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

July 2020

MSAC application no. 1592

Contracted Assessment

ISSN (Online) 1443-7139

Internet site http://www.msac.gov.au/

Electronic copies of the report can be obtained from the Medical Service Advisory Committee's Internet site at http://www.msac.gov.au/

Enquiries about the content of the report should be emailed to hta@health.gov.au.

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

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

This report was prepared by ASERNIP-S of the Royal Australasian College of Surgeons. Clinical advice was provided by the Immunoglobulin Review Reference Group. The report was commissioned by the Australian Government Department of Health.

The suggested citation for this document is:

Duncan, J., Forel, D., Gaget, V., Vandepeer, M., Tivey, D. Wendy, B. (2020). Immunoglobulin (Ig) for Primary Immunodeficiency Diseases (PID). MSAC Application 1592, Assessment Report. Commonwealth of Australia, Canberra, ACT.

CONTENTS

TABLES

BOXES

FIGURES

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] (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.).

[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.

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). 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)

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 syndrome[A]	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 agammaglobulinaemia[B]	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)
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 TAKEN TO THE EVIDENCE ASSESSMENT

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

Outcome (units, follow-up)	No. of studies and study design	Risk of bias	Effect Ig	Effect no treatment	Quality	Importance
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					

Year	2021	2022	2023	2024	2025
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	Australian Institute of Health and Welfare
ARAG	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

Acronym/abbreviation	Meaning
NHMRC	National Health and Medical Research Council
NK	natural killer
PASC	PICO Confirmation Advisory Sub-Committee of the MSAC
PID	primary immunodeficiency diseases
QALY	Quality Adjusted Life Year
QoL	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.

A.1. 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.

A.2. 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).

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). 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). 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). 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).

Ig preparations were first used in the 1950s as replacement therapy for a range of PID (Palabrica et al., 2013). 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). 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, Palabrica et al., 2013). 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). 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).

Dosage and clinical review

In Australia, Version 3.1 of the *Criteria for Clinical Use of Immunoglobulin in Australia*[b] (herein described as *'the Criteria Version 3'*) outlines which patients are eligible for Ig treatment (NBA, 2018). *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)*

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	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	6 months, annually thereafter.

[b] 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.

Loading Dose	Maintenance Dose	Review by an Immunologist
the serum IgG level is < 4g/L.	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.	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). SCIg, which delivers smaller volumes, may be self-administered at home (following appropriate training by a registered nurse or technician) (Ness, 2019).

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, Palabrica et al., 2013). Because IVIg is administered under medical supervision its adverse events can usually be treated quickly and effectively (Ness, 2019). SCIg requires more frequent dosages (due to smaller infusion volumes) via multiple injection sites around the body (Ness, 2019, Palabrica et al., 2013). Adverse events for SCIg are typically localised to the injection site and smaller infusion volumes allow for steady absorption of Ig (Ness, 2019). Serious adverse events of Ig therapy overall are rare and may include antibiotic allergy, anaphylaxis, veno-occlusive events and acute renal failure (Ness, 2019).

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)	Privilgen 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

ARTG no.	Product name	Product description	Sponsor
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).

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

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). 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).

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).

A.3. PROPOSAL FOR PUBLIC FUNDING

There are no proposed MBS items relevant to this Assessment.

A.4. POPULATION

Immunodeficiency disorders are characterised by an immune system defect that prevents a person's body from fighting infections and diseases (Healtline, 2019). People with immunodeficiency

disorders are prone to infection (increased frequency and severity), abnormal inflammation, cancer and autoimmune diseases (Immunodeficiency Australia, 2019, McCusker et al., 2018). 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). Secondary immunodeficiency diseases are mostly caused by another disease, illness, injury or medication (Immunodeficiency Australia, 2019). 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). 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). Over 350 different PID disorders are recognised by the World Health Organization (WHO), with new ones continually being discovered (IDF, 2020a). 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). 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). A total of 1,209 patients across 88 centres and 56 PID syndromes responded to the voluntary questionnaire (Kirkpatrick and Riminton, 2007b). 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).

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). 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).

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). Despite this, 15 per cent of all infants with SCID have a gene defect of unknown origin (NIAID, 2019). 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). 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).

- Combined immunodeficiency

Combined immunodeficiency (CID) is generally less profound than SCID due to hypomorphic (partial) gene mutations (Su, 2014). 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).

- 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). 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). 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).

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). Ataxia telangiectasia is caused by mutations in the ATM gene, which assists in normal cell division and DNA repair (NLM, 2019a). These mutations result in impaired or eliminated function of the ATM protein which causes cells to become unstable and die (NLM, 2019a). Approximately half of all people with ataxia telangiectasia are immunodeficient (Staples et al., 2008). 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). T-cell function is generally normal; therefore, opportunistic infections are rare (Staples et al., 2008).

- 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), as well as T-cell defects, namely reduced proliferative capacity (Strober and Chua, 2000). 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). Unlike other PID, CVID may be diagnosed in adults; however, symptoms may start to appear in childhood (ASCIA, 2019b). Approximately 10 per cent of cases of CVID have a known genetic cause (NLM, 2020). The main symptoms of CVID are hypogammaglobinemia and recurrent infections (particularly in the lungs, sinuses and ears) (NLM, 2020). Pneumonia is common in people with CVID, as well as infection or inflammation of the gastrointestinal tract, enlarged lymph nodes and spleen (NLM, 2020). 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). 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). 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).

- 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). 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).

- 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). 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). In most children, Ig levels normalise by 2 years of age (with some children taking up to age 6) (Knutsen, 2019).

- 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). 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). 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). 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). People with SCID, WAS, ataxia telangiectasia and CVID are also prone to LPS (Angel A Justiz-Vaillant and Christopher M Stang, 2019).

Ig usage for PID conditions

Ig therapy, funded by the NBA, in 2018-19[c] for the above conditions is described in Table 8 (NBA, 2019). 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).

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

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 syndrome[A]	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 agammaglobulinaemia[B]	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)
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):

[c] 1 July 2018 to 30 June 2019.

- 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).

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).

A.5. 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.

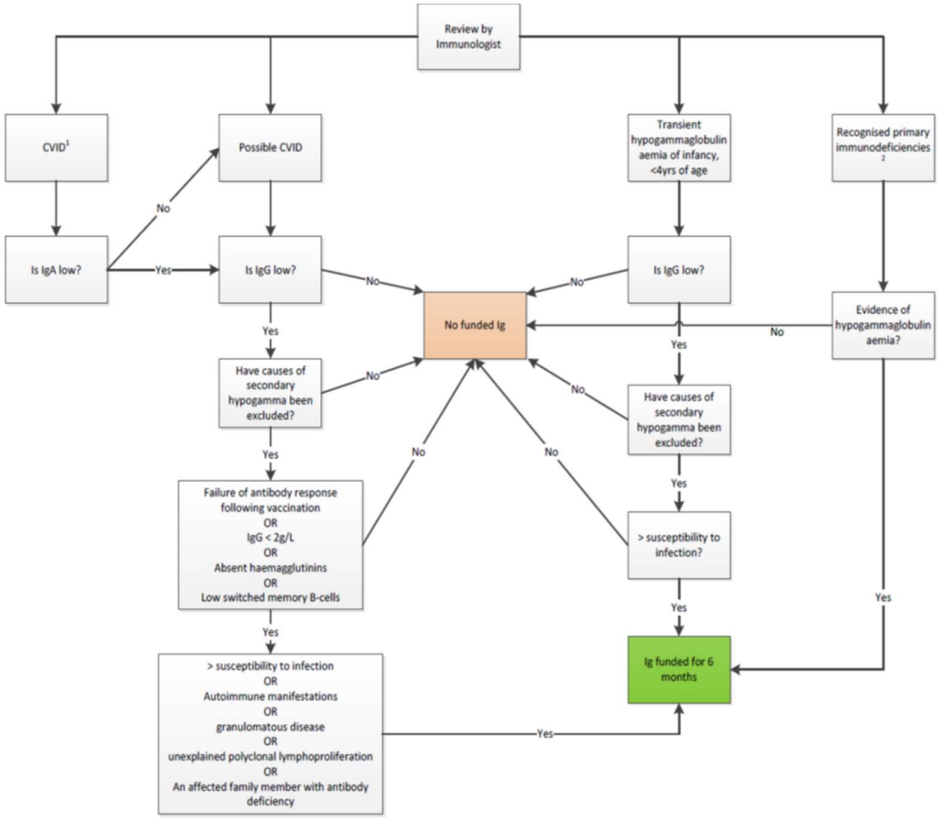
Given the broad range of conditions that comprise PID and their clinical variations in presentation, there is no one standard of care treatment for PID (Kirkpatrick and Riminton, 2007a). Standard therapies, other than Ig, may include haematopoietic stem cell transplant and/or gene therapy, splenectomy, 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.

A.6. 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).

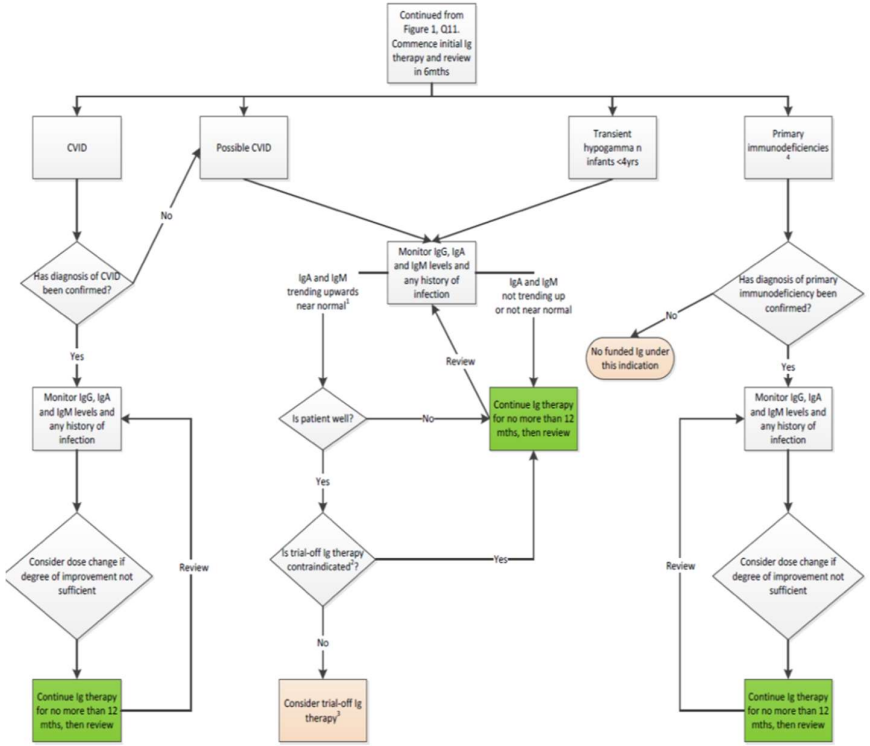
Figure 1 Clinical management algorithm for initial access to Ig for patients with PID with antibody deficiency.



1. ESID diagnostic criteria met
2. Must be a recognised PID for which Ig replacement is universally indicated

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.



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

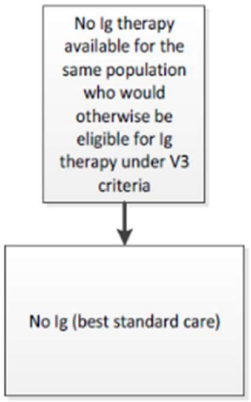
[2] Contraindication reasons for a trial-off Ig therapy include neutropenia, immunosuppressant medication, active bronchiectasis and/or suppurative lung disease or severe hypogammaglobulinaemia persists where no significant improvement has occurred in the underlying condition.

[3] Ig therapy should be extended as required to enable cessation of therapy in September/October, with repeat clinical and/or immunological evaluation before re-commencement of therapy.

[4] Recognised PIDs for which Ig is universally indicated.

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

A.7. 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.

A.8. 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.

A.9. 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.

A.10. 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

B.1. 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.

B.2. 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

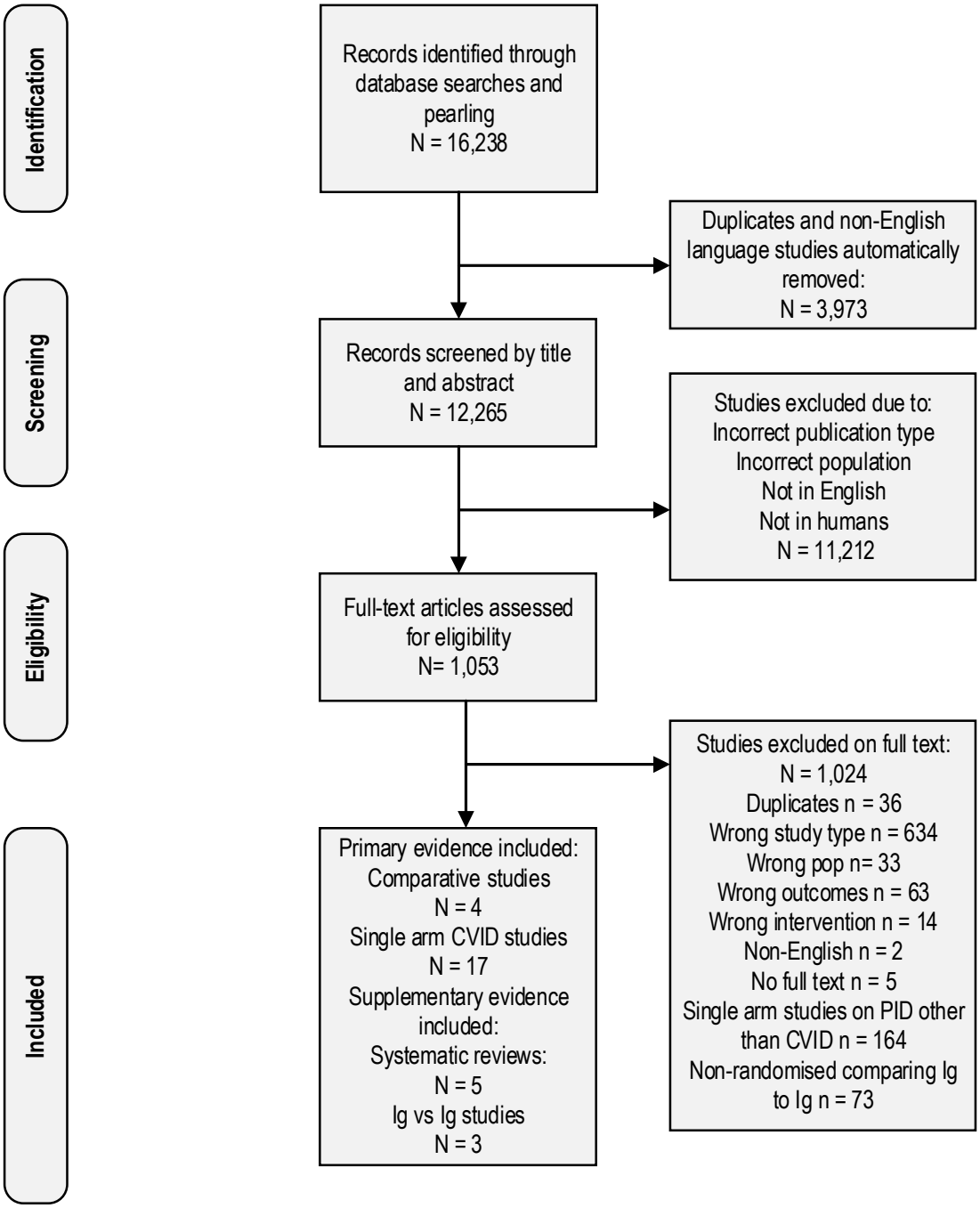
Abbreviations: CVID: common variable immune deficiency; RCT: randomised controlled trial.
Notes: A: the decision to limit case series studies to only those on CVID was in accordance with the PICO confirmation.

