | Y | N | N | Y | Y | N | Y |
| Outcome measure |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 10. Were relevant outcome measures established a priori\* | Y | Y | Y | YT | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| 11. Were outcome assessors blinded to the intervention? | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| 12. Were the outcomes measured using appropriate objective methods? | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| 13. Were the relevant outcome measures made before and after the intervention? | Y | N | Y | Y | Y | Y | N | N | Y | N | Y | Y | Y | N | Y | Y | N |
| Statistical analysis |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 14. Were the statistical tests used to assess the relevant outcomes appropriate? | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Results and conclusions |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 15. Was follow-up long enough for important events and outcomes to occur? | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| 16. Were losses to follow-up reported | N | N | N | N | N | N | Y | N | N | N | N | N | N | N | N | N | N |
| 17. Did study provide estimates of random variability in the data analysis of relevant outcomes? | Y | Y | N | N | N | N | N/A | N/A | N/A | N/A | Y | N | N | NA | N | N | NA |
| 18. Were the adverse events reported? | Y | Y | N | N | N | Y | Y | Y | N | Y | Y | N | N | Y | N | N | Y |
| 19. Were the conclusions supported by results? | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Competing interest and sources of support |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 20. Were both competing interests and sources of support for the study reported? | N | N | Y | P | N | N | Y | N | N | N | N | N | N | N | N | P | N |

# Appendix D Evidence Profile Tables

Table 38 Evidence profile table example 1 for Ig compared to no treatment for patients with CVID

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Outcome  (units, follow-up) | No. of studies and study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Effect Ig | Effect no treatment | Quality | Importance |
| Adverse events  follow up: range 1 years to 12 years (count) | 8 observational studies | Serious | Not serious | Not serious | Not serious | None | 184/434 (42.4%) | N/A | ⨁⨁⨁⨀  **Moderate quality** | Critical |
| Serious adverse events (count) | 5 observational studies | Serious | Not serious | Not serious | Not serious | None | 20/519 (3.9%) | N/A | ⨁⨁⨁⨀  **Moderate quality** | Critical |
| Lower respiratory infection rates (per patient per year) | 8 observational studies | Very serious | Not serious | Not serious | Not serious | Plausible residual confounding may reduce the effect | Range of means  0.16-0.34 | Range of means  0.28-2.04 | ⨁⨀⨀⨀  **Very low quality** | Critical |
| IgG trough levels (mg/dl) | 7 observational studies | Serious | Not serious | Not serious | Not serious | none | Range of means  455-891 | Range of means  195-416 | ⨁⨁⨀⨀  **Low quality** | Critical |
| Hospitalisations (per patient per year) | 4 observational studies | Very serious | Not serious | Not serious | Not serious | Plausible residual confounding may reduce the effect | Range of means  0.13-0.7 | Range of means  1.35-3.4 | ⨁⨀⨀⨀  **Very low quality** | Critical |

Risk of bias is discussed in Section B.3. Hospitalisations and infection rates were assessed to be at higher risk of bias due to the potential for confounding for these outcomes.

⨁⨁⨁⨁ **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.

# Appendix E Excluded Studies

## Cohort studies not reporting Ig outcomes (n = 10)

Jones, C. A., Rojavin, M. & Baggish, J. S. 2012. Patients with primary immunodeficiency receiving subcutaneous immune globulin Hizentra maintain health-related quality of life and treatment satisfaction in a multicentre extension study of efficacy, tolerability and safety. Journal of Pharmaceutical Health Services Research, 3, 41-47.

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Ramirez-Vargas, N., Arablin-Oropeza, S. E., Mojica-Martinez, D., Yamazaki-Nakashimada, M. A., De La Luz Garcia-Cruz, M., Teran-Juarez, L. M., Cortes-Grimaldo, R. M., Torres-Lozano, C., Madrigal-Beas, I., Ortega-Cisneros, M., Vargas-Camano, M. E., Staines-Boone, T., Pietropaolo-Cienfuegos, D., Berron-Ruiz, L., Espinosa-Rosales, F. J., Guevara-Cruz, M. & Blancas-Galicia, L. 2014. Clinical and immunological features of common variable immunodeficiency in Mexican patients. Allergol Immunopathol (Madr), 42, 235-40.

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Tabolli, S., Giannantoni, P., Pulvirenti, F., La Marra, F., Granata, G., Milito, C. & Quinti, I. 2014. Longitudinal study on health-related quality of life in a cohort of 96 patients with common variable immune deficiencies. Frontiers in Immunology, 5 (NOV) (no pagination).

Tcheurekdjian, H., Palermo, T. & Hostoffer, R. 2004. Quality of life in common variable immunodeficiency requiring intravenous immunoglobulin therapy. Ann Allergy Asthma Immunol, 93, 160-5.

Van Der Hilst, J. C., Smits, B. W. & Van Der Meer, J. W. 2002. Hypogammaglobulinaemia: cumulative experience in 49 patients in a tertiary care institution. Neth J Med, 60, 140-7.

Wiesik-Szewczyk, E., Zietkiewicz, M., Matyja-Bednarczyk, A., Napiorkowska-Baran, K., Suchanek, H. & Jahnz-Rozyk, K. 2018. The first Polish cohort of adult patients with common variable immunodeficiency from 4 specialized centers: Do we provide standards of care? Polish Archives of Internal Medicine, 128, 563-566.

## Non-randomised studies comparing Ig to Ig (n = 73)

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Anterasian, C., Duong, R., Gruenemeier, P., Ernst, C., Kitsen, J. & Geng, B. 2019. Quality of Life Differences for Primary Immunodeficiency Patients on Home SCIG versus IVIG. J Clin Immunol.

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Bleasel, K., Heddle, R., Hissaria, P., Stirling, R., Stone, C. & Maher, D. 2012. Pharmacokinetics and safety of Intragam 10 NF, the next generation 10% liquid intravenous immunoglobulin, in patients with primary antibody deficiencies. Intern Med J, 42, 252-9.

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# Appendix F Clinical Trials Searches

Table 39 Search terms used for ClinicalTrials.gov and ANZCTR searches

| Search Term | Source | Total Trials | Date |
| --- | --- | --- | --- |
| Primary Immunodeficiency | Clinical trials.gov | 163 | 28/02/2020 |
| Common variable immunodeficiency | Clinical trials.gov | 46 | 29/02/2020 |
| X-linked agammaglobulinaemia | Clinical trials.gov | 12 | 1/03/2020 |
| Severe immunodeficiency | Clinical trials.gov | 88 | 2/03/2020 |
| Wiskott-Aldrich syndrome | Clinical trials.gov | 36 | 2/03/2020 |

Table 40 Identified trials in patients with PID.