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)

B.3. 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). 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). 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.

B.4. CHARACTERISTICS OF THE EVIDENCE BASE

Four non-randomised comparative studies (Aghamohammadi et al., 2009b, Cunningham-Rundles, 1989, Gardulf et al., 1993, Waniewski et al., 1994) and seventeen case series studies were identified for inclusion in this Assessment (Aghamohammadi et al., 2003, Aghamohammadi et al., 2008, Alkan et al., 2017, Baris et al., 2011, Bayrakci et al., 2005, Busse et al., 2002, de Gracia 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, Aghamohammadi et al., 2004, Berger et al., 2007, Bichuetti-Silva et al., 2014, Dashti-Khavidaki et al., 2009). 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, Gardulf et al., 1993, Waniewski et al., 1994). 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] 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.

[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).

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.

Potential applicability issue	Evidence base	Ig use in Australia	How has issue been addressed?
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.

Potential applicability issue	Evidence base	Ig use in Australia	How has issue been addressed?
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.

Criteria	Serum Ig
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

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)
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

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. (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

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)
Bayrakci et al. (2005) Turkey[A]	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 IVIg[B]	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

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)
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

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)
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.

B.5. 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). 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).

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). 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.

B.6. 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) Turkey[B]	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%)

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
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

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
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

	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**
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, Baris et al., 2011, Busse et al., 2002, de Gracia et al., 2004, Martinez Garcia et al., 2001, Pourpak et al., 2006, Quinti et al., 2007, Salehzadeh et al., 2010). 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, Baris et al., 2011, de Gracia et al., 2004, Quinti et al., 2007, Salehzadeh et al., 2010), 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, Aghamohammadi et al., 2008, de Gracia et al., 2004, Pourpak et al., 2006) while three studies reported a numerical increase without commenting on the statistical significance of the results (Baris et al., 2011, Quinti et al., 2007, Salehzadeh et al., 2010).

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)	Bronchi
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
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
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	Bronchie associat increase delay an of lower infection

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
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 infection[A] 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) Turkey[B]	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 IVIg[C]	NR	Pneumonia prevalence (%) Pre: 42/50 (84%) Post: 11/50 (22%)	NR	NR	NR	NR

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
De Garcia et al. (2004) Spain	24 2 yrs	Pre: 239 (SD 138) Post: 806 (SD 167) P < 0.0001	Serious infection[B] Pre: 0.48 (SD 0.45) Post: 0.047 (SD 0.15) P = 0.001 Mild infection[C] 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

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
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 Recurrent[E] 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.

.

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, Garbett et al., 1989, Nolte et al., 1979).

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, Nolte et al., 1979).

- 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, Jones et al., 2018, Lingman-Framme and Fasth, 2013, Shabaninejad et al., 2016, Shrestha et al., 2019b). 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, Shabaninejad et al., 2016, Shrestha et al., 2019b), 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, Lingman-Framme and Fasth, 2013, Shabaninejad et al., 2016, Shrestha et al., 2019b).

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

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
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

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
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.

B.7. 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).

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).

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).

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.

B.8. 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] 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	⊕⊕⊕⊙	Critical

[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.

Outcome (units, follow-up)	No. of studies and study design	Risk of bias	Effect Ig	Effect no treatment	Quality	Importance
					Moderate quality	
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

D.1. 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).

D.2. 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), one study was a cost-utility analysis (Windegger et al., 2020), and the other four studies were cost-minimisation analyses (Beaute et al., 2010, Igarashi et al., 2014, Martin et al., 2013, Perraudin et al., 2016). 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, Menzin et al., 2014, Pollock and Meckley, 2018, Sadeghi et al., 2015, Gholami et al., 2017, Viti et al., 2018). Two of these studies examined the CVID subtype of PID (Sadeghi et al., 2015, Viti et al., 2018).

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). 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). 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). 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	Australian healthcare system perspective	PID patients NOS IVIg in hospitals and SCIg at home	**CUA** via Markov cohort transition model with six	Incremental cost = $45,835;

Author Publish year Country	Model settings Data sources	Population Comparison Economic Outcome	Modelling approach Sensitivity analysis	Results and Conclusion
Australia	Data from Sunshine Coast Hospital and Health Services	Incremental costs per QALY gained	health states with 10-year TH and weekly cycle; Both DSA and PSA to identify key drivers of the model	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)

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
				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, Pollock and Meckley, 2018, Sadeghi et al., 2015), and the other three examined the cost burden at a local level (Fu et al., 2018, Gholami et al., 2017, Menzin et al., 2014). 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, Fu et al., 2018, Gholami et al., 2017, Sadeghi et al., 2015), and three of these were limited to specific PID subtypes of CVID and XLA (Viti et al., 2018, Fu et al., 2018, Sadeghi et al.,

2015). 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, Pollock and Meckley, 2018). 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) to less than half (42.1% of the PID patients in Switzerland) (Pollock and Meckley, 2018). 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). 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). 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). 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). 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). 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). 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). 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, Igarashi et al., 2014). 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.

D.3. 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). 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). 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, Windegger et al., 2020) 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) 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). 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;

D.4. 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). 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). 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) 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.

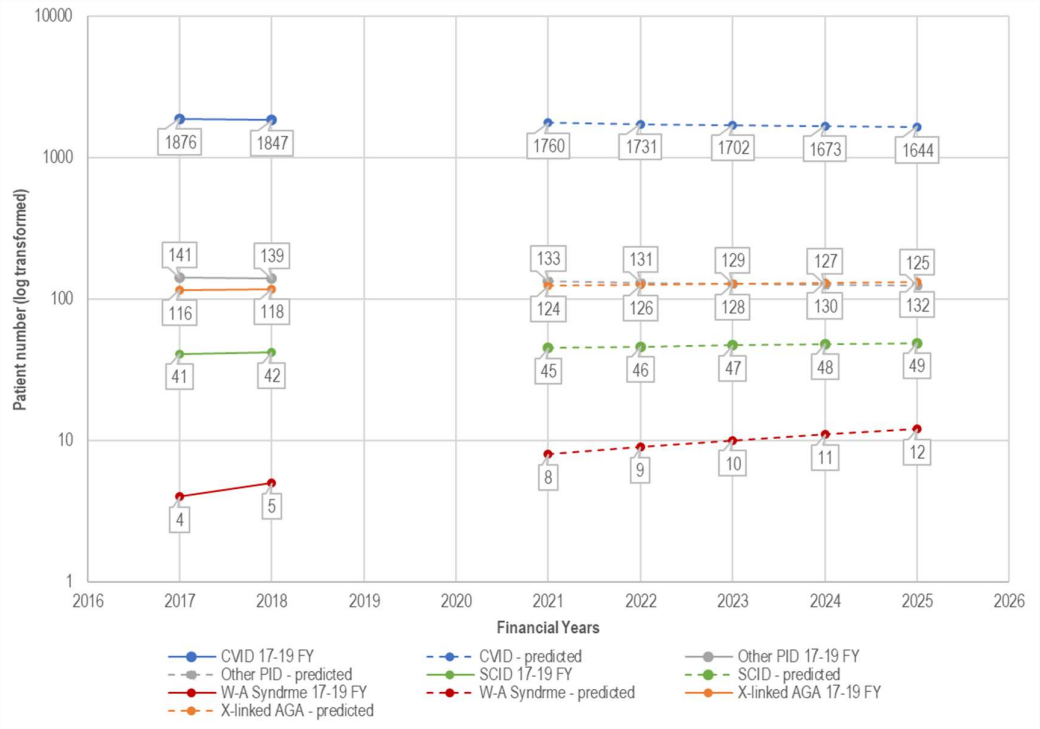
1. PID subtypes (based on the six reported ones) are analysed where their trends are derived to predict patient numbers at the subtype level. For disease subtypes which were not reported from the first FY, the patient counts were carried forward (Last Observation Carry Forward, LOCF) assuming no change. 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.

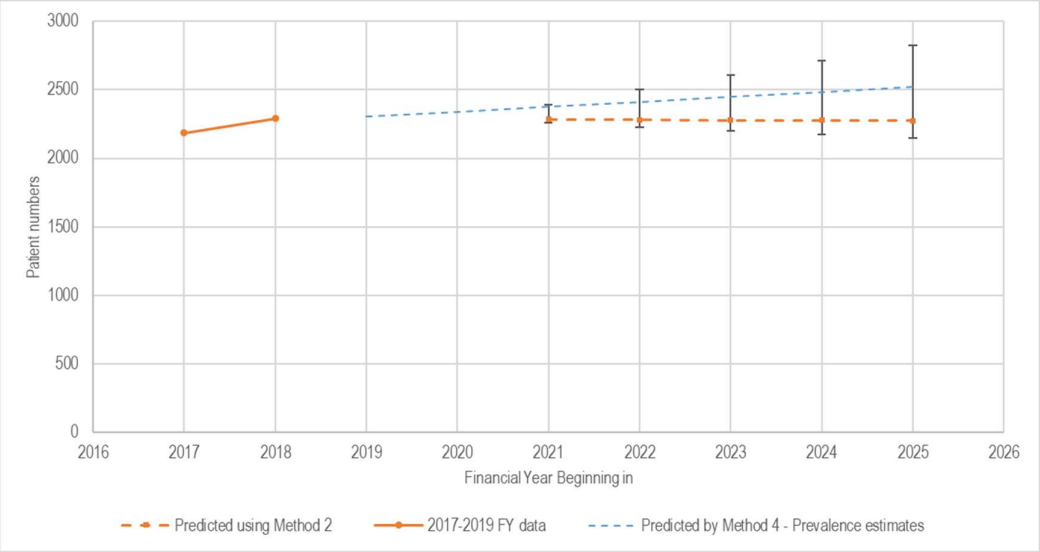
It is clear that all the methods above are associated with some uncertainty. To illustrate this, results of projection from all the four methods were plotted in the same graph (Figure 6). Among the four methods used, Method 2 (average reduction of 2.58 patients annually) seems reasonable, and Method 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)
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	C_1 = B × 0.93
IVIg Imported	126	128	130	132	134	Table 25	C_2 = B × 0.07
Domestic IVIg consumption	528842	536775	544826	552999	561294	Table 26	D_1 = C_1 × 315
Imported IVIg consumption	40184	40787	41399	42020	42650	Table 26	D_2 = C_2 × 318
Cost of IVIg domestic	$31,947,346	$32,426,556	$32,912,954	$33,406,648	$33,907,748	Table 27	E_1 = D_1 × 60.41
Cost of IVIg imported	$2,427,540	$2,463,953	$2,500,913	$2,538,426	$2,576,503	Table 27	E_2 = D_2 × 60.41

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**		$F = E_1 + E_2$

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	$B = A \times 0.76$
SCIg domestic	200	203	206	209	212	35% domestic	$C_1 = B \times 0.35$
SCIg Imported	371	376	382	388	393	65% imported	$C_2 = B \times 0.65$
Domestic SCIg consumption	44688	45365	46043	46739	47435	Table 26	$D_1 = C_1 \times 224$
Imported SCIg consumption	107445	109074	110702	112376	114050	Table 26	$D_2 = C_2 \times 290$
Cost of SCIg domestic	$2,699,602	$2,740,522	$2,781,443	$2,823,500	$2,865,557	Table 27	$E_1 = D_1 \times 60.41$
Cost of SCIg imported	$6,490,752	$6,589,139	$6,687,525	$6,788,644	$6,889,763	Table 27	$E_2 = D_2 \times 60.41$
Total cost of SCIg	**$9,190,355**	**$9,329,661**	**$9,468,967**	**$9,612,143**	**$9,755,319**		$F = E_1 + E_2$

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 χ^2 test and a test of correlation were applied to the data obtained (Pearson).

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
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)

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)
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) Turkey[A]	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

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)
Busse et al. (2002) USA	CS, Retro, SC High	Mean 6.6 yrs on IVIg[B]	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)

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)
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):

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																	

	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)
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

	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)
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.

Lucas, M., Lee, M., Lortan, J., Lopez-Granados, E., Misbah, S. & Chapel, H. 2010. Infection outcomes in patients with common variable immunodeficiency disorders: relationship to immunoglobulin therapy over 22 years. J Allergy Clin Immunol, 125, 1354-1360.e4.

Quinti, I., Soresina, A., Guerra, A., Rondelli, R., Spadaro, G., Agostini, C., Milito, C., Trombetta, A. C., Visentini, M., Martini, H., Plebani, A. & Fiorilli, M. 2011. Effectiveness of immunoglobulin replacement therapy on clinical outcome in patients with primary antibody deficiencies: results from a multicenter prospective cohort study. J Clin Immunol, 31, 315-22.

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.

Slade, C. A., Bosco, J. J., Giang, T. B., Kruse, E., Stirling, R. G., Cameron, P. U., Hore-Lacy, F., Sutherland, M. F., Barnes, S. L., Holdsworth, S., Ojaimi, S., Unglik, G. A., De Luca, J., Patel, M., Mccomish, J., Spriggs, K., Tran, Y., Auyeung, P., Nicholls, K., O'hehir, R. E., Hodgkin, P. D., Douglass, J. A., Bryant, V. L. & Van Zelm, M. C. 2018. Delayed diagnosis and complications of predominantly antibody deficiencies in a cohort of Australian adults. Frontiers in Immunology, 9 (MAY) (no pagination).

Sperlich, J. M., Grimbacher, B., Workman, S., Haque, T., Seneviratne, S. L., Burns, S. O., Reiser, V., Vach, W., Hurst, J. R. & Lowe, D. M. 2018. Respiratory Infections and Antibiotic Usage in Common Variable Immunodeficiency. J Allergy Clin Immunol Pract, 6, 159-168.e3.

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)

Ammann, A. J., Ashman, R. F. & Buckley, R. H. 1982. Use of intravenous gamma-globulin in antibody immunodeficiency: Results of a multicenter controlled trial. Clinical Immunology and Immunopathology, 22, 60-67.

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.

Bal, K., Kaluzinska-Parzyszek, I., Sobocinska, A., Podlecka, D., Jerzynska, J. & Stelmach, I. 2015. Efficacy and Safety of Hospital-Based Intravenous Immunoglobulin and Home-Based Self-Administered Subcutaneous Immunoglobulin in Polish Children with Primary Immunodeficiency Diseases. Indian J Pediatr, 82, 768-9.

Ballow, M., Berger, M., Bonilla, F. A., Buckley, R. H., Cunningham-Rundles, C. H., Fireman, P., Kaliner, M., Ochs, H. D., Skoda-Smith, S., Sweetser, M. T., Taki, H. & Lathia, C. 2003. Pharmacokinetics and tolerability of a new intravenous immunoglobulin preparation, IGIV-C, 10% (Gamunex, 10%). Vox Sang, 84, 202-10.

Berger, M., Murphy, E., Riley, P. & Bergman, G. E. 2010. Improved quality of life, immunoglobulin G levels, and infection rates in patients with primary immunodeficiency diseases during self-treatment with subcutaneous immunoglobulin G. South Med J, 103, 856-63.

Bernatowska, E., Madalinski, K. & Janowicz, W. 1987. Results of a prospective controlled two-dose crossover study with intravenous immunoglobulin and comparison (retrospective) with plasma treatment. Clinical Immunology and Immunopathology, 43, 153-162.

Bienvenu, B., Cozon, G., Hoarau, C., Pasquet, M., Cherin, P., Clerson, P., Hachulla, E., Crave, J. C., Delain, J. C. & Jaussaud, R. 2016. Does the route of immunoglobin replacement therapy impact quality of life and satisfaction in patients with primary immunodeficiency? Insights from the French cohort "Visages". Orphanet J Rare Dis, 11, 83.

Bienvenu, B., Cozon, G., Mataix, Y., Lachaud, D., Alix, A., Hoarau, C., Antier, D., Hachulla, E., Brice, S., Viallard, J. F., Tamisier, S., Fauchais, A. L., Renon-Carron, F., Clerson, P., Fardini, Y., Crave, J. C. & Miossec, P. 2018. Rapid Push vs Pump-Infused Subcutaneous Immunoglobulin Treatment: a Randomized Crossover Study of Quality of Life in Primary Immunodeficiency Patients. J Clin Immunol, 38, 503-512.

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.

Borte, M., Bernatowska, E., Ochs, H. D. & Roifman, C. M. 2011. Efficacy and safety of home-based subcutaneous immunoglobulin replacement therapy in paediatric patients with primary immunodeficiencies. Clin Exp Immunol, 164, 357-64.

Borte, M., Davies, S. V., Touraine, J. L., Farber, C. M., Lipsic, T., Adams, C., Spath, P., Bolli, R., Morell, A. & Andresen, I. 2004. Clinical properties of a novel liquid intravenous immunoglobulin: Studies in patients with immune thrombocytopenic purpura and primary immunodeficiencies. Transfusion Medicine and Hemotherapy, 31, 126-134.

Borte, M., Krivan, G., Derfalvi, B., Marodi, L., Harrer, T., Jolles, S., Bourgeois, C., Engl, W., Leibl, H., Mccoy, B., Gelmont, D. & Yel, L. 2017a. Efficacy, safety, tolerability and pharmacokinetics of a novel human immune globulin subcutaneous, 20%: a Phase 2/3 study in Europe in patients with primary immunodeficiencies. Clin Exp Immunol, 187, 146-159.

Borte, M., Melamed, I. R., Pulka, G., Pyringer, B., Knutsen, A. P., Ochs, H. D., Kobayashi, R. H., Kobayashi, A. L., Gupta, S., Strach, M., Smits, W., Pituch-Noworolska, A. & Moy, J. N. 2017b. Efficacy and Safety of Human Intravenous Immunoglobulin 10% (Panzyga(R)) in Patients with Primary Immunodeficiency Diseases: a Two-Stage, Multicenter, Prospective, Open-Label Study. J Clin Immunol, 37, 603-612.

Buckley, R. H. 1982. Long term use of intravenous immune globulin in patients with primary immunodeficiency diseases: inadequacy of current dosage practices and approaches to the problem. Journal of Clinical Immunology, 2, 15S-21S.

Canessa, C., Gallo, V., Pignata, C., Trizzino, A., Graziani, S., Martire, B., Moschese, V., Palladino, V., Boggia, G. M., Matucci, A., Pecoraro, A., Spadaro, G., Vultaggio, A. & Azzari, C. 2019. Subcutaneous Immunoglobulin Twenty Percent Every Two Weeks in Pediatric Patients with Primary Immunodeficiencies: Subcohort Analysis of the IBIS Study. Pediatr Allergy Immunol Pulmonol, 32, 70-75.

Canessa, C., Iacopelli, J., Pecoraro, A., Spadaro, G., Matucci, A., Milito, C., Vultaggio, A., Agostini, C., Cinetto, F., Danieli, M. G., Gambini, S., Marasco, C., Trizzino, A., Vacca, A., De Mattia, D., Martire, B.,

Plebani, A., Di Gioacchino, M., Gatta, A., Finocchi, A., Licciardi, F., Martino, S., De Carli, M., Moschese, V. & Azzari, C. 2017. Shift from intravenous or 16% subcutaneous replacement therapy to 20% subcutaneous immunoglobulin in patients with primary antibody deficiencies. Int J Immunopathol Pharmacol, 30, 73-82.

Chouksey, A., Duff, K., Wasserbauer, N. & Berger, M. 2005. Subcutaneous immunoglobulin-g replacement therapy with preparations currently available in the United States for intravenous or intramuscular use: reasons and regimens. Allergy Asthma Clin Immunol, 1, 120-30.

Cunningham-Rundles, C. 1985. Intravenous immune serum globulin in immunodeficiency. Vox Sang, 49 Suppl 1, 8-14.

Eijkhout, H. W., Van Der Meer, J. W. M., Kallenberg, C. G. M., Weening, R. S., Van Dissel, J. T., Sanders, L. a. M., Strengers, P. F. W., Nienhuis, H. & Schellekens, P. T. A. 2001. The effect of two different dosages of intravenous immunoglobulin on the incidence of recurrent infections in patients with primary hypogammaglobulinemia: A randomized, double-blind, multicenter crossover trial. Annals of Internal Medicine, 135, 165-174.

Espanol, T., Prevot, J., Drabwell, J., Sondhi, S. & Olding, L. 2014. Improving current immunoglobulin therapy for patients with primary immunodeficiency: quality of life and views on treatment. Patient Prefer Adherence, 8, 621-9.

Fasth, A. & Nystrom, J. 2007. Safety and efficacy of subcutaneous human immunoglobulin in children with primary immunodeficiency. Acta Paediatr, 96, 1474-8.

Fasth, A. & Nystrom, J. 2008. Quality of life and health-care resource utilization among children with primary immunodeficiency receiving home treatment with subcutaneous human immunoglobulin. J Clin Immunol, 28, 370-8.

Fu, L. W., Song, C., Isaranuwatchai, W. & Betschel, S. 2018. Home-based subcutaneous immunoglobulin therapy vs hospital-based intravenous immunoglobulin therapy: A prospective economic analysis. Ann Allergy Asthma Immunol, 120, 195-199.

Gardulf, A., Andersen, V., Bjorkander, J., Ericson, D., Froland, S. S., Gustafson, R., Hammarstrom, L., Jacobsen, M. B., Jonsson, E., Moller, G. & Et Al. 1995. Subcutaneous immunoglobulin replacement in patients with primary antibody deficiencies: safety and costs. Lancet, 345, 365-9.

Gardulf, A., Borte, M., Ochs, H. D. & Nicolay, U. 2008. Prognostic factors for health-related quality of life in adults and children with primary antibody deficiencies receiving SCIG home therapy. Clin Immunol, 126, 81-8.

Gardulf, A., Hammarstrom, L. & Smith, C. I. 1991. Home treatment of hypogammaglobulinaemia with subcutaneous gammaglobulin by rapid infusion. Lancet, 338, 162-6.

Gardulf, A., Nicolay, U., Asensio, O., Bernatowska, E., Bock, A., Carvalho, B. C., Granert, C., Haag, S., Hernandez, D., Kiessling, P., Kus, J., Pons, J., Niehues, T., Schmidt, S., Schulze, I. & Borte, M. 2006. Rapid subcutaneous IgG replacement therapy is effective and safe in children and adults with primary immunodeficiencies--a prospective, multi-national study. J Clin Immunol, 26, 177-85.

Gaspar, J., Gerritsen, B. & Jones, A. 1998. Immunoglobulin replacement treatment by rapid subcutaneous infusion. Arch Dis Child, 79, 48-51.

Gelfand, E. W. & Hanna, K. 2006. Safety and tolerability of increased rate of infusion of intravenous immunoglobulin G, 10% in antibody-deficient patients. J Clin Immunol, 26, 284-90.

Gupta, S., Stein, M., Hussain, I., Paris, K., Engl, W., Mccoy, B., Rabbat, C. J. & Yel, L. 2019. Tolerability of Ig20Gly during onboarding in patients with primary immunodeficiency diseases. Ann Allergy Asthma Immunol, 123, 271-279.e1.

Haddad, E., Berger, M., Wang, E. C., Jones, C. A., Bexon, M. & Baggish, J. S. 2012. Higher doses of subcutaneous IgG reduce resource utilization in patients with primary immunodeficiency. J Clin Immunol, 32, 281-9.

Hajjar, J., Kutac, C., Rider, N. L., Seeborg, F. O., Scalchunes, C. & Orange, J. 2018. Fatigue and the wear-off effect in adult patients with common variable immunodeficiency. Clin Exp Immunol, 194, 327-338.

Heimall, J., Chen, J., Church, J. A., Griffin, R., Melamed, I. & Kleiner, G. I. 2016. Pharmacokinetics, Safety, and Tolerability of Subcutaneous Immune Globulin Injection (Human), 10 % Caprylate/Chromatography Purified (GAMUNEX(R)-C) in Pediatric Patients with Primary Immunodeficiency Disease. J Clin Immunol, 36, 600-9.

Igarashi, A., Kanegane, H., Kobayashi, M., Miyawaki, T. & Tsutani, K. 2014. Cost-minimization analysis of IgPro20, a subcutaneous immunoglobulin, in Japanese patients with primary immunodeficiency. Clin Ther, 36, 1616-24.

Jolles, S., Bernatowska, E., De Gracia, J., Borte, M., Cristea, V., Peter, H. H., Belohradsky, B. H., Wahn, V., Neufang-Huber, J., Zenker, O. & Grimbacher, B. 2011. Efficacy and safety of Hizentra((R)) in patients with primary immunodeficiency after a dose-equivalent switch from intravenous or subcutaneous replacement therapy. Clin Immunol, 141, 90-102.

Jolles, S., Rojavin, M. A., Lawo, J. P., Nelson, R., Jr., Wasserman, R. L., Borte, M., Tortorici, M. A., Imai, K. & Kanegane, H. 2018. Long-Term Efficacy and Safety of Hizentra(R) in Patients with Primary Immunodeficiency in Japan, Europe, and the United States: a Review of 7 Phase 3 Trials. J Clin Immunol, 38, 864-875.

Kallenberg, C. G. 2007. A 10% ready-to-use intravenous human immunoglobulin offers potential economic advantages over a lyophilized product in the treatment of primary immunodeficiency. Clin Exp Immunol, 150, 437-41.

Kanegane, H., Imai, K., Yamada, M., Takada, H., Ariga, T., Bexon, M., Rojavin, M., Hu, W., Kobayashi, M., Lawo, J. P., Nonoyama, S., Hara, T. & Miyawaki, T. 2014. Efficacy and safety of IgPro20, a subcutaneous immunoglobulin, in Japanese patients with primary immunodeficiency diseases. J Clin Immunol, 34, 204-11.

Knutsen, A. P., Leiva, L. E., Caruthers, C., Rodrigues, J. & Sorensen, R. U. 2015. Streptococcus pneumoniae antibody titres in patients with primary antibody deficiency receiving intravenous immunoglobulin (IVIG) compared to subcutaneous immunoglobulin (SCIG). Clinical and Experimental Immunology, 182, 51-56.

Liese, J. G., Wintergerst, U., Tympner, K. D. & Belohradsky, B. H. 1992. High- vs low-dose immunoglobulin therapy in the long-term treatment of X-linked agammaglobulinemia. Am J Dis Child, 146, 335-9.

Mallick, R., Jolles, S., Kanegane, H., Agbor-Tarh, D. & Rojavin, M. 2018. Treatment Satisfaction with Subcutaneous Immunoglobulin Replacement Therapy in Patients with Primary Immunodeficiency: a Pooled Analysis of Six Hizentra(R) Studies. J Clin Immunol, 38, 886-897.

Melamed, I. R., Borte, M., Trawnicek, L., Kobayashi, A. L., Kobayashi, R. H., Knutsen, A., Gupta, S., Smits, W., Pituch-Noworolska, A., Strach, M., Pulka, G., Ochs, H. D. & Moy, J. N. 2018. Pharmacokinetics of a novel human intravenous immunoglobulin 10% in patients with primary immunodeficiency diseases: Analysis of a phase III, multicentre, prospective, open-label study. Eur J Pharm Sci, 118, 80-86.

Montanaro, A. & Pirofsky, B. 1984. Prolonged interval high-dose intravenous immunoglobulin in patients with primary immunodeficiency states. American Journal of Medicine, 76, 67-72.

Nicolay, U., Haag, S., Eichmann, F., Herget, S., Spruck, D. & Gardulf, A. 2005. Measuring treatment satisfaction in patients with primary immunodeficiency diseases receiving lifelong immunoglobulin replacement therapy. Qual Life Res, 14, 1683-91.

Nicolay, U., Kiessling, P., Berger, M., Gupta, S., Yel, L., Roifman, C. M., Gardulf, A., Eichmann, F., Haag, S., Massion, C. & Ochs, H. D. 2006. Health-related quality of life and treatment satisfaction in North American patients with primary immunedeficiency diseases receiving subcutaneous IgG self-infusions at home. J Clin Immunol, 26, 65-72.

Ochs, H. D., Fischer, S. H., Wedgwood, R. J., Wara, D. W., Cowan, M. J., Ammann, A. J., Saxon, A., Budinger, M. D., Allred, R. U. & Rousell, R. H. 1984. Comparison of high-dose and low-dose

intravenous immunoglobulin therapy in patients with primary immunodeficiency diseases. American Journal of Medicine, 76, 78-82.

Pasquet, M., Pellier, I., Aladjidi, N., Auvrignon, A., Cherin, P., Clerson, P., Cozon, G. J. N., Jaussaud, R., Bienvenu, B. & Hoarau, C. 2017. A cohort of French pediatric patients with primary immunodeficiencies: are patient preferences regarding replacement immunotherapy fulfilled in real-life conditions? Patient Prefer Adherence, 11, 1171-1180.

Pirofsky, B. 1987. Clinical use of a new pH 4.25 intravenous immunoglobulin preparation (gamimune-N). Journal of Infection, 15, 29-37.

Pirofsky, B., Campbell, S. M. & Montanaro, A. 1982. Individual patient variations in the kinetics of intravenous immune globulin administration. Journal of Clinical Immunology, 2, 7S-14S.

Pulvirenti, F., Cinetto, F., Pecoraro, A., Carrabba, M., Crescenzi, L., Neri, R., Bonanni, L., Fabio, G., Agostini, C., Spadaro, G., Tabolli, S., Farrugia, A., Quinti, I. & Milito, C. 2019. Health-Related Quality of Life in Patients with CVID Under Different Schedules of Immunoglobulin Administration: Prospective Multicenter Study. J Clin Immunol, 39, 159-170.

Rich, A. L., Le Jeune, I. R., Mcdermott, L. & Kinnear, W. J. 2008. Serial lung function tests in primary immune deficiency. Clin Exp Immunol, 151, 110-3.

Rider, N. L., Kutac, C., Hajjar, J., Scalchunes, C., Seeborg, F. O., Boyle, M. & Orange, J. S. 2017. Health-Related Quality of Life in Adult Patients with Common Variable Immunodeficiency Disorders and Impact of Treatment. J Clin Immunol, 37, 461-475.

Roifman, C. M., Levison, H. & Gelfand, E. W. 1987. High-dose versus low-dose intravenous immunoglobulin in hypogammaglobulinaemia and chronic lung disease. Lancet, 1, 1075-7.

Roifman, C. M., Schroeder, H., Berger, M., Sorensen, R., Ballow, M., Buckley, R. H., Gewurz, A., Korenblat, P., Sussman, G., Lemm, G., Stein, M., Stark, D., Ermitano, M. L., Desroches, A., Mazer, B., Church, J., Ballas, Z., Filipovich, A., Friday, G., Graffino, D., Haysman, M., Knutsen, A., Richmond, W., Rubinstein, A., Marquinez, F., Mcneil, D. & Skoda-Smith, S. 2003. Comparison of the efficacy of IGIV-C, 10% (caprylate/chromatography) and IGIV-SD, 10% as replacement therapy in primary immune deficiency: A randomized double-blind trial. International Immunopharmacology, 3, 1325-1333.

Sanford, M. 2014. Human immunoglobulin 10 % with recombinant human hyaluronidase: replacement therapy in patients with primary immunodeficiency disorders. BioDrugs, 28, 411-20.