| Trial identifier | Conditions | Intervention | Comparator | Study design (Allocation, Intervention/Observational model, Masking, Location, Primary purpose, Time perspective) | Country(s) | Status, Completion date |
| --- | --- | --- | --- | --- | --- | --- |
| NCT02881437 | Primary  Immunodeficiency | IgHy10 |  | Single Group Assignment, Open Label, Multi-centre, Treatment | France | Completed, November 2018 |
| NCT01150240 | Primary  Immunodeficiency |  |  | Cohort, multi-centre | Switzerland | Unknown, December 2018 |
| NCT02123615 | Primary  Immunodeficiency | Gammagard via injection device | Gammagard via subcutaneous injection | RCT, Parallel Assignment, Double-blinded, single-centre, treatment | USA | Unknown,  June 2018 |
| NCT03896932 | Primary  Immunodeficiency | minipooled- Intravenous immunoglobulin(MP-IVIG) |  | Single Group Assignment, Open Label, single-centre, Treatment | Egypt | Not yet recruiting,  December 2021 |
| NCT03610802 | Primary  Immunodeficiency |  |  | Cohort, multi-centre, Prospective | USA  Turkey | Recruiting, March 2038 |
| NCT03814798 | Primary  Immunodeficiency | IGSC 20% dose schedule comparison | IGSC 20% dose schedule comparison | RCT, Crossover Assignment (Cohort), Open Label, Multi-centre, Treatment, Prospective | USA | Not yet recruiting, September 2020 |
| NCT03907241 | Primary  Immunodeficiency | Octanorm 16.5% |  | Single Group Assignment, Open Label, single-centre, Treatment | Canada | Completed, August 2019 |
| NCT03394053 | Primary  Immunodeficiency |  |  | Family-Based, multi-centre, Prospective | USA | Recruiting, December 2042 |
| NCT03252548 | Primary  Immunodeficiency |  |  | Case-Only, multi-centre, Prospective | China | Not yet recruiting, August 2022 |
| NCT03339778 | Primary  Immunodeficiency | Octagam 5% | IVIG 10% | Cohort, Prospective | USA | Completed, September 2017 |
| NCT03033745 | Primary  Immunodeficiency | IgPro20 (Hizentra) dose schedule comparison | IgPro20 (Hizentra) dose schedule comparison | Non-RCT, Parallel Assignment, Open Label, Multi-centre, Treatment | USA  Canada | Completed, December 2018 |
| NCT02806986 | Primary  Immunodeficiency | IGSC 20% |  | Single Group Assignment, Open Label, Multi-centre, Treatment | Australia, Czechia, France, Germany, Hungary, Poland, Spain, Sweden, UK | Completed, May 2019 |
| NCT02604810 | Primary  Immunodeficiency | IGSC 20% | IGIV-C 10% | Non-RCT, Sequential Assignment, Open Label, Multi-centre, Treatment | USA  Canada | Completed, December 2017 |
| NCT03961009 | Primary  Immunodeficiency | Kedrion IVIG 10% |  | Single Group Assignment, Open Label, Multi-centre, Treatment, Prospective | USA  Canada | Recruiting, February 2021 |
| NCT01465958 | Primary  Immunodeficiency | GAMUNEX-C IV | GAMUNEX-C SC | Non-RCT, Crossover Assignment, Open Label, Multi-centre, Treatment | USA | Completed, October 2013 |
| NCT02627300 | Primary  Immunodeficiency | Octanorm 16.5% |  | Single Group Assignment, Open Label, Multi-centre, Treatment | USA | Completed, September 2019 |
| NCT01012323 | Primary  Immunodeficiency | NewGam |  | Single Group Assignment, Open Label, Multi-centre, Treatment | USA | Completed, June 2012 |
| NCT02176239 | Primary  Immunodeficiency | Gammaplex IVIg 5% |  | Cohort, Multi-centre, Prospective | USA | Completed, August 2019 |
| NCT00546871 | Primary  Immunodeficiency | IGIV 10% | SCIG 10% | Non-RCT, Parallel Assignment, Open Label, Multi-centre, Treatment | USA | Completed, September 2009 |
| NCT03618147 | Primary  Immunodeficiency |  |  | Cohort, single-centre, Other (time perspective) | Kuwait | Completed, May 2019 |
| NCT02490956 | Primary  Immunodeficiency | Verorab |  | Single Group Assignment, Open Label, single-centre, Diagnostic | Thailand | Unknown, September 2016 |
| NCT01883921 | Primary  Immunodeficiency | Gamma Globulin |  | Cohort, single-centre, Prospective | USA | Terminated, August 2019 |
| NCT03988426 | Primary  Immunodeficiency | Octanorm |  | Single Group Assignment, Open Label, Multi-centre, Treatment | Russia | Completed, January 2018 |
| NCT01313507 | Primary  Immunodeficiency | NewGam |  | Single Group Assignment, Open Label Multi-centre, Treatment | USA | Completed, September 2012 |
| NCT03939533 | Primary  Immunodeficiency | CUTAQUIG – dose study | CUTAQUIG – dose study | RCT, Parallel Assignment, Open Label, Multi-centre, Treatment | USA | Recruiting, March 2021 |
| NCT03037359 | Primary  Immunodeficiency | Bivigam | Other IGIV | Cohort, multi-centre, Prospective | USA | Recruiting, March 2021 |
| NCT01814800 | Primary  Immunodeficiency | RI-002 |  | Single Group Assignment, Open Label, Multi-centre, Treatment | USA | Completed, January 2015 |
| NCT01131858 | Primary  Immunodeficiency | Vigantol (vitamin D supplementation) | Placebo | RCT, Single Group Assignment, Quadruple , Prevention | Sweden | Completed, June 2011 |
| NCT02269163 | Primary  Immunodeficiency | Prometic IGIV 10% | IVIg | Non-RCT, Sequential Assignment, Open Label, Multi-centre, Treatment | USA | Completed, January 2019 |
| NCT00751621 | Primary  Immunodeficiency | IgPro20 |  | Single Group Assignment, Open Label,  Multi-centre, Treatment | France, Germany, Poland, Romania, Spain, Sweden, Switzerland, UK | Completed, December 2011 |
| NCT03277313 | Primary  Immunodeficiency | HYQVIA 10% | GAMMAGARD LIQUID 10% | Non-RCT, Single Group Assignment, Open Label, Multi-centre, Prevention | USA | Active, not recruiting, October 2023 |
| NCT03116347 | Primary  Immunodeficiency | HYQVIA 10% | KIOVIG 10%  Cuvitru 20% | Non-RCT, Single Group Assignment, Open Label, Multi-centre, Treatment | Czechia, Denmark, France, Greece, Slovakia, Sweden, UK | Recruiting, April 2023 |
| NCT01412385 | Primary  Immunodeficiency | IGSC 20%  GAMMAGARD LIQUID 10%  KIOVIG 10%  SUBCUVIA |  | Non-RCT, Parallel Assignment, Open Label, Multi-centre, Treatment | Austria, Germany, Hungary, Sweden, UK | Completed, May 2014 |
| NCT00391131 | Primary  Immunodeficiency | IgNextGen 16% |  | Single Group Assignment, Open Label, Multi-centre, Treatment | Australia  New Zealand | Completed, October 2009 |
| NCT01485796 | Primary  Immunodeficiency | IGI 10% +rHuPH20 |  | Single Group Assignment, Open Label, Multi-centre, Treatment | USA | Completed, January 2013 |
| NCT01218438 | Primary  Immunodeficiency | IGIV 10%  IGSC 20% |  | Single Group Assignment, Open Label, Multi-centre, Treatment | USA  Canada | Completed, March 2015 |
| NCT01175213 | Primary  Immunodeficiency | HYQVIA  GAMMAGARD LIQUID  KIOVIG |  | Non-RCT, Single Group Assignment, Open Label, Multi-centre, Treatment | USA | Completed, August 2013 |
| NCT00782106 | Primary  Immunodeficiency | IGIV 10% +rHuPH20 |  | Parallel Assignment, Open Label, Multi-centre, Treatment | USA | Completed, November 2007 |
| NCT00814320 | Primary  Immunodeficiency | IGIV 10% +rHuPH20 |  | Non-RCT, Parallel Assignment, Open Label, Multi-centre, Treatment | USA | Completed, November 2010 |
| NCT00157079 | Primary Immunodeficiency,  Immune Thrombocytopenic Purpura (ITP),  Kawasaki Syndrome | IGIV 10% |  | RCT, Crossover Assignment, Multi-centre, Treatment | USA | Completed, December 2013 |
| NCT02180763 | Primary  Immunodeficiency | Gammanorm |  | Single Group Assignment, Open Label, Multi-centre, Treatment | France | Completed, August 2017 |
| NCT00538915 | Primary  Immunodeficiency | Nabi-IGIV 10% |  | Single Group Assignment, Open Label, Multi-centre, Treatment | USA | Completed, July 20109 |
| NCT00579137 | Severe Combined Immunodeficiency Disease  Severe Primary Immunodeficiency Disorder  Undefined T Cell Deficiency Disorder  Wiskott-Aldrick Syndrome | Fludarabine  Stem cell infusion (Anti-CD45)  Campath -1H |  | Single Group Assignment, Open Label, Single-centre, Treatment | USA | Terminated, October 2009 |
| NCT01458171 | Primary  Immunodeficiency | IgPro20 |  | Single Group Assignment, Open Label, Multi-centre, Treatment | Japan | Completed,  April 2012 |
| NCT02503293 | Primary  Immunodeficiency | Chrono Super PID + Gammanorm – delivery device comparison |  | RCT, Crossover Assignment, Open Label, Multi-centre, Treatment | Australia  Germany  Italy  UK | Completed, December 2017 |
| NCT02810444 | Primary  Immunodeficiency | BT595 |  | Single Group Assignment, Open Label, Multi-centre, Treatment | USA | Recruiting, April 2020 |
| NCT01888484 | Primary  Immunodeficiency | Octanorm 16.5% |  | Single Group Assignment, Open Label, Multi-centre, Treatment | USA  Canada  Czechia  Hungary  Poland  Russia  Slovakia | Active, not recruiting, July 2020 |
| NCT01985373 | Primary  Immunodeficiency | IVIG Nanogam |  | Single Group Assignment, Open Label, Multi-centre, Treatment | Netherlands | Completed, March 2015 |
| NCT03668288 | Secondary or Primary Immunodeficiency | IGHy |  | Cohort, Single-centre, Prospective | France | Recruiting, August 2021 |
| NCT01354587 | Primary  Immunodeficiency | Vivaglobin + Hizentra |  | Non-RCT, Single Group Assignment, Open Label, single-centre, Treatment | USA | Unknown, August 2012 |
| NCT03716700 | Primary  Immunodeficiency | CUVITRU (IGSC 20%) |  | Cohort, Multi-centre, Prospective | Canada | Recruiting, July 2020 |
| NCT01461018 | Primary  Immunodeficiency | IgPro20 (Hizentra) |  | Single Group Assignment, Open Label, Multi-centre, Treatment | Japan | Completed, July 2014 |
| NCT02593188 | Primary  Immunodeficiency | HYQVIA |  | Cohort, Multi-centre, Prospective | USA | Recruiting, June 2021 |
| NCT03148028 | Inflammatory Bowel Diseases  Primary Immune Deficiency Disorder |  |  | Cohort, Multi-centre, Other | Israel | Recruiting, December 2020 |
| NCT02327351 | Primary Immune Deficiency Disorder  Hematopoietic Stem Cell Transplantation | TCR alfa beta T cell depletion |  | Single Group Assignment, Open Label, single-centre, Treatment | Russia | Unknown, December 2018 |
| NCT00001788 | Primary  Immunodeficiency |  |  | Cohort, Single-centre, Retrospective | USA | Recruiting |
| NCT00113464 | Immune System Diseases |  |  |  | USA | Completed, April 2007 |
| NCT02868333 | Primary  Immunodeficiency |  |  | Cohort, Multi-centre, Prospective | France | Unknown, January 2017 |
| NCT02579967 | Primary T-cell Immunodeficiency Disorders  Common Variable Immunodeficiency  Immune System Diseases  Autoimmune Lymphoproliferative  Lymphoproliferative Disorders | Pentostatin  GVHD Prophylaxis |  | Non-RCT, Parallel Assignment, Open Label, single-centre, Treatment | USA | Recruiting, December 2028 |
| NCT02735824 | Immunologic Deficiency Syndromes | blood sampling and skin biopsy |  | Case-Only, Multi-centre, Prospective | Switzerland | Recruiting, July 2022 |
| NCT00680446 | Primary Immune Deficiency | Ig NextGen 16% |  | Single Group Assignment, Open Label, Multi-centre, Treatment | Australia  New Zealand | Completed, May 2013 |
| NCT00266513 | Hyper-IgM Syndrome  Ectodermal Dysplasia |  |  |  | USA | Terminated, July 2013 |
| NCT02990819 | Immunodeficiencies  Immune Dysregulation Syndromes | Apha/beta T and CD19+ cell depletion |  | Non-RCT, Parallel Assignment, Open Label, single-centre, Treatment | USA | Recruiting, December 2023 |
| NCT00719680 | Primary Immune Deficiency | IgPro20 |  | Single Group Assignment, Open Label, Multi-centre, Treatment | USA | Completed, June 2010 |
| NCT00811174 | Immunologic Deficiency Syndromes | Octagam 10% | Octagam 5% | Single Group Assignment, Open Label, Single-centre, Treatment | Austria | Terminated, September 2010 |
| NCT01406470 | Immunologic Deficiency Syndrome | IVIG-SN 5% |  | Single Group Assignment, Open Label, Multi-centre, Treatment | USA  Canada | Completed, July 2013 |
| NCT00006319 | Wiskott- Aldrich Syndrome  ADA Deficient SCID |  |  | Cohort, Single-centre, Prospective | USA | Active, not recruiting |
| NCT00389324 | Immunologic Deficiency Syndrome | Gamunex (IGIV 10%) |  | Non-RCT, Crossover Assignment, Open Label, Multi-centre, Treatment | USA  Canada | Completed, August 2008 |
| NCT01859754 | Primary Immune Deficiency Disorder | Octagam 5% | Other IVIG product | Cohort, Multi-centre, Prospective | USA | Completed, May 2019 |
| NCT00895271 | Primary Immunodeficiency  DOCK8 |  |  | Cohort, single-centre, Prospective | USA | Enrolling by invitation |
| NCT02888535 | Primary Immune Deficiency Disorder | Internal Medicine consultation |  | Cohort, single-centre, Prospective | France | Unknown, December 2019 |
| NCT00358657 | Immunodeficiency Syndrome  Non-Cancer Diagnosis  Severe Aplastic Anemia  Donor | Cyclophosphamide  Fludarabine Phosphate  Mycophenolate Mofetil  Sirolimus  Tacrolimus |  | Single Group Assignment, Open Label, Multi-centre, Treatment | USA | Active, not recruiting, December 2023 |
| NCT03054181 | Primary Immunodeficiency  Secondary Immune Deficiency | HyQvia |  | Cohort, Multi-centre, Prospective | France  Germany  Italy | Recruiting, March 31, 2020 |
| NCT03330795 | Primary Immunodeficiency | CD3/CD19 neg allogeneic BMT |  | Single Group Assignment, Open Label, single-centre, Treatment | USA | Recruiting, November 2024 |
| NCT01856582 | Waning Donor Chimerism  Waning Immune Function  Primary Immunodeficiency Disease(s)  Bone Marrow Failure | CD34+ |  | Single Group Assignment, Open Label, single-centre, Treatment | USA | Terminated, August 2018 |
| NCT03492710 | Primary Immune Deficiency Disorder | IGIV-SN |  | Single Group Assignment, Open Label, Multi-centre, Treatment, Prospective |  | Not yet recruiting, December 2021 |
| NCT04197596 | Viral Infection  Primary Immune Deficiency Disorder | BK CTL |  | Single Group Assignment, Open Label, Multi-centre, Treatment | USA | Not yet recruiting, June 30, 2024 |
| NCT03266640 | Cytomegalovirus Infections  Primary Immune Deficiency Disorder | CMV CTLs |  | Single Group Assignment, Open Label, Multi-centre, Treatment | USA | Recruiting, December 2021 |
| NCT01199705 | Primary Immune Deficiency | IgPro20 |  | Single Group Assignment, Open Label, Multi-centre, Treatment | Japan | Completed, November 2011 |
| NCT03266653 | Epstein-Barr Virus Infections  Primary Immune Deficiency Disorder | CTLs |  | Single Group Assignment, Open Label, Multi-centre, Treatment | USA | Recruiting, December 2021 |
| NCT00419341 | Primary Immune Deficiency | IgPro20 |  | Single Group Assignment, Open Label, Multi-centre, Treatment, Prospective | USA | Completed, October 2008 |
| NCT01287689 | Primary Immunodeficiency (PID)  Secondary Immunodeficiency (SID)  Neurological Autoimmune Disease | any IgG |  | Cohort, Multi-centre, Prospective | Germany | Completed, December 2016 |
| NCT00634569 | Primary Immune Deficiency Disease | Flebogamma 5% DIF |  | Single Group Assignment, Open Label, Multi-centre, Treatment | USA | Completed, May 2011 |
| NCT01196702 | Common Variable Immunodeficiency  Granulomatous Disease  Bronchiectasis  Immunoglobulin Treatment |  |  | Case control, Single-centre, Cross-sectional | UK | Unknown, July 2011 |
| NCT00553098 | Immunodeficiency Syndrome  Non-Cancer Diagnosis | Alemtuzumab  Cyclosporine  Fludarabine Phosphate  Mycophenolate Mofetil |  | Single Group Assignment, Open Label, Multi-centre, Treatment | USA | Completed, March 2015 |