Scheuerlein, P., Pietsch, L., Camacho-Ordonez, N., Reiser, V., Patel, S., Burns, S. O., Warnatz, K. & Grimbacher, B. 2018. Is It Safe to Switch From Intravenous Immunoglobulin to Subcutaneous Immunoglobulin in Patients With Common Variable Immunodeficiency and Autoimmune Thrombocytopenia? Front Immunol, 9, 1656.

Schiff, R. I., Sedlak, D. & Buckley, R. H. 1991. Rapid infusion of Sandoglobulin in patients with primary humoral immunodeficiency. Journal of Allergy and Clinical Immunology, 88, 61-67.

Shapiro, R. 2010. Subcutaneous immunoglobulin therapy by rapid push is preferred to infusion by pump: a retrospective analysis. J Clin Immunol, 30, 301-7.

Shapiro, R. 2013a. Subcutaneous immunoglobulin (16 or 20%) therapy in obese patients with primary immunodeficiency: a retrospective analysis of administration by infusion pump or subcutaneous rapid push. Clin Exp Immunol, 173, 365-71.

Shapiro, R. S. 2013b. Subcutaneous immunoglobulin therapy given by subcutaneous rapid push vs infusion pump: a retrospective analysis. Ann Allergy Asthma Immunol, 111, 51-5.

Shapiro, R. S. 2013c. Subcutaneous immunoglobulin: rapid push vs. infusion pump in pediatrics. Pediatr Allergy Immunol, 24, 49-53.

Sleasman, J. W., Duff, C. M., Dunaway, T., Rojavin, M. A. & Stein, M. R. 2010. Tolerability of a new 10% liquid immunoglobulin for intravenous use, Privigen, at different infusion rates. J Clin Immunol, 30, 442-8.

Sleasman, J. W., Lumry, W. R., Hussain, I., Wedner, H. J., Harris, J. B., Courtney, K. L., Mondou, E., Lin, J. & Stein, M. R. 2019. Immune globulin subcutaneous, human - klhw 20% for primary humoral immunodeficiency: an open-label, Phase III study. Immunotherapy, 11, 1371-1386.

Soler-Palacin, P., Gaso-Gago, I., Fernandez-Polo, A., Martin-Nalda, A., Oliveras, M., Martinez-Cutillas, J. & Figueras, C. 2014. Intravenous and subcutaneous immunoglobulin replacement: a two-way road. Optimizing healthcare quality in patients with primary immunodeficiencies. J Clin Immunol, 34, 1015-7.

Stubbs, A., Bangs, C., Shillitoe, B., Edgar, J. D., Burns, S. O., Thomas, M., Alachkar, H., Buckland, M., Mcdermott, E., Arumugakani, G., Jolles, M. S., Herriot, R. & Arkwright, P. D. 2018. Bronchiectasis and deteriorating lung function in agammaglobulinaemia despite immunoglobulin replacement therapy. Clinical and Experimental Immunology, 191, 212-219.

Suez, D., Stein, M., Gupta, S., Hussain, I., Melamed, I., Paris, K., Darter, A., Bourgeois, C., Fritsch, S., Leibl, H., Mccoy, B., Gelmont, D. & Yel, L. 2016. Efficacy, Safety, and Pharmacokinetics of a Novel Human Immune Globulin Subcutaneous, 20 % in Patients with Primary Immunodeficiency Diseases in North America. J Clin Immunol, 36, 700-12.

Thepot, S., Malphettes, M., Gardeur, A., Galicier, L., Asli, B., Karlin, L., Gerard, L., Laumont, R., Doize, M. L., Arnulf, B., Fieschi, C., Bengoufa, D. & Oksenhendler, E. 2010. Immunoglobulin dosage and switch from intravenous to subcutaneous immunoglobulin replacement therapy in patients with

primary hypogammaglobulinemia: decreasing dosage does not alter serum IgG levels. J Clin Immunol, 30, 602-6.

Viallard, J. F., Brion, J. P., Malphettes, M., Durieu, I., Gardembas, M., Schleinitz, N., Hoarau, C., Lazaro, E. & Puget, S. 2017. A multicentre, prospective, non-randomized, sequential, open-label trial to demonstrate the bioequivalence between intravenous immunoglobulin new generation (IGNG) and standard IV immunoglobulin (IVIG) in adult patients with primary immunodeficiency (PID). Rev Med Interne, 38, 578-584.

Wasserman, R. L., Irani, A. M., Tracy, J., Tsoukas, C., Stark, D., Levy, R., Chen, J., Sorrells, S., Roberts, R. & Gupta, S. 2010. Pharmacokinetics and safety of subcutaneous immune globulin (human), 10% caprylate/chromatography purified in patients with primary immunodeficiency disease. Clin Exp Immunol, 161, 518-26.

Wasserman, R. L., Ito, D., Xiong, Y., Ye, X., Bonnet, P. & Li-Mcleod, J. 2017a. Impact of Site of Care on Infection Rates Among Patients with Primary Immunodeficiency Diseases Receiving Intravenous Immunoglobulin Therapy. J Clin Immunol, 37, 180-186.

Wasserman, R. L., Melamed, I., Nelson, R. P., Jr., Knutsen, A. P., Fasano, M. B., Stein, M. R., Rojavin, M. A. & Church, J. A. 2011. Pharmacokinetics of subcutaneous IgPro20 in patients with primary immunodeficiency. Clin Pharmacokinet, 50, 405-14.

Wasserman, R. L., Melamed, I. R., Stein, M. R., Jolles, S., Norton, M. & Moy, J. N. 2017b. Evaluation of the Safety, Tolerability, and Pharmacokinetics of Gammaplex 10% Versus Gammaplex 5% in Subjects with Primary Immunodeficiency. Journal of Clinical Immunology, 37, 301-310.

Wasserman, R. L., Stein, M. R., Younger, M. E. M., Fatteh, S. & Haddad, E. 2016. 20% subcutaneous immunoglobulin dosed biweekly for primary immunodeficiency. Annals of Allergy, Asthma and Immunology, 117, 93-94.

SINGLE ARM STUDIES ON PID OTHER THAN CVID (N = 164)

Abbott, J. K. & Church, J. A. 2010. In vivo assessment of clinically relevant autoantibodies in intravenous immunoglobulin preparations. Pediatric, Allergy, Immunology, and Pulmonology, 23, 121-123.

Adam, E. & Church, J. A. 2015. Antibody levels to Bordetella pertussis and Neisseria meningitidis in immunodeficient patients receiving immunoglobulin replacement therapy. J Clin Immunol, 35, 213-7.

Aghamohammadi, A., Moin, M., Farhoudi, A., Rezaei, N., Pourpak, Z., Movahedi, M., Gharagozlou, M., Nabavi, M. & Shahrokhi, A. 2004. Efficacy of intravenous immunoglobulin on the prevention of pneumonia in patients with agammaglobulinemia. FEMS Immunol Med Microbiol, 40, 113-8.

Aiuti, F., Businco, L., Fiorilli, M., Galli, E., Quinti, I., Le Moli, S., Seminara, R. & Goldstein, G. 1983a. Therapy with thymopoietin pentapeptide (TP-5) in 25 patients with primary immunodeficiencies. Birth Defects: Original Article Series, 19, 267-272.

Aiuti, F., Businco, L., Fiorilli, M., Galli, E., Quinti, I., Rossi, P., Seminara, R. & Goldstein, G. 1983b. Thymopoietin pentapeptide treatment of primary immunodeficiencies. Lancet, 1, 551-555.

Al-Herz, W., Zainal, M. E., Alenezi, H. M., Husain, K. & Alshemmari, S. H. 2010. Performance status and deaths among children registered in Kuwait National Primary ImmunoDeficiency Disorders Registry. Asian Pac J Allergy Immunol, 28, 141-6.

Al-Saud, B., Al-Mousa, H., Al Gazlan, S., Al-Ghonaium, A., Arnaout, R., Al-Seraihy, A., Elshorbagi, S., Elsayed, N., Afzal, J., Al-Dhekri, H. & Al-Muhsen, S. 2015. Primary Immunodeficiency Diseases in Saudi Arabia: a Tertiary Care Hospital Experience over a Period of Three Years (2010-2013). Journal of Clinical Immunology, 35, 651-660.

Al-Saud, B. K., Al-Sum, Z., Alassiri, H., Al-Ghonaium, A., Al-Muhsen, S., Al-Dhekri, H., Arnaout, R., Alsmadi, O., Borrero, E., Abu-Staiteh, A., Rawas, F., Al-Mousa, H. & Hawwari, A. 2013. Clinical, immunological, and molecular characterization of Hyper-IgM syndrome due to CD40 deficiency in eleven patients. Journal of Clinical Immunology, 33, 1325-1335.

Al-Tamemi, S., Elnour, I. & Dennison, D. 2012. Primary immunodeficiency diseases in oman: Five years' experience at sultan qaboos university hospital. World Allergy Organization Journal, 5, 52-56.

Alangari, A., Abutaleb, M., Albarraq, A. & Al-Dhowailie, A. 2008. Immediate adverse reactions of intravenous immunoglobulins. Current Pediatric Research, 12, 31-34.

Albert, M. H., Bittner, T. C., Nonoyama, S., Notarangelo, L. D., Burns, S., Imai, K., Espanol, T., Fasth, A., Pellier, I., Strauss, G., Morio, T., Gathmann, B., Noordzij, J. G., Fillat, C., Hoenig, M., Nathrath, M., Meindl, A., Pagel, P., Wintergerst, U., Fischer, A., Thrasher, A. J., Belohradsky, B. H. & Ochs, H. D. 2010. X-linked thrombocytopenia (XLT) due to WAS mutations: clinical characteristics, long-term outcome, and treatment options. Blood, 115, 3231-8.

Alyanakian, M. A., Bernatowska, E., Scherrmann, J. M., Aucouturier, P. & Poplavsky, J. L. 2003. Pharmacokinetics of total immunoglobulin G and immunoglobulin G subclasses in patients undergoing replacement therapy for primary immunodeficiency syndromes. Vox Sang, 84, 188-92.

Amayiri, N., Al-Zaben, A., Ghatasheh, L., Frangoul, H. & Hussein, A. A. 2013. Hematopoietic stem cell transplantation for children with primary immunodeficiency diseases: Single center experience in Jordan. Pediatric Transplantation, 17, 394-402.

Ameratunga, R., Sinclair, J. & Kolbe, J. 2004. Increased risk of adverse events when changing intravenous immunoglobulin preparations. Clin Exp Immunol, 136, 111-3.

Amos, C. L., Ensom, M. H. H., Pi, D. & Schellenberg, R. R. 2005. A prospective, two-phase study of intravenous immunoglobin (IVIG) in hypogammaglobulinemia: Pharmacokinetic characterization and a dosing nomogram. Canadian Journal of Hospital Pharmacy, 58, 71-78.

Aukrust, P., Froland, S. S., Liabakk, N. B., Muller, F., Nordoy, I., Haug, C. & Espevik, T. 1994. Release of cytokines, soluble cytokine receptors, and interleukin-1 receptor antagonist after intravenous immunoglobulin administration in vivo. Blood, 84, 2136-43.

Ballow, M., Pinciaro, P. J., Craig, T., Kleiner, G., Moy, J., Ochs, H. D., Sleasman, J. & Smits, W. 2016a. Flebogamma((R)) 5 % DIF Intravenous Immunoglobulin for Replacement Therapy in Children with Primary Immunodeficiency Diseases. J Clin Immunol, 36, 583-9.

Ballow, M., Pinciaro, P. J., Craig, T., Kleiner, G., Moy, J., Ochs, H. D., Sleasman, J. & Smits, W. 2016b. Flebogamma 5 % DIF Intravenous Immunoglobulin for Replacement Therapy in Children with Primary Immunodeficiency Diseases. Journal of Clinical Immunology, 36, 583-589.

Banatvala, N., Davies, J., Kanariou, M., Strobel, S., Levinsky, R. & Morgan, G. 1994. Hypogammaglobulinaemia associated with normal or increased IgM (the hyper IgM syndrome): a case series review. Arch Dis Child, 71, 150-2.

Barlogis, V., Mahlaoui, N., Auquier, P., Fouyssac, F., Pellier, I., Vercasson, C., Allouche, M., De Azevedo, C. B., Moshous, D., Neven, B., Pasquet, M., Jeziorski, E., Aladjidi, N., Thomas, C., Gandemer, V., Mazingue, F., Picard, C., Blanche, S., Michel, G. & Fischer, A. 2018. Burden of Poor Health Conditions and Quality of Life in 656 Children with Primary Immunodeficiency. Journal of Pediatrics, 194, 211-217.e5.

Berger, M. 2007. A multicenter, prospective, open label, historically controlled clinical trial to evaluate efficacy and safety in primary immunodeficiency diseases (PID) patients of Flebogamma 5% DIF, the next generation of Flebogamma. J Clin Immunol, 27, 628-33.

Berger, M., Pinciaro, P. J., Althaus, A., Ballow, M., Chouksey, A., Moy, J., Ochs, H. & Stein, M. 2010. Efficacy, pharmacokinetics, safety, and tolerability of Flebogamma 10% DIF, a high-purity human intravenous immunoglobulin, in primary immunodeficiency. J Clin Immunol, 30, 321-9.

Bernatowska, E., Madalinski, K., Michalkiewicz, J. & Gregorek, H. 1988. Primary immunodeficiency diseases in children treated in the Children's Memorial Hospital, Poland. Immunological Investigations, 17, 107-120.

Bhattacharya, A., Slatter, M. A., Chapman, C. E., Barge, D., Jackson, A., Flood, T. J., Abinun, M., Cant, A. J. & Gennery, A. R. 2005. Single centre experience of umbilical cord stem cell transplantation for primary immunodeficiency. Bone Marrow Transplant, 36, 295-9.

Bjorkander, J., Nikoskelainen, J., Leibl, H., Lanbeck, P., Wallvik, J., Lumio, J. T., Braconier, J. H., Pavlova, B. G., Birthistle, K., Engl, W., Walter, S. & Ehrlich, H. J. 2006. Prospective open-label study of pharmacokinetics, efficacy and safety of a new 10% liquid intravenous immunoglobulin in patients with hypo- or agammaglobulinemia. Vox Sang, 90, 286-93.

Bjorkander, J., Wadsworth, C. & Hanson, L. A. 1985. 1040 prophylactic infusions with an unmodified intravenous immunoglobulin product causing few side-effects in patients with antibody deficiency syndromes. Infection, 13, 102-110.

Borte, M., Pac, M., Serban, M., Gonzalez-Quevedo, T., Grimbacher, B., Jolles, S., Zenker, O., Neufang-Hueber, J. & Belohradsky, B. 2011a. Efficacy and safety of hizentra(R), a new 20% immunoglobulin preparation for subcutaneous administration, in pediatric patients with primary immunodeficiency. J Clin Immunol, 31, 752-61.

Borte, M., Pac, M., Serban, M., Gonzalez-Quevedo, T., Grimbacher, B., Jolles, S., Zenker, O., Neufang-Hueber, J. & Belohradsky, B. 2011b. Efficacy and safety of Hizentra, a new 20% immunoglobulin preparation for subcutaneous administration, in pediatric patients with primary immunodeficiency. Journal of Clinical Immunology, 31, 752-761.

Borte, M., Quinti, I., Soresina, A., Fernandez-Cruz, E., Ritchie, B., Schmidt, D. S. & Mccusker, C. 2011c. Efficacy and safety of subcutaneous vivaglobin(R) replacement therapy in previously untreated patients with primary immunodeficiency: a prospective, multicenter study. J Clin Immunol, 31, 952-61.

Bortin, M. M. & Rimm, A. A. 1977. Severe combined immunodeficiency disease. Characterization of the disease and results of transplantation. Jama, 238, 591-600.