| NCT04232085 | Primary Immune Deficiency Disorder  Immune Deficiency Disease  Bone Marrow Failure | Alemtuzumab  Fludarabine  Melphalan  Cyclophosphamide  Tacrolimus  Mycophenolate Mofetil |  | Non-RCT, Parallel Assignment, Open Label, Single-centre, Treatment | USA | Recruiting, December 2026 |
| NCT02349906 | Primary Immunodeficiencies  Inborn Errors of Metabolism  Haemoglobinopathies  Bone Marrow Failure Syndromes | Treosulfan | Busilvex | RCT, Parallel Assignment, Open Label, Multi-centre, Treatment | Czechia  Germany  Italy  Poland | Active, not recruiting, December 2022 |
| NCT03335605 | Common Variable Immunodeficiency |  |  | Case-control, Single-centre, Prospective | USA | Recruiting, May 2020 |
| NCT01962415 | Primary Immunodeficiency (PID)  Congenital Bone Marrow Failure Syndromes  Inherited Metabolic Disorders (IMD)  Hereditary Anemias  Inflammatory Conditions | Hydroxyurea  Alemtuzumab  Fludarabine  Melphalan  Thiotepa |  | Non-RCT, Parallel Assignment, Open Label, Single-centre, Treatment | USA | Recruiting, November 2021 |
| NCT02231710 | Primary Immune Deficiency Disorders  Hemophagocytic Lymphohistiocytosis  Inherited Bone Marrow Failure Syndrome  Hemoglobinopathies  Metabolic Disorders | BPX-501 + AP1903 |  | Single Group Assignment, Open Label, Single-centre, Treatment | USA | Active, not recruiting, July 2030 |
| NCT01966367 | Bone Marrow Failure Syndrome  Severe Aplastic Anemia  Severe Congenital Neutropenia  Amegakaryocytic Thrombocytopenia  Diamond-Blackfan Anemia  Schwachman Diamond Syndrome  Primary Immunodeficiency Syndromes  Acquired Immunodeficiency Syndromes  Histiocytic Syndrome  Familial Hemophagocytic Lymphocytosis  Lymphohistiocytosis  Macrophage Activation Syndrome  Langerhans Cell Histiocytosis (LCH)  Hemoglobinopathies  Sickle Cell Disease  Sickle Cell-beta-thalassemia | CD34 Stem Cell Selection Therapy |  | Single Group Assignment, Open Label, Single-centre, Treatment | USA | Recruiting, December 2019 |
| NCT04172181 | Severe Combined Immunodeficiency Disease | cord blood stem cell transplantation |  | Cohort, Multi-centre, Prospective | China | Active, not recruiting, October 2023 |
| NCT03733249 | Acute Lymphoblastic Leukemia  Leukemia, Acute Myeloid (AML), Child  Lymphoma, Non-Hodgkin  Myelodysplastic Syndromes  Primary Immunodeficiency  Anemia, Aplastic  Hemoglobinopathies  Cytopenia  Fanconi Anemia  Diamond Blackfan Anemia  Thalassemia  Anemia, Sickle Cell | Rimiducid |  | Single Group Assignment, Open Label, Multi-centre, Treatment | Italy  Saudi Arabia  UK | Enrolling by invitation, June 2035 |
| NCT02065869 | Acute Lymphoblastic Leukemia  Leukemia, Acute Myeloid (AML), Child  Lymphoma, Non-Hodgkin  Myelodysplastic Syndrome  Primary Immunodeficiency  Anemia, Aplastic  Osteopetrosis  Hemoglobinopathies  Cytopenia  Fanconi Anemia  Diamond Blackfan Anemia  Thalassemia  Anemia, Sickle Cell | rimiducid |  | Single Group Assignment, Open Label, Multi-centre, Treatment | Italy  UK | Active, not recruiting, December 2034 |
| NCT03301168 | Acute Lymphoblastic Leukemia  Leukemia, Acute Myeloid (AML), Child  Lymphoma, Non-Hodgkin  Myelodysplastic Syndromes  Primary Immune Deficiency Disorder  Osteopetrosis  Cytopenia  Hemoglobinopathy in Children  Anemia, Aplastic | BPX-501 T cells and AP1903 |  | Single Group Assignment, Open Label, Multi-centre, Treatment | USA | Active, not recruiting, February 2035 |
| NCT00004695 | Common Variable Immunodeficiency | PEG-interleukin-2 |  | RCT, Open Label, Treatment |  | Completed, March 2000 |
| NCT00001467 | DOK 8  STAT1  GATA2  Immunodeficiency  STAT3 |  |  | Other, Single-centre, Cross sectional | USA | Enrolling by invitation |
| NCT00845416 | Severe Combined Immunodeficiency  T Cell Lymphocytopenia |  |  | Cohort, Multi-centre, Prospective | USA | Completed, November 2011 |
| NCT00919503 | Non-Neoplastic Hematologic  Lymphocytic Disorder | Transplantation  Cyclosporine  Fludarabine Phosphate  Methotrexate  Mycophenolate Mofetil  Tacrolimus  Total-Body Irradiation  Treosulfan  Anti-Thymocyte Globulin  Allogeneic Bone Marrow  Peripheral Blood Stem Cell Transplantation  Umbilical Cord Blood Transplantation |  | Non-RCT, Parallel Assignment, Open Label, Multi-centre, Treatment | USA | Recruiting, February 2027 |
| NCT00405184 | Primary Immune Deficiency (PID) | IntragamP | Ig NextGen 10% | Single Group Assignment, Open Label, Multi-centre, Treatment | Australia | Completed, July 2008 |
| NCT00576407 | DiGeorge Syndrome  Complete Typical DiGeorge Anomaly | Cultured Thymus Tissue for Implantation |  | Single Group Assignment, Open Label, Single-centre, Treatment | USA | Completed, December 2017 |
| NCT02061800 | Chronic Myeloid Leukemia (CML)  Acute Myelogenous Leukemia (AML)  Myelodysplastic Syndrome (MDS)  Juvenile Myelomonocytic Leukemia (JMML)  Acute Lymphoblastic Leukemia (ALL)  Lymphoma (Hodgkin's and Non-Hodgkin's) | Alemtuzumab  Cyclophosphamide  Thiotepa  Tacrolimus  Melphalan  Busulfan  Fludarabine  Methylprednisolone | full intensity with total body irradiation | Non-RCT, Parallel Assignment, Open Label, Single-centre, Treatment | USA | Recruiting, December 2019 |
| NCT00006056 | Chediak-Higashi Syndrome  Graft Versus Host Disease  X-Linked Lymphoproliferative Syndrome  Familial Erythrophagocytic Lymphohistiocytosis  Hemophagocytic Lymphohistiocytosis  Virus-Associated Hemophagocytic Syndrome | Anti-thymocyte globulin  Busulfan  Cyclophosphamide  Cyclosporine  Etoposide  Filgrastim  Methotrexate  Allogeneic hematopoietic stem cell transplantation |  | Treatment | USA | Unknown |
| NCT01617122 | Primary Immune Deficiency Diseases | Bacteriophage OX174 |  | Single Group Assignment, Open Label, Single-centre, Diagnostic | USA | Unknown, December 2015 |
| NCT03721146 | Immune Deficiency |  |  | Cohort, Single-centre, Prospective | France | Recruiting, September 2021 |
| NCT03238079 | Primary Immune Deficiency Diseases | IGIV 10% |  | Single Group Assignment, Open Label, Multi-centre, Treatment | USA  Canada | Recruiting, May 2020 |
| NCT02783482 | Immunologic Deficiency Syndromes | GC5107 (IGIV 10%) |  | Single Group Assignment, Open Label, Multi-centre, Treatment | USA  Canada | Unknown, January 2018 |
| NCT00023504 | Primary Immune Deficiency | Pneumovax  Prevnar  Tetanus diphtheria toxoid | Rabavert | Non-RCT, Sequential Assignment, Open Label, Multi-centre, Treatment | USA | Recruiting, September 2026 |
| NCT02711228 | Primary Immune Deficiency  Secondary Immune Deficiency | IgPro20 (Hizentra) |  | Single Group Assignment, Open Label, Multi-centre, Prevention | Canada | Completed, January 30, 2018 |
| NCT03677557 | Primary or Secondary Immunodeficiency Disease | 16.5% Cutaquig |  | Single Group Assignment, Open Label, Single-centre, Treatment | Canada | Not yet recruiting, July 2019 |
| NCT03188419 | Primary T-cell Immunodeficiency Disorders  Common Variable Immunodeficiency | allogeneic hematopoietic stem cell transplant |  | Cohort, Single-centre, Retrospective | USA | Completed, February 2020 |
| NCT02303093 | Primary and Secondary Immunodeficiency and Other Conditions | Octagam IVIG 5%  Octagam IVIG 10%  panzyga |  | Cohort, multi-centre, Prospective | Austria  Canada  France  Spain  UK | Recruiting, December 2019 |
| NCT01166074 | Primary Immune Deficiency | SCIG |  | Cohort, multi-centre, Retrospective | USA | Completed, December 2010 |
| NCT01652092 | SCID  Omenn's Syndrome  Reticular Dysgenesis  Wiskott-Aldrich Syndrome  Bare Lymphocyte Syndrome  Common Variable Immunodeficiency  Chronic Granulomatous Disease  CD40 Ligand Deficiency  Hyper IgM Syndrome  X-linked Lymphoproliferative Disease  Hemophagocytic Lymphohistiocytosis  Griscelli Syndrome  Chediak-Higashi Syndrome  Langerhan's Cell Histiocytosis | Alemtuzumab  Cyclophosphamide  Busulfan  Fludarabine phosphate  Melphalan  MESNA  Stem Cell Transplantation |  | Non-RCT, Single Group Assignment, Open Label, Single-centre, Treatment | USA | Recruiting, December 2022 |
| NCT00246857 | Primary Immune Deficiency |  |  | Other, Multi-centre, Prospective | USA  Turkey | Recruiting |
| NCT02542228 | Immune Deficiency, Antibody |  |  | Cohort, Prospective |  | Completed, September 2016 |
| NCT02247141 | Primary Antibody Deficiency | Subgam |  | Open Label, Multi-centre, Prospective | UK | Completed, January 2005 |
| NCT01793506 | Immunodeficiencies |  |  | Cohort, Single-centre, Prospective | USA | Withdrawn, June 2017 |
| NCT01998633 | Hemophagocytic Lymphohistiocytosis  Chronic Active Epstein-Barr Virus Infection  Chronic Granulomatous Disease  HIGM-1  Leukocyte Adhesion Deficiency  IPEX | Hematopoietic Stem Cell Transplant  Alemtuzumab  Fludarabine  Melphalan |  | Single Group Assignment, Open Label, Single-centre, Treatment | USA  Canada | Completed, December 2016 |
| NCT01222741 | Fungal Infections  Primary Immune Deficiencies |  |  | Family-Based, Single-centre, Prospective | USA | Recruiting |
| NCT00468273 | Immunologic Deficiency Syndromes | Omr-IgG-am IGIV |  | Single Group Assignment, Open Label, Multi-centre, Prevention | USA  Canada | Completed |
| NCT01489618 | Common Variable Immunodeficiency | Primeboost Conjugated anti- Pneumococcal (PnCJ)  Polysaccharide anti- Pneumococcal (PPS) |  | RCT, Parallel Assignment, Open Label, Multi-centre, Prevention | France | Terminated, March 2013 |
| NCT00263237 | Common Variable Immunodeficiency | STA-5326 |  | Single-centre, Treatment | USA | Completed, July 2008 |
| NCT00015431 | Common Variable Immunodeficiency |  |  |  | USA | Completed, July 2013 |
| NCT03335605 | Common Variable Immunodeficiency |  |  | Case-Control, Single-centre, Prospective | USA | Recruiting, December 2019 |
| NCT00004695 | Common Variable Immunodeficiency | PEG-interleukin-2 | placebo | RCT, Open Label, Multi-centre, Treatment |  | Completed, March 2000 |
| NCT01946906 | Common Variable Immunodeficiency | Rifaximin | No treatment | RCT, Parallel Assignment, Open Label, Single-centre, Basic Science | Norway | Completed, December 2014 |
| NCT03534479 | Common Variable Immunodeficiency | Polyclonal IgG |  | RCT, Parallel Assignment, Open Label, Single-centre, Basic Science | Italy | Completed, April 2013 |
| NCT03576469 | Common Variable Immunodeficiency | C1-esterase inhibitor |  | Single Group Assignment, Open Label, Single-centre, Prevention | USA | Recruiting, March 2020 |
| NCT02680652 | Common Variable Immune Deficiency |  |  | Case-Control, Prospective |  | Unknown, July 2018 |
| NCT02435173 | Common Variable Immunodeficiency (CVID) More Specifically Activated PI3Kdelta Syndrome (APDS) p110delta-activating Mutation Causing Senescent T Cells  Lymphadenopathy and Immunodeficiency (PASLI) | CDZ173 | placebo | Non-RCT, Single Group Assignment, Triple, Multi-centre, Treatment | USA  Czechia  Ireland  Italy  Netherlands  Russia  UK | Recruiting, June 2021 |
| NCT02960399 | Common Variable Immune Deficiency  Specific Antibody Deficiency  X-linked Agammaglobulinemia | Zostavax |  | Non-RCT, Parallel Assignment, Open Label, Single-centre, Prevention | USA | Terminated, December 2017 |
| NCT00943514 | Bronchiectasis  Cystic Fibrosis  Autoimmune Disease  Common Variable Immunodeficiency |  |  | Other, Single-centre, Prospective | USA | Recruiting |
| NCT03663933 | Lymphoproliferative Disorders  Autoimmune Lymphoproliferative  Primary T-cell Immunodeficiency Disorders  Immune System Diseases  Common Variable Immunodeficiency | Immunosuppression Only Conditioning  Reduced Intensity Conditioning  GVHD Prophylaxis  Allogeneic HSC | No treatment | Non-RCT, Parallel Assignment, Open Label, Multi-centre, Treatment | USA | Recruiting, May 2024 |
| NCT03513328 | Bone Marrow Failure Syndrome  Thalassemia  Sickle Cell Disease  Diamond Blackfan Anemia  Acquired Neutropenia in Newborn  Acquired Anemia Hemolytic  Acquired Thrombocytopenia  Hemophagocytic Lymphohistiocytoses  Wiskott-Aldrich Syndrome  Chronic Granulomatous Disease  Common Variable Immunodeficiency  X-linked Lymphoproliferative Disease  Severe Combined Immunodeficiency  Hurler Syndrome  Mannosidosis  Adrenoleukodystrophy | Thiotepa--single daily dose  Thiotepa--escalated dose |  | RCT, Sequential Assignment, Open Label, Single-centre, Treatment | USA | Recruiting, June 2022 |
| NCT01821781 | Immune Deficiency Disorders  Severe Combined Immunodeficiency  Chronic Granulomatous Disease  X-linked Agammaglobulinemia  Wiskott-Aldrich Syndrome  Hyper-IgM  DiGeorge Syndrome  Chediak-Higashi Syndrome  Common Variable Immune Deficiency  Immune Dysregulatory Disorders  Hemophagocytic Lymphohistiocytosis  IPEX  Autoimmune Lymphoproliferative Syndrome  X-linked Lymphoproliferative Syndrome | Alemtuzumab  Fludarabine  Thiotepa  Melphalan |  | Single Group Assignment, Open Label, Multi-centre, Treatment | USA | Recruiting, March 2024 |
| NCT01852370 | Severe Combined Immunodeficiency (SCID)  Immunodeficiency with Predominant T-cell Defect, Unspecified  Severe Chronic Neutropenia  Chronic Granulomatous Disease (CGD)  Hyper IgE Syndromes  Hyper IgM Deficiencies  Wiskott-Aldrich Syndrome  Mendelian Susceptibility to Mycobacterial Disease  Common Variable Immune Deficiency (CVID) | CD3/CD19 negative allogeneic hematopoietic stem cells |  | Single Group Assignment, Open Label, Single-centre, Treatment | USA | Enrolling by invitation, November 2024 |
| NCT02234791 | Agammaglobulinemia, BTK |  |  | Cohort, Single-centre, Prospective | China | Unknown, December 2016 |
| NCT01884311 | Primary Immune Deficiency Disorders  Common Variable Immunodeficiency  X-linked Agammaglobulinaemia  Hyperimmunoglobulin M Syndrome |  |  | Single Group Assignment, Open Label, Multi-centre, Other | USA | Completed, May 2017 |
| NCT00004341 | X-Linked Agammaglobulinemia  X-Linked Hyper IgM Syndrome  Wiskott-Aldrich Syndrome  Leukocyte Adhesion Deficiency Syndrome |  |  | Single- centre, Screening | USA | Unknown |
| NCT01963143 | Primary Immune Deficiency Disorders  Common Variable Immunodeficiency  X-linked Agammaglobulinaemia  Hyper-IgM Syndrome | Gammaplex (5%)  Gammaplex (10%) |  | RCT, Crossover Assignment, Open Label, Multi-centre, Treatment | USA  Hungary  UK | Completed, May 2016 |
| NCT01289847 | Primary Immune Deficiency Disorders  Common Variable Immunodeficiency  X-linked Agammaglobulinemia  Hyper-IgM Syndrome  Wiskott-Aldrich Syndrome | Gammaplex |  | Single Group Assignment, Open Label, Multi-centre, Prevention | USA  Chile  Israel | Completed |
| NCT00006054 | Immunologic Deficiency Syndromes  Chediak-Higashi Syndrome  Common Variable Immunodeficiency  Graft Versus Host Disease  X-Linked Lymphoproliferative Syndrome  Familial Erythrophagocytic Lymphohistiocytosis  Hemophagocytic Lymphohistiocytosis  X-linked Agammaglobulinemia  Wiskott-Aldrich Syndrome  Chronic Granulomatous Disease  X-linked Hyper IgM Syndrome  Severe Combined Immunodeficiency  Leukocyte Adhesion Deficiency Syndrome  Virus-Associated Hemophagocytic Syndrome | Anti-thymocyte globulin  Busulfan  Cyclophosphamide  Cyclosporine  Etoposide  Methotrexate  Methylprednisolone  Prednisone  Allogeneic bone marrow transplantation |  | Single-centre, Treatment | USA | Terminated, December 2002 |
| NCT00613561 | Severe Immunodeficiency Diseases | Fludarabine  Busulfan  Anti-Thymocyte Globulin |  | Non-RCT, Single Group Assignment, Open Label, Single-centre, Treatment | USA | Unknown, December 2012 |