Brennan, V. M., Cochrane, S., Fletcher, C., Hendy, D. & Powell, P. 1995. Surveillance of adverse reactions in patients self-infusing intravenous immunoglobulin at home. J Clin Immunol, 15, 116-9.

Brennan, V. M., Salome-Bentley, N. J. & Chapel, H. M. 2003. Prospective audit of adverse reactions occurring in 459 primary antibody-deficient patients receiving intravenous immunoglobulin. Clin Exp Immunol, 133, 247-51.

Brent, J., Guzman, D., Bangs, C., Grimbacher, B., Fayolle, C., Huissoon, A., Bethune, C., Thomas, M., Patel, S., Jolles, S., Alachkar, H., Kumaratne, D., Baxendale, H., Edgar, J. D., Helbert, M., Hambleton, S. & Arkwright, P. D. 2016. Clinical and laboratory correlates of lung disease and cancer in adults with idiopathic hypogammaglobulinaemia. Clin Exp Immunol, 184, 73-82.

Bryan, B. A., Battersby, A., Shillitoe, B. M., Barge, D., Bourne, H., Flood, T., Cant, A. J., Stroud, C. & Gennery, A. R. 2016. Respiratory Health and Related Quality of Life in Patients with Congenital Agammaglobulinemia in the Northern Region of the UK. J Clin Immunol, 36, 472-9.

Buckley, R. H., Schiff, S. E., Schiff, R. I., Markert, L., Williams, L. W., Roberts, J. L., Myers, L. A. & Ward, F. E. 1999. Hematopoietic stem-cell transplantation for the treatment of severe combined immunodeficiency. N Engl J Med, 340, 508-16.

Buckley, R. H., Schiff, S. E., Schiff, R. I., Roberts, J. L., Markert, M. L., Peters, W., Williams, L. W. & Ward, F. E. 1993. Haploidentical bone marrow stem cell transplantation in human severe combined immunodeficiency. Semin Hematol, 30, 92-101; discussion 102-4.

Burroughs, L. M., Storb, R., Leisenring, W. M., Pulsipher, M. A., Loken, M. R., Torgerson, T. R., Ochs, H. D. & Woolfrey, A. E. 2007. Intensive postgrafting immune suppression combined with nonmyeloablative conditioning for transplantation of HLA-identical hematopoietic cell grafts: Results of a pilot study for treatment of primary immunodeficiency disorders. Bone Marrow Transplantation, 40, 633-642.

Cavazzana-Calvo, M., Hacein-Bey, S., De Saint Basile, G., Gross, F., Yvon, E., Nusbaum, P., Selz, F., Hue, C., Certain, S., Casanova, J. L., Bousso, P., Deist, F. L. & Fischer, A. 2000. Gene therapy of human severe combined immunodeficiency (SCID)-X1 disease. Science, 288, 669-72.

Chun, J. K., Lee, T. J., Song, J. W., Linton, J. A. & Kim, D. S. 2008. Analysis of clinical presentations of Bruton disease: a review of 20 years of accumulated data from pediatric patients at Severance Hospital. Yonsei Med J, 49, 28-36.

Church, J. A., Borte, M., Taki, H., Nelson, R. P., Sleasman, J. W., Knutsen, A. P., Le Gall, E., Debre, M. & Kiessling, P. 2009. Efficacy and safety of privigen in children and adolescents with primary immunodeficiency. Pediatric Asthma, Allergy and Immunology, 22, 53-61.

Church, J. A., Leibl, H., Stein, M. R., Melamed, I. R., Rubinstein, A., Schneider, L. C., Wasserman, R. L., Pavlova, B. G., Birthistle, K., Mancini, M., Fritsch, S., Patrone, L., Moore-Perry, K. & Ehrlich, H. J. 2006. Efficacy, safety and tolerability of a new 10% liquid intravenous immune globulin [IGIV 10%] in patients with primary immunodeficiency. J Clin Immunol, 26, 388-95.

Cicalese, M. P., Ferrua, F., Castagnaro, L., Pajno, R., Barzaghi, F., Giannelli, S., Dionisio, F., Brigida, I., Bonopane, M., Casiraghi, M., Tabucchi, A., Carlucci, F., Grunebaum, E., Adeli, M., Bredius, R. G., Puck,

J. M., Stepensky, P., Tezcan, I., Rolfe, K., De Boever, E., Reinhardt, R. R., Appleby, J., Ciceri, F., Roncarolo, M. G. & Aiuti, A. 2016. Update on the safety and efficacy of retroviral gene therapy for immunodeficiency due to adenosine deaminase deficiency. Blood, 128, 45-54.

Costa-Carvalho, B. T., Sullivan, K. E., Fontes, P. M., Aime-Nobre, F., Gonzales, I. G. S., Lima, E. S., Granato, C. & De Moraes-Pinto, M. I. 2018. Low Rates of Poliovirus Antibodies in Primary Immunodeficiency Patients on Regular Intravenous Immunoglobulin Treatment. J Clin Immunol, 38, 628-634.

Dash, C., Gascoigne, E., Gillanders, K. & Gooi, H. 2015a. Experience with Subgam, a Subcutaneously Administered Human Normal Immunoglobulin (ClinicalTrials.gov--NCT02247141). PLoS One, 10, e0131565.

Dash, C., Gascoigne, E., Gillanders, K. & Gooi, H. 2015b. Experience with subgam, a subcutaneously administered human normal immunoglobulin (ClinicalTrials.gov - NCT02247141). PLoS ONE, 10 (7) (no pagination).

Davies, E. G., Cheung, M., Gilmour, K., Maimaris, J., Curry, J., Furmanski, A., Sebire, N., Halliday, N., Mengrelis, K., Adams, S., Bernatoniene, J., Bremner, R., Browning, M., Devlin, B., Erichsen, H. C., Gaspar, H. B., Hutchison, L., Ip, W., Ifversen, M., Leahy, T. R., Mccarthy, E., Moshous, D., Neuling, K., Pac, M., Papadopol, A., Parsley, K. L., Poliani, L., Ricciardelli, I., Sansom, D. M., Voor, T., Worth, A., Crompton, T., Markert, M. L. & Thrasher, A. J. 2017. Thymus transplantation for complete DiGeorge syndrome: European experience. J Allergy Clin Immunol, 140, 1660-1670.e16.

Debes, A., Bauer, M. & Kremer, S. 2007. Tolerability and safety of the intravenous immunoglobulin Octagam: A 10-year prospective observation study. Pharmacoepidemiology and Drug Safety, 16, 1038-1047.

Diaz De Heredia, C., Ortega, J. J., Diaz, M. A., Olive, T., Badell, I., Gonzalez-Vicent, M. & Sanchez De Toledo, J. 2008. Unrelated cord blood transplantation for severe combined immunodeficiency and other primary immunodeficiencies. Bone Marrow Transplant, 41, 627-33.

Dimitrova, D., Gea-Banacloche, J., Steinberg, S. M., Sadler, J. L., Hicks, S. N., Carroll, E., Wilder, J. S., Parta, M., Skeffington, L., Hughes, T. E., Blau, J. E., Broadney, M. M., Rose, J. J., Hsu, A. P., Fletcher, R., Nunes, N. S., Yan, X. Y., Telford, W. G., Kapoor, V., Cohen, J. I., Freeman, A. F., Garabedian, E., Holland, S. M., Lisco, A., Malech, H. L., Notarangelo, L. D., Sereti, I., Shah, N. N., Uzel, G., Zerbe, C. S., Fowler, D. H., Gress, R. E., Kanakry, C. G. & Kanakry, J. A. 2019. Prospective Study of a Novel, Radiation-Free, Reduced-Intensity Bone Marrow Transplantation Platform for Primary Immunodeficiency Diseases. Biol Blood Marrow Transplant.

Dinardo, L., Brown, V., Perez, E., Bunin, N. & Sullivan, K. E. 2012. A single-center study of hematopoietic stem cell transplantation for primary immune deficiencies (PIDD). Pediatr Transplant, 16, 63-72.

Dorsey, M. J., Ho, V., Mabudian, M., Soler-Palacin, P., Dominguez-Pinilla, N., Rishi, R., Rishi, R., Wong, D., Rojavin, M., Hubsch, A. & Berger, M. 2014. Clinical experience with an L-proline-stabilized 10 %intravenous immunoglobulin (Privigen(R)): real-life effectiveness and tolerability. J Clin Immunol, 34, 804-12.

Duse, M., Iacobini, M., Leonardi, L., Smacchia, P., Antonetti, L. & Giancane, G. 2010. Transient hypogammaglobulinemia of infancy: intravenous immunoglobulin as first line therapy. Int J Immunopathol Pharmacol, 23, 349-53.

Eibl, M. M., Cairns, L. & Rosen, F. S. 1984. Safety and efficacy of a monomeric, functionally intact intravenous IgG preparation in patients with primary immunodeficiency syndromes. Clinical Immunology and Immunopathology, 31, 151-160.

Elfeky, R., Shah, R. M., Unni, M. N. M., Ottaviano, G., Rao, K., Chiesa, R., Amrolia, P., Worth, A., Flood, T., Abinun, M., Hambleton, S., Cant, A. J., Gilmour, K., Adams, S., Ahsan, G., Barge, D., Gennery, A. R., Qasim, W., Slatter, M. & Veys, P. 2019. New graft manipulation strategies improve the outcome of mismatched stem cell transplantation in children with primary immunodeficiencies. Journal of Allergy and Clinical Immunology, 144, 280-293.

Elfeky, R. A., Furtado-Silva, J. M., Chiesa, R., Rao, K., Amrolia, P., Lucchini, G., Gilmour, K., Adams, S., Bibi, S., Worth, A., Thrasher, A. J., Qasim, W. & Veys, P. 2018. One hundred percent survival after transplantation of 34 patients with Wiskott-Aldrich syndrome over 20 years. Journal of Allergy and Clinical Immunology, 142, 1654-1656.e7.

Empson, M. B., Tang, M. L. K., Pearce, L. K. C., Rozen, L., Gold, M. S., Katelaris, C. H., Langton, D., Smart, J., Smith, W. B., Steele, R. H., Ziegler, J. B. & Maher, D. 2012. Efficacy, safety and pharmacokinetics of a novel subcutaneous immunoglobulin, evogam, in primary immunodeficiency. Journal of Clinical Immunology, 32, 897-906.

Ferrua, F., Cicalese, M. P., Galimberti, S., Giannelli, S., Dionisio, F., Barzaghi, F., Migliavacca, M., Bernardo, M. E., Calbi, V., Assanelli, A. A., Facchini, M., Fossati, C., Albertazzi, E., Scaramuzza, S., Brigida, I., Scala, S., Basso-Ricci, L., Pajno, R., Casiraghi, M., Canarutto, D., Salerio, F. A., Albert, M. H., Bartoli, A., Wolf, H. M., Fiori, R., Silvani, P., Gattillo, S., Villa, A., Biasco, L., Dott, C., Culme-Seymour, E. J., Van Rossem, K., Atkinson, G., Valsecchi, M. G., Roncarolo, M. G., Ciceri, F., Naldini, L. & Aiuti, A. 2019. Lentiviral haemopoietic stem/progenitor cell gene therapy for treatment of Wiskott-Aldrich syndrome: interim results of a non-randomised, open-label, phase 1/2 clinical study. Lancet Haematol, 6, e239-e253.

Fox, T. A., Chakraverty, R., Burns, S., Carpenter, B., Thomson, K., Lowe, D., Fielding, A., Peggs, K., Kottaridis, P., Uttenthal, B., Bigley, V., Buckland, M., Grandage, V., Denovan, S., Grace, S., Dahlstrom, J., Workman, S., Symes, A., Mackinnon, S., Hough, R. & Morris, E. 2018. Successful outcome following allogeneic hematopoietic stem cell transplantation in adults with primary immunodeficiency. Blood, 131, 917-931.

Gill, P. K. & Betschel, S. D. 2018. Timing of infections in patients with primary immunodeficiencies treated with intravenous immunoglobulin (IVIg). Allergy Asthma Clin Immunol, 14, 35.

Gustafson, R., Gardulf, A., Hansen, S., Leibl, H., Engl, W., Linden, M., Muller, A. & Hammarstrom, L. 2008. Rapid subcutaneous immunoglobulin administration every second week results in high and stable serum immunoglobulin G levels in patients with primary antibody deficiencies. Clin Exp Immunol, 152, 274-9.

Hacein-Bey-Abina, S., Fischer, A. & Cavazzana-Calvo, M. 2002. Gene therapy of X-linked severe combined immunodeficiency. Int J Hematol, 76, 295-8.

Haddad, E., Le Deist, F., Aucouturier, P., Cavazzana-Calvo, M., Blanche, S., De Saint Basile, G. & Fischer, A. 1999. Long-term chimerism and B-cell function after bone marrow transplantation in patients with severe combined immunodeficiency with B cells: A single-center study of 22 patients. Blood, 94, 2923-30.

Haddad, E., Logan, B. R., Griffith, L. M., Buckley, R. H., Parrott, R. E., Prockop, S. E., Small, T. N., Chaisson, J., Dvorak, C. C., Murnane, M., Kapoor, N., Abdel-Azim, H., Hanson, I. C., Martinez, C., Bleesing, J. J. H., Chandra, S., Smith, A. R., Cavanaugh, M. E., Jyonouchi, S., Sullivan, K. E., Burroughs, L., Skoda-Smith, S., Haight, A. E., Tumlin, A. G., Quigg, T. C., Taylor, C., Davila Saldana, B. J., Keller, M. D., Seroogy, C. M., Desantes, K. B., Petrovic, A., Leiding, J. W., Shyr, D. C., Decaluwe, H., Teira, P., Gillio, A. P., Knutsen, A. P., Moore, T. B., Kletzel, M., Craddock, J. A., Aquino, V., Davis, J. H., Yu, L. C., Cuvelier, G. D. E., Bednarski, J. J., Goldman, F. D., Kang, E. M., Shereck, E., Porteus, M. H., Connelly, J. A., Fleisher, T. A., Malech, H. L., Shearer, W. T., Szabolcs, P., Thakar, M. S., Vander Lugt, M. T., Heimall, J., Yin, Z., Pulsipher, M. A., Pai, S. Y., Kohn, D. B., Puck, J. M., Cowan, M. J., O'reilly, R. J. & Notarangelo, L. D. 2018. SCID genotype and 6-month posttransplant CD4 count predict survival and immune recovery. Blood, 132, 1737-1749.

Hadzic, N., Nademi, Z., Deheragoda, M., Zen, Y., Elfeky, R., Worth, A., Veys, P., Mieli-Vergani, G. & Davies, E. G. 2019. Chronic Cholangiopathy Associated with Primary Immune Deficiencies Can Be Resolved by Effective Hematopoietic Stem Cell Transplantation. Journal of Pediatrics, 209, 97-106.e2.

Hagan, J. B., Fasano, M. B., Spector, S., Wasserman, R. L., Melamed, I., Rojavin, M. A., Zenker, O. & Orange, J. S. 2010. Efficacy and safety of a new 20% immunoglobulin preparation for subcutaneous administration, IgPro20, in patients with primary immunodeficiency. J Clin Immunol, 30, 734-45.

Hamidieh, A. A., Behfar, M., Pourpak, Z., Faghihi-Kashani, S., Fazlollahi, M. R., Hosseini, A. S., Movahedi, M., Mozafari, M., Moin, M. & Ghavamzadeh, A. 2016. Long-term outcomes of fludarabine, melphalan and antithymocyte globulin as reduced-intensity conditioning regimen for allogeneic hematopoietic stem cell transplantation in children with primary immunodeficiency disorders: a prospective single center study. Bone Marrow Transplant, 51, 219-26.