| NCT00295971 | Congenital Amegakaryocytic Thrombocytopenia  Leukemia  Myelodysplastic Syndromes  Severe Congenital Neutropenia | Anti-thymocyte globulin  Therapeutic allogeneic lymphocytes  Fludarabine phosphate  Thiotepa  Allogeneic bone marrow transplantation  Allogeneic hematopoietic stem cell transplantation  In vitro-treated peripheral blood stem cell transplantation  Total-body irradiation |  | Single Group Assignment, Open Label, Multi-centre, Treatment | USA | Completed, December 2011 |
| NCT02860559 | Severe Combined Immunodeficiency | TBX-1400 |  | Single Group Assignment, Open Label, Multi-centre, Treatment | Israel | Not yet recruiting, March 2023 |
| NCT02244450 | Severe Combined Immunodeficiency, Atypical | SCID screening |  | Non-RCT, Parallel Assignment, Open Label, Multi-centre, Screening | France | Completed, April 2018 |
| NCT00152100 | Severe Combined Immunodeficiency | Stem cell transplant  Filgrastim  Alemtuzumab |  | Non-RCT, Single Group Assignment, Open Label, Single-centre, Treatment | USA | Completed, August 2007 |
| NCT03597594 | Severe Combined Immunodeficiency | Anti-thymocyte globulin  Busulfan  Fludarabine  Thiotepa |  | Non-RCT, Single Group Assignment, Open Label, Single-centre, Treatment | USA | Not yet recruiting, July 2027 |
| NCT02231983 | Severe Combined Immunodeficiency | gene sequencing |  | Cohort, Single-centre, Prospective | China | Unknown, September 2016 |
| NCT01410019 | X-linked Severe Combined Immunodeficiency | Gene transfer |  | Single Group Assignment, Open Label, Single-centre, Treatment | France | Unknown, July 2015 |
| NCT02999984 | Severe Combined Immunodeficiency Due to ADA Deficiency | Infusion of autologous cryopreserved EFS-ADA LV CD34+ cells (OTL-101) |  | Single Group Assignment, Open Label, Single-centre, Treatment | USA | Completed, September 2019 |
| NCT00028236 | Severe Combined Immunodeficiency | Gene-Transduced Autologous CD34+ Stem Cells |  | Single-centre, Treatment | USA | Completed, July 2011 |
| NCT02590328 | Severe Combined Immunodeficiency  Neonatal Screening |  |  | Cohort, Single-centre, Prospective | China | Recruiting, December 2020 |
| NCT01512888 | Severe Combined Immunodeficiency Disease  X-linked | Busulfan |  | Single Group Assignment, Open Label, Multi-centre, Treatment | USA | Recruiting, August 2034 |
| NCT00228852 | T-Cell Immune Deficiency Diseases  Severe Combined Immunodeficiency | Busulfan  Fludarabine  ATG |  | Non-RCT, Single Group Assignment, Open Label, Single-centre | USA | Completed, November 2006 |
| NCT00001255 | Severe Combined Immunodeficiency | ADA PBSC  ADA Umbilical Cord Blood Cells  Transduced Lymphocytes |  |  | USA | Completed, July 2002 |
| NCT01129544 | Severe Combined Immunodeficiency | Gene transfer |  | Single Group Assignment, Open Label, Multi-centre, Treatment | USA | Active, not recruiting, March 2023 |
| NCT03645460 (17) | Adenosine DeAminase Severe Combined ImmunoDeficiency (ADA-SCID) | TYF-ADA gene-modified autologous stem cells |  | Single Group Assignment, Open Label, Single-centre, Treatment | China | Recruiting, December 2021 |
| NCT03538899 | Severe Combined Immunodeficiency | Busulfan  AProArt |  | Single Group Assignment, Open Label, Single-centre, Treatment | USA | Recruiting, June 2038 |
| NCT01306019 | X-Linked Severe Combined Immune Deficiency | Palifermin  Busulfan  CD34+ HSC |  | Single Group Assignment, Open Label, Single-centre, Treatment | USA | Recruiting, December 2030 |
| NCT01175239 | X-linked Severe Combined Immunodeficiency | autologous CD34+ cells |  | Single Group Assignment, Open Label, Single-centre, Treatment | UK | Unknown, December 2018 |
| NCT02127892 | Severe Combined Immunodeficiency | Unrelated BM with T cell depletion  Haplo BM with T cell depletion |  | Non-RCT, Single Group Assignment, Open Label, Single-centre, Treatment | USA | Terminated, August 2016 |
| NCT00794508 | Severe Combined Immunodeficiency | CD34+ cells ADA gene transfer |  | Single Group Assignment, Open Label, Single-centre, Treatment | USA | Completed, January 2015, December 2012 |
| NCT04246840 | Severe Combined Immunodeficiency |  |  | Case-Control, Prospective |  | Not yet recruiting, February 2021 |
| NCT00006335 | Severe Combined Immunodeficiency |  |  |  | USA | Completed, September 2008 |
| NCT01182675 | Severe Combined Immunodeficiency | Transplant Conditioning with Mobilization + Alemtuzumab | Transplant Conditioning with Mobilization Only | Non-RCT, Parallel Assignment, Open Label, Single-centre, Treatment | USA | Terminated, September 2013 |
| NCT00055172 | Severe Combined Immunodeficiency |  |  | Family-Based, Multi-centre, Cross-sectional | Chile  USA |  |
| NCT03601286 | Severe Combined Immunodeficiency  X-Linked | Lentiviral vector transduced CD34+ cells |  | Single Group Assignment, Open Label, Single-centre, Treatment | UK | Recruiting, December 2024 |
| NCT04140539 | Severe Combined Immunodeficiency Due to ADA Deficiency | OTL-101 |  | Single Group Assignment, Open Label, Single-centre, Treatment | USA | Recruiting, February 2021 |
| NCT00490100 | Growth Failure  X-linked Severe Combined Immunodeficiency (XSCID)  Growth Hormone Resistance | Increlex |  | Single Group Assignment, Open Label, Single-centre, Treatment | USA | Terminated, December 2012 |
| NCT00018018 | Severe Combined Immunodeficiency Syndrome | CD34+ cells transduced with ADA retrovir |  | Single-Centre, Treatment | USA | Completed, September 2014 |
| NCT03478670 | Immunologic Deficiency Syndromes | Strimvelis |  | Cohort, Single-centre, Prospective | Italy | Enrolling by invitation, May 2037 |
| NCT03232203 | Severe Combined Immunodeficiency Due to ADA Deficiency | STRIMVELIS |  | Cohort, Single-centre, Cross-sectional | Italy | Recruiting, September 2020 |
| NCT02177760 | Severe Combined Immunodeficiency  Transplacental Maternal Engraftment  Stem Cell Transplant | Sirolimus |  | Single Group Assignment, Open Label, Single-centre, Prevention | USA | Withdrawn, November 2015 |
| NCT04286815 | Gene Therapy | Lentiviral Vector Gene Therapy |  | Single Group Assignment, Open Label, Single-centre, Treatment | China | Recruiting, March 2025 |
| NCT01852071 | ADA-SCID | autologous EFS-ADA LV CD34+ (OTL-101) |  | Single Group Assignment, Open Label, Multi-centre, Treatment | USA | Completed, August 2018 |
| NCT00599781 | Severe Combined Immunodeficiency Syndrome | gene transduced PBL and/or gene transduced HSC |  | Non-RCT, Single Group Assignment, Open Label, Multi-centre, Treatment |  | Completed, January 2007 |
| NCT03878069 | Adenosine Deaminase Deficiency  Severe Combined Immunodeficiency | elapegademase-lvlr |  | Cohort, Open Label, Multi-centre, Prospective | USA | Recruiting, July 2023 |
| NCT00008450 | Adenosine Deaminase Deficiency  Autosomal Recessive Disorder  Immune System Disorder  Purine-Nucleoside Phosphorylase Deficiency  Severe Combined Immunodeficiency  Severe Combined Immunodeficiency With Absence of T and B Cells  X-Linked Severe Combined Immunodeficiency | Cyclosporine  Mycophenolate Mofetil  Allogeneic Bone Marrow Transplantation |  | Single Group Assignment, Open Label, Single-centre, Treatment | USA | Completed, December 2018 |
| NCT01380990 | Adenosine Deaminase Deficiency  Severe Combined Immunodeficiencies (SCID) | EF1αS-ADA lentiviral vector transduced patient Cd34+ cells |  | Single Group Assignment, Open Label, Single-centre, Treatment | UK | Active, not recruiting, December 2018 |
| NCT03311503 | Severe Combined Immunodeficiency  X Linked  Gene Therapy | autologous CD34+ cell transduced with G2SCID vector |  | Single Group Assignment, Open Label, Multi-centre, Treatment | USA  UK | Recruiting, January 2024 |
| NCT01420627 | Adenosine Deaminase Deficiency  Severe Combined Immunodeficiency | EZN-2279 | Adagen | Non-RCT, Crossover Assignment, Open Label, Multi-centre, Treatment | USA | Completed, May 2019 |
| NCT03879876 | Any Type of Severe Combined Immunodeficiency (SCID)  Partial HLA Incompatible Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) | Human T Lymphoid Progenitor (HTLP) |  | Single Group Assignment, Open Label, Single-centre, Treatment | France | Not yet recruiting, April 2024 |
| NCT03217617 | SCID, X Linked | TYF-IL-2Rg gene-modified autologous stem cells |  | Single Group Assignment, Open Label, Multi-centre, Treatment | China | Recruiting, December 2020 |
| NCT01019876 | Bone Marrow Failure  Osteopetrosis  Fanconi Anemia  Severe Combined Immunodeficiency | Fludarabine  Cyclophosphamide |  | Non-RCT, Parallel Assignment, Open Label, Single-centre, Treatment | USA | Unknown, May 2013 |
| NCT02963064 | Severe Combined Immunodeficiency | Humanized anti-CD117 Monoclonal Antibody  Blood Forming Stem Cell Transplant (CD34+CD90+) |  | Single Group Assignment, Open Label, Multi-centre, Treatment | USA | Recruiting, August 2020 |
| NCT01346150 | SCID  ADA-SCID  XSCID  Leaky SCID  Omenn Syndrome  Reticular Dysgenesis |  |  | Cohort, Multi-centre, Retrospective | Canada  USA | Recruiting, August 2019 |
| NCT00695279 | Severe Combined Immunodeficiency  Malignancy, Hematologic  Neuroblastoma  Neoplasm  Mucopolysaccharidosis I | Venipuncture |  | Cohort, Single-centre, Prospective | USA | Recruiting, December 2036 |
| NCT01182857 | ADA-SCID |  |  | Prospective |  | Withdrawn, September 2014 |
| NCT03619551 | SCID | Busulfan |  | RCT, Parallel Assignment, Open Label, Multi-centre, Treatment | USA | Recruiting, August 2026 |
| NCT01279720 | Adenosine Deaminase Deficiency | Intravenous infusion of transduced cells |  | Non-RCT, Single Group Assignment, Open Label, Single-centre, Treatment | UK | Completed, November 2013 |
| NCT00000603 | Anemia, Aplastic  Fanconi Anemia  Hematologic Diseases  Leukemia  Neoplasms  Severe Combined Immunodeficiency  Hematopoietic Stem Cell Transplantation  Myelodysplastic Syndromes | stem cell transplantation |  |  |  | Completed, October 2007 |
| NCT02064933 | Wiskott-Aldrich Syndrome |  |  | Cohort, Multi-centre, Other | Canada  USA | Active, not recruiting, August 2019 |
| NCT03198195 | Wiskott-Aldrich Syndrome | cyclophosphamide |  | Other, Prospective |  | Enrolling by invitation, July 2020 |
| NCT00885833 | Fludarabine  Busulfan  Thymoglobulin |  |  | Single Group Assignment, Open Label, Single-centre, Treatment | Korea Republic | Completed, March 2012 |
| NCT03837483 | Wiskott-Aldrich Syndrome | OTL-103 |  | Single Group Assignment, Open Label, Single-centre, Treatment | Italy | Recruiting, December 2022 |
| NCT01347242 | Wiskott-Aldrich Syndrome | CD34+ cells transduced with a lentiviral vector + human WASP gene |  | Single Group Assignment, Open Label, Multi-centre, Treatment | UK | Completed, November 2019 |
| NCT02333760 | Wiskott-Aldrich Syndrome | Autologous CD34+ cells transduced with WASP lentiviral vector |  | Single Group Assignment, Open Label, Multi-centre, Other | UK | Recruiting, December 2027 |
| NCT01515462 | Wiskott-Aldrich Syndrome | OTL-103 |  | Single Group Assignment, Open Label, Single-centre, Treatment | Italy | Completed, February 2009 |
| NCT01410825 | Wiskott-Aldrich Syndrome | Retrovirus-mediated gene transfer |  | Single Group Assignment, Open Label, Single-centre, Treatment | USA | Active, not recruiting, July 2023 |
| NCT01347346 | Wiskott-Aldrich Syndrome | Autologous CD34 positive cells transduced with a lentiviral vector containing human WAS gene |  | Non-RCT, Single Group Assignment, Open Label, Single-centre, Treatment | France | Completed, January 2017 |
| NCT00774358 | Wiskott-Aldrich Syndrome (WAS)  X-linked Thrombocytopenia | Interleukin-2 |  | Single Group Assignment, Open Label, Multi-centre, Treatment | USA | Completed, September 2016 |
| NCT00909363 | Wiskott-Aldrich Syndrome  Thrombocytopenia  Bleeding | Promacta |  | Non-RCT, Single Group Assignment, Open Label, Single-centre, Treatment | USA | Terminated, June 2017 |
| NCT03019809 | Wiskott-Aldrich Syndrome  Hematopoietic Stem Cell Transplantation  Graft Failure | G-CSF for Conditioning before HSCT  Plerixafor for Conditioning before HSCT |  | Single Group Assignment, Open Label, Multi-centre, Treatment | Russia | Recruiting, July 2019 |
| NCT01319851 | Thalassemia  Sickle Cell Disease  Glanzmann Thrombasthenia  Wiskott-Aldrich Syndrome  Chronic-granulomatous Disease  Severe Congenital Neutropenia  Leukocyte Adhesion Deficiency  Schwachman-Diamond Syndrome  Diamond-Blackfan Anemia  Fanconi Anemia  Dyskeratosis-congenita  Chediak-Higashi Syndrome  Severe Aplastic Anemia | Alefacept |  | Single Group Assignment, Open Label, Single-centre, Treatment | USA | Terminated, September 2013 |
| NCT00730314 | Sickle Cell Disease  Thalassemia  Anemia  Granuloma  Wiskott-Aldrich Syndrome  Chediak Higashi Syndrome  Osteopetrosis  Neutropenia  Thrombocytopenia  Hurler Disease  Niemann-Pick Disease  Fucosidosis | Hematopoietic stem cell transplantation |  | Non-RCT, Parallel Assignment, Open Label, Single-centre, Treatment | USA | Completed, August 2015 |
| NCT01917708 | Hurler Syndrome  Fanconi Anemia  Glanzmann Thrombasthenia  Wiskott-Aldrich Syndrome  Chronic Granulomatous Disease  Severe Congenital Neutropenia  Leukocyte Adhesion Deficiency  Shwachman-Diamond Syndrome  Diamond-Blackfan Anemia  Dyskeratosis-congenita  Chediak-Higashi Syndrome  Severe Aplastic Anemia  Thalassemia Major  Hemophagocytic Lymphohistiocytosis  Sickle Cell Disease | Abatacept |  | Single Group Assignment, Open Label, Single-centre, Supportive care | USA | Completed, September 2019 |
| NCT03333486 | Wiskott-Aldrich Syndrome  Immunodeficiency Syndrome | Cyclophosphamide  Fludarabine Phosphate  Peripheral Blood Stem Cell Transplantation  Total-Body Irradiation |  | Single Group Assignment, Open Label, Single-centre, Treatment | USA | Recruiting, September 2022 |
| NCT02512679 | Stem Cell Transplantation  Bone Marrow Transplantation  Peripheral Blood Stem Cell Transplantation  Allogeneic Transplantation  Genetic Diseases  Thalassemia  Pediatrics  Diamond-Blackfan Anemia  Combined Immune Deficiency  Wiskott-Aldrich Syndrome  Chronic Granulomatous Disease  X-linked Lymphoproliferative Disease  Metabolic Diseases | Cyclophosphamide |  | Non-RCT, Single Group Assignment, Open Label, Treatment |  | Terminated, February 2014 |
| ACTRN12620000264987 | Immune-mediated dermatological diseases | PRN473 Topical | Placebo | RCT, Double-Blind, Prospective | Ausatralia | Not yet recruiting, |
| ACTRN12619001322123 | Autoimmune disease  Inflammatory bowel disease  Lupus | bDMARDs | Other types of immune-suppressing medications  No treatment  Placebo | Retrospective | Australia | Recruiting |
| ACTRN12618001511224 | Immunoglobulin A Nephropathy | Sparsentan | Irbesartan | RCT, Parallel assignment, Double-blind, multi-centre, treatment | Australia USA  UK  Belgium  Czech Republic  France  Germany  Italy  Lithuania  Poland  Portugal  New Zealand  Taiwan China  Croatia  Estonia  Hong Kong  Spain  Korea DR | Not yet recruiting |
| ACTRN12618001502224 | Auto-Immune Diseases | HL161BKN | Placebo | RCT | Australia | Terminated |
| ACTRN12618001394235 | Lung Transplantation | Intravenous immunoglobulin | Placebo (Human Albumin) | RCT, Double-blind, treatment | Australia | Recruiting |