Horn, B., Viele, M., Mentzer, W., Mogck, N., Desantes, K. & Cowan, M. 1999. Autoimmune hemolytic anemia in patients with SCID after T cell-depleted BM and PBSC transplantation. Bone Marrow Transplant, 24, 1009-13.

Ikinciogullari, A., Cagdas, D., Dogu, F., Tugrul, T., Karasu, G., Haskologlu, S., Aksoylar, S., Uygun, V., Kupesiz, A., Yildiran, A., Gursel, O., Ates, C., Elhan, A., Kansoy, S., Yesilipek, A. & Tezcan, I. 2019. Clinical Features and HSCT Outcome for SCID in Turkey. J Clin Immunol, 39, 316-323.

Imbach, P., Perret, B. A., Babington, R., Kaminski, K., Morell, A. & Heiniger, H. J. 1991. Safety of intravenous immunoglobulin preparations: a prospective multicenter study to exclude the risk of non-A, non-B hepatitis. Vox Sang, 61, 240-3.

Jolles, S., Borte, M., Nelson, R. P., Jr., Rojavin, M., Bexon, M., Lawo, J. P. & Wasserman, R. L. 2014. Long-term efficacy, safety, and tolerability of Hizentra(R) for treatment of primary immunodeficiency disease. Clin Immunol, 150, 161-9.

Kane, L., Gennery, A. R., Crooks, B. N., Flood, T. J., Abinun, M. & Cant, A. J. 2001. Neonatal bone marrow transplantation for severe combined immunodeficiency. Arch Dis Child Fetal Neonatal Ed, 85, F110-3.

Kayan Ocakoglu, B., Karaca, N. E., Ocakoglu, F. T. & Erermis, S. 2018. Psychological burden of pediatric primary immunodeficiency. Pediatr Int, 60, 911-917.

Kearns, S., Kristofek, L., Bolgar, W., Seidu, L. & Kile, S. 2017. Clinical Profile, Dosing, and Quality-of-Life Outcomes in Primary Immune Deficiency Patients Treated at Home with Immunoglobulin G: Data from the IDEaL Patient Registry. J Manag Care Spec Pharm, 23, 400-406.

Knutsen, A. P., Kelly, M. E. & Wall, D. A. 2005. Umbilical cord blood stem cell transplantation in severe T-cell immunodeficiency disorders. Pediatric Asthma, Allergy and Immunology, 18, 189-200.

Kobayashi, N., Gohya, N. & Matsumoto, S. 1981. Clinical trial of sulfonated immunoglobulin preparation for intravenous administration. I. Replacement therapy for primary immunodeficiency syndromes. European Journal of Pediatrics, 136, 159-165.

Kobayashi, R., Ariga, T., Nonoyama, S., Kanegane, H., Tsuchiya, S., Morio, T., Yabe, H., Nagatoshi, Y., Kawa, K., Tabuchi, K., Tsuchida, M., Miyawaki, T. & Kato, S. 2006. Outcome in patients with Wiskott-

Aldrich syndrome following stem cell transplantation: an analysis of 57 patients in Japan. Br J Haematol, 135, 362-6.

Kobayashi, R. H., Gupta, S., Melamed, I., Mandujano, J. F., Kobayashi, A. L., Ritchie, B., Geng, B., Atkinson, T. P., Rehman, S., Turpel-Kantor, E. & Litzman, J. 2019. Clinical efficiency, safety and tolerability of a new subcutaneous immunoglobin 16.5% (octanorm cutaquig in the treatment of patients with primary immunodefieciencies. Frontiers in Immunology, 10 (FEB) (no pagination).

Kobayashi, R. H., Kobayashi, A. D., Lee, N., Fischer, S. & Ochs, H. D. 1990. Home self-administration of intravenous immunoglobulin therapy in children. Pediatrics, 85, 705-9.

Krasovec, S., Ornani, A., Oleastro, M., Rosenzweig, S., Roy, A., Perez, L., Campos, G., Marin, N., Martinez, A., Mahieu, C., Manfredi, M. J., Sisti, A. & Zelazko, M. 2007. Efficacy and tolerability of an argentine intravenous immunoglobulin in pediatric patients with primary immunodeficiency diseases. J Clin Immunol, 27, 227-32.

Kratka, Z., Bartova, J., Krystufkova, O., Benetkova, K., Mrklas, L. & Fucikova, T. 2002. Effect of intravenous immunoglobulins on in vitro immunoglobulin formation in patients with antibody immunodeficiency. Apmis, 110, 205-13.

Kreuz, W., Erdos, M., Rossi, P., Bernatowska, E., Espanol, T. & Marodi, L. 2010. A multi-centre study of efficacy and safety of Intratect(R), a novel intravenous immunoglobulin preparation. Clin Exp Immunol, 161, 512-7.

Krivan, G., Chernyshova, L., Kostyuchenko, L., Lange, A., Nyul, Z., Derfalvi, B., Musial, J., Bellon, A., Kappler, M., Sadoun, A. & Bernatowska, E. 2017. A Multicentre Study on the Efficacy, Safety and Pharmacokinetics of IqYmune(R), a Highly Purified 10% Liquid Intravenous Immunoglobulin, in Patients with Primary Immune Deficiency. J Clin Immunol, 37, 539-547.

Krivan, G., Konigs, C., Bernatowska, E., Salama, A., Wartenberg-Demand, A., Sonnenburg, C. & Linde, R. 2015. An open, prospective trial investigating the pharmacokinetics and safety, and the tolerability of escalating infusion rates of a 10% human normal immunoglobulin for intravenous infusion (IVIg), BT090, in patients with primary immunodeficiency disease. Vox Sang, 109, 248-56.

Levy, J., Espanol-Boren, T., Thomas, C., Fischer, A., Tovo, P., Bordigoni, P., Resnick, I., Fasth, A., Baer, M., Gomez, L., Sanders, E. a. M., Tabone, M. D., Plantaz, D., Etzioni, A., Monafo, V., Abinun, M., Hammarstrom, L., Abrahamsen, T., Jones, A., Finn, A., Klemola, T., Devries, E., Sanal, O., Peitsch, M. C. & Notarangelo, L. D. 1997. Clinical spectrum of X-linked hyper-IgM syndrome. Journal of Pediatrics, 131, 47-54.

Lin, M., Epport, K., Azen, C., Parkman, R., Kohn, D. B. & Shah, A. J. 2009. Long-term neurocognitive function of pediatric patients with severe combined immune deficiency (SCID): pre- and post-hematopoietic stem cell transplant (HSCT). J Clin Immunol, 29, 231-7.

Lush, R. J., Haynes, A. P., Byrne, J., Cull, G. M., Carter, G. I., Pagliuca, A., Parker, J. E., Mufti, G., Mahendra, P., Craddock, C. F., Lui Yin, J. A., Garg, M., Prentice, H. G., Potter, M. N. & Russell, N. H. 2001. Allogeneic stem-cell transplantation for lymphoproliferative disorders using BEAM-CAMPATH (+/- fludarabine) conditioning combined with post-transplant donor-lymphocyte infusion. Cytotherapy, 3, 203-10.

Mahlaoui, N., Pellier, I., Mignot, C., Jais, J. P., Bilhou-Nabera, C., Moshous, D., Neven, B., Picard, C., De Saint-Basile, G., Cavazzana-Calvo, M., Blanche, S. & Fischer, A. 2013. Characteristics and outcome of early-onset, severe forms of Wiskott-Aldrich syndrome. Blood, 121, 1510-1516.

Manor, U., Lev, A., Simon, A. J., Hutt, D., Toren, A., Bielorai, B., Goldberg, L., Stauber, T. & Somech, R. 2019. Immune reconstitution after HSCT in SCID-a cohort of conditioned and unconditioned patients. Immunol Res, 67, 166-175.

Markert, M. L., Devlin, B. H., Alexieff, M. J., Li, J., Mccarthy, E. A., Gupton, S. E., Chinn, I. K., Hale, L. P., Kepler, T. B., He, M., Sarzotti, M., Skinner, M. A., Rice, H. E. & Hoehner, J. C. 2007. Review of 54 patients with complete DiGeorge anomaly enrolled in protocols for thymus transplantation: Outcome of 44 consecutive transplants. Blood, 109, 4539-4547.

Markert, M. L., Sarzotti, M., Ozaki, D. A., Sempowski, G. D., Rhein, M. E., Hale, L. P., Le Deist, F., Alexieff, M. J., Li, J., Hauser, E. R., Haynes, B. F., Rice, H. E., Skinner, M. A., Mahaffey, S. M., Jaggers, J., Stein, L. D. & Mill, M. R. 2003. Thymus transplantation in complete DiGeorge syndrome: immunologic and safety evaluations in 12 patients. Blood, 102, 1121-30.

Marsh, R. A., Bleesing, J. J., Chandrakasan, S., Jordan, M. B., Davies, S. M. & Filipovich, A. H. 2014. Reduced-intensity conditioning hematopoietic cell transplantation is an effective treatment for patients with SLAM-associated protein deficiency/X-linked lymphoproliferative disease type 1. Biol Blood Marrow Transplant, 20, 1641-5.

Mazzolari, E., De Martiis, D., Forino, C., Lanfranchi, A., Giliani, S., Marzollo, R., Airo, P., Imberti, L., Porta, F. & Notarangelo, L. D. 2009. Single-center analysis of long-term outcome after hematopoietic cell transplantation in children with congenital severe T cell immunodeficiency. Immunol Res, 44, 4-17.

Mckinney Jr, R. E., Katz, S. L. & Wilfert, C. M. 1987. Chronic enteroviral meningoencephalitis in agammaglobulinemic patients. Reviews of infectious diseases, 9, 334-356.

Melamed, I. R., Gupta, S., Stratford Bobbitt, M., Hyland, N. & Moy, J. N. 2016a. Efficacy and safety of Gammaplex((R)) 5% in children and adolescents with primary immunodeficiency diseases. Clin Exp Immunol, 184, 228-36.

Melamed, I. R., Gupta, S., Stratford Bobbitt, M., Hyland, N. & Moy, J. N. 2016b. Efficacy and safety of Gammaplex 5% in children and adolescents with primary immunodeficiency diseases. Clinical and Experimental Immunology.

Memmedova, L., Azarsiz, E., Edeer Karaca, N., Aksu, G. & Kutukculer, N. 2013. Does intravenous immunoglobulin therapy prolong immunodeficiency in transient hypogammaglobulinemia of infancy? Pediatr Rep, 5, e14.

Menzin, J., Sussman, M., Munsell, M. & Zbrozek, A. 2014. Economic impact of infections among patients with primary immunodeficiency disease receiving IVIG therapy. Clinicoecon Outcomes Res, 6, 297-302.

Miggelbrink, A. M., Logan, B. R., Buckley, R. H., Parrott, R. E., Dvorak, C. C., Kapoor, N., Abdel-Azim, H., Prockop, S. E., Shyr, D., Decaluwe, H., Hanson, I. C., Gillio, A., Davila Saldana, B. J., Eibel, H., Hopkins, G., Walter, J. E., Whangbo, J. S., Kohn, D. B., Puck, J. M., Cowan, M. J., Griffith, L. M., Haddad, E., O'reilly, R. J., Notarangelo, L. D. & Pai, S. Y. 2018. B-cell differentiation and IL-21 response in IL2RG/JAK3 SCID patients after hematopoietic stem cell transplantation. Blood, 131, 2967-2977.

Miot, C., Imai, K., Imai, C., Mancini, A. J., Kucuk, Z. Y., Kawai, T., Nishikomori, R., Ito, E., Pellier, I., Girod, S. D., Rosain, J., Sasaki, S., Chandrakasan, S., Schmid, J. P., Okano, T., Colin, E., Olaya-Vargas, A., Yamazaki-Nakashimada, M., Qasim, W., Padilla, S. E., Jones, A., Krol, A., Cole, N., Jolles, S., Bleesing, J., Vraetz, T., Gennery, A. R., Abinun, M., Gungor, T., Costa-Carvalho, B., Condino-Neto, A., Veys, P., Holland, S. M., Uzel, G., Moshous, D., Neven, B., Blanche, S., Ehl, S., Doffinger, R., Patel, S. Y., Puel, A., Bustamante, J., Gelfand, E. W., Casanova, J. L., Orange, J. S. & Picard, C. 2017. Hematopoietic stem cell transplantation in 29 patients hemizygous for hypomorphic IKBKG/NEMO mutations. Blood, 130, 1456-1467.

Morris, E. C., Fox, T. A., Burns, S., Carpenter, B., Thomson, K. J., Lowe, D., Fielding, A. K., Peggs, K. S., Kottaridis, P., Grandage, V., Van Deno, S., Grace, S., Dahlstrom, J., Workman, S., Symes, A., Mackinnon, S., Chakraverty, R. & Hough, R. 2016. Successful outcome following allogeneic haematopoietic stem cell transplantation in adults with inherited primary immunodeficiency (PID). Blood. Conference: 58th Annual Meeting of the American Society of Hematology, ASH, 128.

Moy, J. N., Scharenberg, A. M., Stein, M. R., Suez, D., Roberts, R. L., Levy, R. J., Ballow, M., Fasano, M. B., Dash, C. H. & Leach, S. J. 2010a. Efficacy and safety of a new immunoglobulin G product, Gammaplex((R)), in primary immunodeficiency diseases. Clin Exp Immunol, 162, 510-5.

Moy, J. N., Scharenberg, A. M., Stein, M. R., Suez, D., Roberts, R. L., Levy, R. J., Ballow, M., Fasano, M. B., Dash, C. H. & Leach, S. J. 2010b. Efficacy and safety of a new immunoglobulin G product, Gammaplex, in primary immunodeficiency diseases. Clinical and Experimental Immunology, 162, 510-515.

Munoz, A., Olive, T., Martinez, A., Bureo, E., Maldonado, M. S., Diaz De Heredia, C., Sastre, A. & Gonzalez-Vicent, M. 2007. Allogeneic hemopoietic stem cell transplantation (HSCT) for Wiskott-Aldrich syndrome: a report of the Spanish Working Party for Blood and Marrow Transplantation in Children (GETMON). Pediatr Hematol Oncol, 24, 393-402.

Myers, L. A., Patel, D. D., Puck, J. M. & Buckley, R. H. 2002. Hematopoietic stem cell transplantation for severe combined immunodeficiency in the neonatal period leads to superior thymic output and improved survival. Blood, 99, 872-8.

Neven, B., Diana, J. S., Castelle, M., Magnani, A., Rosain, J., Touzot, F., Moreira, B., Fremond, M. L., Briand, C., Bendavid, M., Levy, R., Morelle, G., Vincent, M., Magrin, E., Bourget, P., Chatenoud, L., Picard, C., Fischer, A., Moshous, D. & Blanche, S. 2019. Haploidentical Hematopoietic Stem Cell Transplantation with Post-Transplant Cyclophosphamide for Primary Immunodeficiencies and Inherited Disorders in Children. Biology of Blood and Marrow Transplantation, 25, 1363-1373.

Nobre, F. A., Gonzalez, I. G., Simao, R. M., De Moraes Pinto, M. I. & Costa-Carvalho, B. T. 2014a. Antibody levels to tetanus, diphtheria, measles and varicella in patients with primary immunodeficiency undergoing intravenous immunoglobulin therapy: a prospective study. BMC Immunol, 15, 26.

Nobre, F. A., Gonzalez, I. G. D. S., Simao, R. M., De Moraes Pinto, M. I. & Costa-Carvalho, B. T. 2014b. Antibody levels to tetanus, diphtheria, measles and varicella in patients with primary immunodeficiency undergoing intravenous immunoglobulin therapy: A prospective study. BMC Immunology, 15 (1) (no pagination).

Ochs, H. D., Gupta, S., Kiessling, P., Nicolay, U. & Berger, M. 2006. Safety and efficacy of self-administered subcutaneous immunoglobulin in patients with primary immunodeficiency diseases. J Clin Immunol, 26, 265-73.