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1. The most recent version of these *Criteria*, Version 3.1, were published by the National Blood Authority on October 22, 2018. The National Blood Authority is a statutory body responsible for the supply of blood and blood products in Australia, on behalf of the Australian Government and state and territory governments. [↑](#footnote-ref-2)
2. The most recent version of these *Criteria*, Version 3.1, were published by the National Blood Authority on October 22, 2018. The National Blood Authority is a statutory body responsible for the supply of blood and blood products in Australia, on behalf of the Australian Government and state and territory governments. [↑](#footnote-ref-3)
3. 1 July 2018 to 30 June 2019. [↑](#footnote-ref-4)
4. Additionally, the comparative studies were assessed to see if they met the inclusion criteria for single arm studies reporting pre/post Ig outcomes in patients with CVID. Aghamohammadi et al. (2009) did not report pre-post treatment data. Cunningham-Rundles (1989) and Gardulf et al. (1993) pooled post-SCIg data for patients who had previously been on no treatment and previously been on IMIg; therefore, this data was not extracted as the use of IMIg at baseline may have underestimated the effectiveness of SCIg in the follow-up measurements. Waniewski et al. (1994) included pre/post data for only six patients and therefore did not meet the minimum patient inclusion criteria (10 or more patients). [↑](#footnote-ref-5)
5. This study and others like it were not included in our analysis as they did not investigate the effectiveness of Ig treatment. These studies are listed in Appendix E. [↑](#footnote-ref-6)