Ochs, H. D., Lee, M. L., Fischer, S. H., Kingdon, H. S. & Wedgewood, R. J. 1987. Efficacy of a new intravenous immunoglobulin preparation in primary immunodeficient patients. Clinical Therapeutics, 9, 512-522.

Ochs, H. D., Melamed, I., Borte, M., Moy, J. N., Pyringer, B., A.L, D. K., Knutsen, A. P., Smits, W., Pituch-Noworolska, A. & Kobayashi, R. H. 2018. Intravenous immunoglobulin 10% in children with primary immunodeficiency diseases. Immunotherapy, 10, 1193-1202.

Ochs, H. D. & Pinciaro, P. J. 2004. Octagam 5%, an intravenous IgG product, is efficacious and well tolerated in subjects with primary immunodeficiency diseases. J Clin Immunol, 24, 309-14.

Ochs, H. D., Pinciaro, P. J., Berger, M., Kao, N., Kishiyama, J., Kobayashi, R., Shearer, W., Skoda-Smith, S., Smits, W. & Stein, M. 2004. Octagam 5%, an intravenous IgG product, is efficacious and well tolerated in subjects with primary immunodeficiency diseases. Journal of Clinical Immunology, 24, 309-314.

Okano, T., Imai, K., Tsujita, Y., Mitsuiki, N., Yoshida, K., Kamae, C., Honma, K., Mitsui-Sekinaka, K., Sekinaka, Y., Kato, T., Hanabusa, K., Endo, E., Takashima, T., Hiroki, H., Yeh, T. W., Tanaka, K., Nagahori, M., Tsuge, I., Bando, Y., Iwasaki, F., Shikama, Y., Inoue, M., Kimoto, T., Moriguchi, N., Yuza, Y., Kaneko, T., Suzuki, K., Matsubara, T., Maruo, Y., Kunitsu, T., Waragai, T., Sano, H., Hashimoto, Y., Tasaki, K., Suzuki, O., Shirakawa, T., Kato, M., Uchiyama, T., Ishimura, M., Tauchi, T., Yagasaki, H., Jou, S. T., Yu, H. H., Kanegane, H., Kracker, S., Durandy, A., Kojima, D., Muramatsu, H., Wada, T., Inoue, Y., Takada, H., Kojima, S., Ogawa, S., Ohara, O., Nonoyama, S. & Morio, T. 2019. Hematopoietic stem cell transplantation for progressive combined immunodeficiency and lymphoproliferation in patients with activated phosphatidylinositol-3-OH kinase delta syndrome type 1. Journal of Allergy and Clinical Immunology, 143, 266-275.

Olinder-Nielsen, A. M., Granert, C., Forsberg, P., Friman, V., Vietorisz, A. & Bjorkander, J. 2007. Immunoglobulin prophylaxis in 350 adults with IgG subclass deficiency and recurrent respiratory tract infections: a long-term follow-up. Scand J Infect Dis, 39, 44-50.

Ozsahin, H., Le Deist, F., Benkerrou, M., Cavazzana-Calvo, M., Gomez, L., Griscelli, C., Blanche, S. & Fischer, A. 1996. Bone marrow transplantation in 26 patients with Wiskott-Aldrich syndrome from a single center. J Pediatr, 129, 238-44.

Pac, M., Mikoluc, B., Pietrucha, B., Wolska, K. B., Piatosa, B., Michalkiewicz, J., Gregorek, H. & Bernatowska, E. 2013. Clinical and immunological analysis of patients with X-linked agammaglobulinemia: Single center experience. Central-European Journal of Immunology, 38, 367-371.

Pai, S. Y., Demartiis, D., Forino, C., Cavagnini, S., Lanfranchi, A., Giliani, S., Moratto, D., Mazza, C., Porta, F., Imberti, L., Notarangelo, L. D. & Mazzolari, E. 2006. Stem cell transplantation for the Wiskott-Aldrich syndrome: A single-center experience confirms efficacy of matched unrelated donor transplantation. Bone Marrow Transplantation, 38, 671-679.

Pai, S. Y., Logan, B. R., Griffith, L. M., Buckley, R. H., Parrott, R. E., Dvorak, C. C., Kapoor, N., Hanson, I. C., Filipovich, A. H., Jyonouchi, S., Sullivan, K. E., Small, T. N., Burroughs, L., Skoda-Smith, S., Haight, A. E., Grizzle, A., Pulsipher, M. A., Chan, K. W., Fuleihan, R. L., Haddad, E., Loechelt, B., Aquino, V. M., Gillio, A., Davis, J., Knutsen, A., Smith, A. R., Moore, T. B., Schroeder, M. L., Goldman, F. D., Connelly, J. A., Porteus, M. H., Xiang, Q., Shearer, W. T., Fleisher, T. A., Kohn, D. B., Puck, J. M., Notarangelo, L.

D., Cowan, M. J. & O'reilly, R. J. 2014. Transplantation outcomes for severe combined immunodeficiency, 2000-2009. N Engl J Med, 371, 434-46.

Paris, K., Haddad, E., Borte, M., Brodszki, N., Derfalvi, B., Marodi, L., Hussain, I., Darter, A., Engl, W., Leibl, H., Mccoy, B. & Yel, L. 2019. Tolerability of subcutaneous immunoglobulin 20%, Ig20Gly, in pediatric patients with primary immunodeficiencies. Immunotherapy, 11, 397-406.

Patel, N. C., Chinen, J., Rosenblatt, H. M., Hanson, I. C., Krance, R. A., Paul, M. E., Abramson, S. L., Noroski, L. M., Davis, C. M., Seeborg, F. O., Foster, S. B., Leung, K. S., Brown, B. S., Ritz, J. & Shearer, W. T. 2009. Outcomes of patients with severe combined immunodeficiency treated with hematopoietic stem cell transplantation with and without preconditioning. J Allergy Clin Immunol, 124, 1062-9.e1-4.

Patel, N. C., Gallagher, J. L., Ochs, H. D., Atkinson, T. P., Wahlstrom, J., Dorsey, M., Bonilla, F. A., Heimall, J., Kobrynski, L., Morris, D. & Haddad, E. 2015. Subcutaneous Immunoglobulin Replacement Therapy with Hizentra(R) is Safe and Effective in Children Less Than 5 Years of Age. J Clin Immunol, 35, 558-65.

Plebani, A., Soresina, A., Rondelli, R., Amato, G. M., Azzari, C., Cardinale, F., Cazzola, G., Consolini, R., De Mattia, D., Dell'erba, G., Duse, M., Fiorini, M., Martino, S., Martire, B., Masi, M., Monafo, V., Moschese, V., Notarangelo, L. D., Orlandi, P., Panei, P., Pession, A., Pietrogrande, M. C., Pignata, C., Quinti, I., Ragno, V., Rossi, P., Sciotto, A. & Stabile, A. 2002. Clinical, immunological, and molecular analysis in a large cohort of patients with X-linked agammaglobulinemia: an Italian multicenter study. Clin Immunol, 104, 221-30.

Quartier, P., Bustamante, J., Sanal, O., Plebani, A., Debre, M., Deville, A., Litzman, J., Levy, J., Fermand, J. P., Lane, P., Horneff, G., Aksu, G., Yalcin, I., Davies, G., Tezcan, I., Ersoy, F., Catalan, N., Imai, K., Fischer, A. & Durandy, A. 2004. Clinical, immunologic and genetic analysis of 29 patients with autosomal recessive hyper-IgM syndrome due to Activation-Induced Cytidine Deaminase deficiency. Clin Immunol, 110, 22-9.

Quartier, P., Debre, M., De Blic, J., De Sauverzac, R., Sayegh, N., Jabado, N., Haddad, E., Blanche, S., Casanova, J. L., Smith, C. I., Le Deist, F., De Saint Basile, G. & Fischer, A. 1999. Early and prolonged intravenous immunoglobulin replacement therapy in childhood agammaglobulinemia: a retrospective survey of 31 patients. J Pediatr, 134, 589-96.

Quinti, I., Pierdominici, M., Marziali, M., Giovannetti, A., Donnanno, S., Chapel, H., Bjorkander, J. & Aiuti, F. 2002. European surveillance of immunoglobulin safety--results of initial survey of 1243 patients with primary immunodeficiencies in 16 countries. Clin Immunol, 104, 231-6.

Rao, K., Adams, S., Qasim, W., Allwood, Z., Worth, A., Silva, J., Lucchini, G., Chiesa, R., Veys, P. & Amrolia, P. 2016. Effect of stem cell source on long-term chimerism and event-free survival in

children with primary immunodeficiency disorders after fludarabine and melphalan conditioning regimen. Journal of Allergy and Clinical Immunology, 138, 1152-1160.

Renke, J., Lange, M., Dawicka, J. & Adamkiewicz-Drozynska, E. 2016. Transient hypogammaglobulinaemia of infants in children with mastocytosis - Strengthened indications for vaccinations. Central European Journal of Immunology, 41, 282-286.

Roberton, D. M. & Hosking, C. S. 1987. The long term treatment of childhood hypogammaglobulinaemia in Melbourne with intravenous gammaglobulin, 1972-1985. Dev Biol Stand, 67, 273-80.

Scarselli, A., Di Cesare, S., Capponi, C., Cascioli, S., Romiti, M. L., Di Matteo, G., Simonetti, A., Palma, P., Finocchi, A., Lucarelli, B., Pinto, R. M., Rana, I., Palumbo, G., Caniglia, M., Rossi, P., Carsetti, R., Cancrini, C. & Aiuti, A. 2015. Longitudinal Evaluation of Immune Reconstitution and B-cell Function After Hematopoietic Cell Transplantation for Primary Immunodeficiency. J Clin Immunol, 35, 373-83.

Schiff, R. I., Williams, L. W., Nelson, R. P., Buckley, R. H., Burks, W. & Good, R. A. 1997. Multicenter crossover comparison of the safety and efficacy of Intraglobin-F with Gamimune-N, Sandoglobulin, and Gammagard in patients with primary immunodeficiency diseases. J Clin Immunol, 17, 21-8.

Sharma, T. & Gupta, S. 2019. Reconstitution of IgG Subclasses following Immunoglobulin Therapy in Adult Primary Hypogammaglobulinemia. Int Arch Allergy Immunol, 180, 221-232.

Shaw, K. L., Garabedian, E., Mishra, S., Barman, P., Davila, A., Carbonaro, D., Shupien, S., Silvin, C., Geiger, S., Nowicki, B., Smogorzewska, E. M., Brown, B., Wang, X., De Oliveira, S., Choi, Y., Ikeda, A., Terrazas, D., Fu, P. Y., Yu, A., Fernandez, B. C., Cooper, A. R., Engel, B., Podsakoff, G., Balamurugan, A., Anderson, S., Muul, L., Jagadeesh, G. J., Kapoor, N., Tse, J., Moore, T. B., Purdy, K., Rishi, R., Mohan, K., Skoda-Smith, S., Buchbinder, D., Abraham, R. S., Scharenberg, A., Yang, O. O., Cornetta, K., Gjertson, D., Hershfield, M., Sokolic, R., Candotti, F. & Kohn, D. B. 2017. Clinical efficacy of gene-modified stem cells in adenosine deaminase-deficient immunodeficiency. J Clin Invest, 127, 1689-1699.

Simao-Gurge, R. M., Costa-Carvalho, B. T., Nobre, F. A., Gonzalez, I. G. & De Moraes-Pinto, M. I. 2017. Prospective evaluation of Streptococcus pneumoniae serum antibodies in patients with primary immunodeficiency on regular intravenous immunoglobulin treatment. Allergol Immunopathol (Madr), 45, 55-62.

Skull, S. & Kemp, A. 1996. Treatment of hypogammaglobulinaemia with intravenous immunoglobulin, 1973-93. Archives of Disease in Childhood, 74, 527-530.

Slatter, M. A., Rao, K., Abd Hamid, I. J., Nademi, Z., Chiesa, R., Elfeky, R., Pearce, M. S., Amrolia, P., Worth, A., Flood, T., Abinun, M., Hambleton, S., Qasim, W., Gaspar, H. B., Cant, A. J., Gennery, A. R.

& Veys, P. 2018. Treosulfan and Fludarabine Conditioning for Hematopoietic Stem Cell Transplantation in Children with Primary Immunodeficiency: UK Experience. Biol Blood Marrow Transplant, 24, 529-536.

Smogorzewska, E. M., Brooks, J., Annett, G., Kapoor, N., Crooks, G. M., Kohn, D. B., Parkman, R. & Weinberg, K. I. 2000. T cell depleted haploidentical bone marrow transplantation for the treatment of children with severe combined immunodeficiency. Arch Immunol Ther Exp (Warsz), 48, 111-8.

Solberg, C. O., Matsen, J. M., Biggar, W. D., Park, B. H., Niosi, P. & Good, R. A. 1974. Infectious complications in patients with combined immunodeficiency diseases receiving bone marrow transplants. Scand J Infect Dis, 6, 223-31.

Soresina, A., Nacinovich, R., Bomba, M., Cassani, M., Molinaro, A., Sciotto, A., Martino, S., Cardinale, F., De Mattia, D., Putti, C., Dellepiane, R. M., Felici, L., Parrinello, G., Neri, F. & Plebani, A. 2009. The quality of life of children and adolescents with X-linked agammaglobulinemia. J Clin Immunol, 29, 501-7.

Stein, M., Nemet, A., Kumar, S., Lumry, W., Gajek, H., Macchia, R., Zamfirova, V., Bergman, G., Mcneil, D., Hooper, J., Moy, J., Pesek, R., Upton, J., Shapiro, R., Sussman, G. & Roifman, C. M. 2016. Efficacy, safety, and tolerability of Kedrion 10% IVIG in primary immunodeficiency. LymphoSign Journal, 3, 99-109.

Stein, M. R., Koterba, A., Rodden, L. & Berger, M. 2011. Safety and efficacy of home-based subcutaneous immunoglobulin G in elderly patients with primary immunodeficiency diseases. Postgrad Med, 123, 186-93.

Stein, M. R., Nelson, R. P., Church, J. A., Wasserman, R. L., Borte, M., Vermylen, C. & Bichler, J. 2009. Safety and efficacy of Privigen, a novel 10% liquid immunoglobulin preparation for intravenous use, in patients with primary immunodeficiencies. J Clin Immunol, 29, 137-44.

Stein, M. R., Wasserman, R. L., Moy, J., Lumry, W., Grunebaum, E., Nemet, A., Roifman, C. M. & Sussman, G. 2015. Efficacy, safety, and tolerability of IVIG-SN in patients with primary immunodeficiency. LymphoSign Journal, 2, 21-29.

Suez, D., Krivan, G., Jolles, S., Stein, M., Gupta, S., Paris, K., Van Hagen, P. M., Brodszki, N., Engl, W., Leibl, H., Mccoy, B. & Yel, L. 2019. Safety and tolerability of subcutaneous immunoglobulin 20% in primary immunodeficiency diseases from two continents. Immunotherapy, 11, 1057-1065.

Sultan, S., Rondeau, E., Levasseur, M. C., Dicaire, R., Decaluwe, H. & Haddad, E. 2017. Quality of Life, Treatment Beliefs, and Treatment Satisfaction in Children Treated for Primary Immunodeficiency with SCIg. J Clin Immunol, 37, 496-504.

Suri, D., Bhattad, S., Sharma, A., Gupta, A., Rawat, A., Sehgal, S., Singh, S. & Gupta, S. 2017. Serial Serum Immunoglobulin G (IgG) Trough Levels in Patients with X-linked Agammaglobulinemia on Replacement Therapy with Intravenous Immunoglobulin: Its Correlation with Infections in Indian Children. J Clin Immunol, 37, 311-318.

Tcheurekdjian, H., Martin, J., Kobayashi, R., Wasserman, R. & Hostoffer, R. 2006. Intrainfusion and postinfusion adverse events related to intravenous immunoglobulin therapy in immunodeficiency states. Allergy Asthma Proc, 27, 532-6.

Torabi Sagvand, B., Mirminachi, B., Abolhassani, H., Shokouhfar, T., Keihanian, T., Amirzargar, A., Mahdaviani, A. & Aghamohammadi, A. 2015. IgG anti-IgA antibodies in paediatric antibody-deficient patients receiving intravenous immunoglobulin. Allergol Immunopathol (Madr), 43, 403-8.

Tsuji, Y., Imai, K., Kajiwara, M., Aoki, Y., Isoda, T., Tomizawa, D., Imai, M., Ito, S., Maeda, H., Minegishi, Y., Ohkawa, H., Yata, J., Sasaki, N., Kogawa, K., Nagasawa, M., Morio, T., Nonoyama, S. & Mizutani, S. 2006. Hematopoietic stem cell transplantation for 30 patients with primary immunodeficiency diseases: 20 years experience of a single team. Bone Marrow Transplant, 37, 469-77.

Tuerlinckx, D., Florkin, B., Ferster, A., De Schutter, I., Chantrain, C., Haerynck, F., Philippet, P., Strengers, P. & Laub, R. 2014. Pneumococcal antibody levels in children with PID receiving immunoglobulin. Pediatrics, 133, e154-62.

Van Der Meer, J. W. M., Van Beem, R. T., Robak, T., Deptala, A. & Strengers, P. F. W. 2011. Efficacy and safety of a nanofiltered liquid intravenous immunoglobulin product in patients with primary immunodeficiency and idiopathic thrombocytopenic purpura. Vox Sanguinis, 101, 138-146.

Viallard, J. F., Agape, P., Barlogis, V., Cozon, G., Faure, C., Fouyssac, F., Gaud, C., Gourin, M. P., Hamidou, M., Hoarau, C., Husseini, F., Ojeda-Uribe, M., Pavic, M., Pellier, I., Perlat, A., Schleinitz, N. & Slama, B. 2016. Treatment with Hizentra in patients with primary and secondary immunodeficiencies: a real-life, non-interventional trial. BMC Immunol, 17, 34.

Vultaggio, A., Azzari, C., Milito, C., Finocchi, A., Toppino, C., Spadaro, G., Trizzino, A., Baldassarre, M., Paganelli, R., Moschese, V., Soresina, A. & Matucci, A. 2015. Subcutaneous immunoglobulin replacement therapy in patients with primary immunodeficiency in routine clinical practice: the VISPO prospective multicenter study. Clin Drug Investig, 35, 179-85.

Vultaggio, A., Azzari, C., Ricci, S., Martire, B., Palladino, V., Gallo, V., Pecoraro, A., Pignata, C., Spadaro, G., Graziani, S., Moschese, V., Trizzino, A., Boggia, G. M. & Matucci, A. 2018. Biweekly hizentra in primary immunodeficiency: A multicenter, observational cohort study (IBIS). Journal of Clinical Immunology, 38, 602-609.

Wasserman, R. L., Church, J. A., Peter, H. H., Sleasman, J. W., Melamed, I., Stein, M. R. & Bichler, J. 2009. Pharmacokinetics of a new 10% intravenous immunoglobulin in patients receiving replacement therapy for primary immunodeficiency. Eur J Pharm Sci, 37, 272-8.

Wasserman, R. L., Church, J. A., Stein, M., Moy, J., White, M., Strausbaugh, S., Schroeder, H., Ballow, M., Harris, J., Melamed, I., Elkayam, D., Lumry, W., Suez, D. & Rehman, S. M. 2012a. Safety, efficacy and pharmacokinetics of a new 10% liquid intravenous immunoglobulin (IVIG) in patients with primary immunodeficiency. J Clin Immunol, 32, 663-9.

Wasserman, R. L., Lumry, W., Harris, J., 3rd, Levy, R., Stein, M., Forbes, L., Cunningham-Rundles, C., Melamed, I., Kobayashi, A. L., Du, W. & Kobayashi, R. 2016a. Efficacy, Safety, and Pharmacokinetics of a New 10 % Liquid Intravenous Immunoglobulin Containing High Titer Neutralizing Antibody to RSV and Other Respiratory Viruses in Subjects with Primary Immunodeficiency Disease. J Clin Immunol, 36, 590-9.

Wasserman, R. L., Melamed, I., Kobrynski, L., Puck, J., Gupta, S., Doralt, J., Sharkhawy, M., Engl, W., Leibl, H., Gelmont, D. & Yel, L. 2016b. Recombinant human hyaluronidase facilitated subcutaneous immunoglobulin treatment in pediatric patients with primary immunodeficiencies: long-term efficacy, safety and tolerability. Immunotherapy, 8, 1175-86.

Wasserman, R. L., Melamed, I., Kobrynski, L., Strausbaugh, S. D., Stein, M. R., Sharkhawy, M., Engl, W., Leibl, H., Sobolevsky, L., Gelmont, D., Schiff, R. I. & Grossman, W. J. 2011. Efficacy, safety, and pharmacokinetics of a 10% liquid immune globulin preparation (GAMMAGARD LIQUID, 10%) administered subcutaneously in subjects with primary immunodeficiency disease. J Clin Immunol, 31, 323-31.

Wasserman, R. L., Melamed, I., Stein, M. R., Engl, W., Sharkhawy, M., Leibl, H., Puck, J., Rubinstein, A., Kobrynski, L., Gupta, S., Grant, A. J., Ratnayake, A., Richmond, W. G., Church, J., Yel, L. & Gelmont, D. 2016c. Long-Term Tolerability, Safety, and Efficacy of Recombinant Human Hyaluronidase-Facilitated Subcutaneous Infusion of Human Immunoglobulin for Primary Immunodeficiency. J Clin Immunol, 36, 571-82.

Wasserman, R. L., Melamed, I., Stein, M. R., Gupta, S., Puck, J., Engl, W., Leibl, H., Mccoy, B., Empson, V. G., Gelmont, D., Schiff, R. I. & Igsc, W. R. S. G. 2012b. Recombinant human hyaluronidase-facilitated subcutaneous infusion of human immunoglobulins for primary immunodeficiency. The Journal of allergy and clinical immunology, 130, 951-957.e11.

Wegmuller, E. 1998. Effect of intravenous immunoglobulin therapy on plasma complement. Transfus Sci, 19, 307-18.

Williams, P. E., Yap, P. L., Gillon, J., Crawford, R. J., Urbaniak, S. J. & Galea, G. 1989. Transmission of non-A, non-B hepatitis by pH4-treated intravenous immunoglobulin. Vox Sang, 57, 15-8.

Ziegner, U. H., Kobayashi, R. H., Cunningham-Rundles, C., Espanol, T., Fasth, A., Huttenlocher, A., Krogstad, P., Marthinsen, L., Notarangelo, L. D., Pasic, S., Rieger, C. H., Rudge, P., Sankar, R., Shigeoka, A. O., Stiehm, E. R., Sullivan, K. E., Webster, A. D. & Ochs, H. D. 2002. Progressive neurodegeneration in patients with primary immunodeficiency disease on IVIG treatment. Clin Immunol, 102, 19-24.

Zuber, Z., Gornicka-Banach, M., Szymanowska, Z., Turowska-Heydel, D., Sobczyk, M. & Rutkowska-Sak, L. 2014. The use of intravenous immunoglobulin in pediatric rheumatology. Reumatologia, 52, 160-165.

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

Trial identifier	Conditions	Intervention	Comparator	Study design (Allocation, Intervention/Observational model, Masking, Location, Primary purpose, Time perspective)	Country(s)	Status, Completion date
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

Trial identifier	Conditions	Intervention	Comparator	Study design (Allocation, Intervention/Observational model, Masking, Location, Primary purpose, Time perspective)	Country(s)	Status, Completion date
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

Trial identifier	Conditions	Intervention	Comparator	Study design (Allocation, Intervention/Observational model, Masking, Location, Primary purpose, Time perspective)	Country(s)	Status, Completion date
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,	Recruiting, April 2023

Trial identifier	Conditions	Intervention	Comparator	Study design (Allocation, Intervention/Observational model, Masking, Location, Primary purpose, Time perspective)	Country(s)	Status, Completion date
					Slovakia, Sweden, UK	
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,	IGIV 10%		RCT, Crossover Assignment, Multi-centre, Treatment	USA	Completed, December 2013

Trial identifier	Conditions	Intervention	Comparator	Study design (Allocation, Intervention/Observational model, Masking, Location, Primary purpose, Time perspective)	Country(s)	Status, Completion date
	Immune Thrombocytopenic Purpura (ITP), Kawasaki Syndrome					
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

Trial identifier	Conditions	Intervention	Comparator	Study design (Allocation, Intervention/Observational model, Masking, Location, Primary purpose, Time perspective)	Country(s)	Status, Completion date
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

Trial identifier	Conditions	Intervention	Comparator	Study design (Allocation, Intervention/Observational model, Masking, Location, Primary purpose, Time perspective)	Country(s)	Status, Completion date
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

Trial identifier	Conditions	Intervention	Comparator	Study design (Allocation, Intervention/Observational model, Masking, Location, Primary purpose, Time perspective)	Country(s)	Status, Completion date
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	Cyclophosphamide Fludarabine Phosphate Mycophenolate Mofetil		Single Group Assignment, Open Label, Multi-centre, Treatment	USA	Active, not recruiting, December 2023

Trial identifier	Conditions	Intervention	Comparator	Study design (Allocation, Intervention/Observational model, Masking, Location, Primary purpose, Time perspective)	Country(s)	Status, Completion date
	Donor	Sirolimus Tacrolimus				
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

Trial identifier	Conditions	Intervention	Comparator	Study design (Allocation, Intervention/Observational model, Masking, Location, Primary purpose, Time perspective)	Country(s)	Status, Completion date
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		Single Group Assignment, Open Label, Multi-centre, Treatment	USA	Completed, March 2015

Trial identifier	Conditions	Intervention	Comparator	Study design (Allocation, Intervention/Observational model, Masking, Location, Primary purpose, Time perspective)	Country(s)	Status, Completion date
		Mycophenolate Mofetil				
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	BPX-501 + AP1903		Single Group Assignment, Open Label, Single-centre, Treatment	USA	Active, not recruiting, July 2030

Trial identifier	Conditions	Intervention	Comparator	Study design (Allocation, Intervention/Observational model, Masking, Location, Primary purpose, Time perspective)	Country(s)	Status, Completion date
	Hemophagocytic Lymphohistiocytosis Inherited Bone Marrow Failure Syndrome Hemoglobinopathies Metabolic Disorders					
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	CD34 Stem Cell Selection Therapy		Single Group Assignment, Open Label, Single-centre, Treatment	USA	Recruiting, December 2019

Trial identifier	Conditions	Intervention	Comparator	Study design (Allocation, Intervention/Observational model, Masking, Location, Primary purpose, Time perspective)	Country(s)	Status, Completion date
	Langerhans Cell Histiocytosis (LCH) Hemoglobinopathies Sickle Cell Disease Sickle Cell-beta-thalassemia					
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	rimiducid		Single Group Assignment, Open Label, Multi-centre, Treatment	Italy UK	Active, not recruiting, December 2034

Trial identifier	Conditions	Intervention	Comparator	Study design (Allocation, Intervention/Observational model, Masking, Location, Primary purpose, Time perspective)	Country(s)	Status, Completion date
	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					
NCT03301168	Acute Lymphoblastic Leukemia Leukemia, Acute Myeloid (AML), Child Lymphoma, Non-Hodgkin Myelodysplastic Syndromes Primary Immune Deficiency Disorder Osteopetrosis Cytopenia	BPX-501 T cells and AP1903		Single Group Assignment, Open Label, Multi-centre, Treatment	USA	Active, not recruiting, February 2035

Trial identifier	Conditions	Intervention	Comparator	Study design (Allocation, Intervention/Observational model, Masking, Location, Primary purpose, Time perspective)	Country(s)	Status, Completion date
	Hemoglobinopathy in Children Anemia, Aplastic					
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		Non-RCT, Parallel Assignment, Open Label, Multi-centre, Treatment	USA	Recruiting, February 2027

Trial identifier	Conditions	Intervention	Comparator	Study design (Allocation, Intervention/Observational model, Masking, Location, Primary purpose, Time perspective)	Country(s)	Status, Completion date
		Umbilical Cord Blood Transplantation				
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	Anti-thymocyte globulin Busulfan Cyclophosphamide Cyclosporine Etoposide Filgrastim Methotrexate		Treatment	USA	Unknown

Trial identifier	Conditions	Intervention	Comparator	Study design (Allocation, Intervention/Observational model, Masking, Location, Primary purpose, Time perspective)	Country(s)	Status, Completion date
	Familial Erythrophagocytic Lymphohistiocytosis Hemophagocytic Lymphohistiocytosis Virus-Associated Hemophagocytic Syndrome	Allogeneic hematopoietic stem cell transplantation				
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

Trial identifier	Conditions	Intervention	Comparator	Study design (Allocation, Intervention/Observational model, Masking, Location, Primary purpose, Time perspective)	Country(s)	Status, Completion date
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	Alemtuzumab Cyclophosphamide Busulfan Fludarabine phosphate Melphalan MESNA Stem Cell Transplantation		Non-RCT, Single Group Assignment, Open Label, Single-centre, Treatment	USA	Recruiting, December 2022

Trial identifier	Conditions	Intervention	Comparator	Study design (Allocation, Intervention/Observational model, Masking, Location, Primary purpose, Time perspective)	Country(s)	Status, Completion date
	X-linked Lymphoproliferative Disease Hemophagocytic Lymphohistiocytosis Griscelli Syndrome Chediak-Higashi Syndrome Langerhan's Cell Histiocytosis					
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

Trial identifier	Conditions	Intervention	Comparator	Study design (Allocation, Intervention/Observational model, Masking, Location, Primary purpose, Time perspective)	Country(s)	Status, Completion date
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

Trial identifier	Conditions	Intervention	Comparator	Study design (Allocation, Intervention/Observational model, Masking, Location, Primary purpose, Time perspective)	Country(s)	Status, Completion date
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	Immunosuppression Only Conditioning Reduced Intensity Conditioning GVHD Prophylaxis	No treatment	Non-RCT, Parallel Assignment, Open Label, Multi-centre, Treatment	USA	Recruiting, May 2024

Trial identifier	Conditions	Intervention	Comparator	Study design (Allocation, Intervention/Observational model, Masking, Location, Primary purpose, Time perspective)	Country(s)	Status, Completion date
	Primary T-cell Immunodeficiency Disorders Immune System Diseases Common Variable Immunodeficiency	Allogeneic HSC				
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	Thiotepa--single daily dose Thiotepa--escalated dose		RCT, Sequential Assignment, Open Label, Single-centre, Treatment	USA	Recruiting, June 2022

Trial identifier	Conditions	Intervention	Comparator	Study design (Allocation, Intervention/Observational model, Masking, Location, Primary purpose, Time perspective)	Country(s)	Status, Completion date
	Severe Combined Immunodeficiency Hurler Syndrome Mannosidosis Adrenoleukodystrophy					
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	Alemtuzumab Fludarabine Thiotepa Melphalan		Single Group Assignment, Open Label, Multi-centre, Treatment	USA	Recruiting, March 2024

Trial identifier	Conditions	Intervention	Comparator	Study design (Allocation, Intervention/Observational model, Masking, Location, Primary purpose, Time perspective)	Country(s)	Status, Completion date
	X-linked Lymphoproliferative Syndrome					
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			Single Group Assignment, Open Label, Multi-centre, Other	USA	Completed, May 2017

Trial identifier	Conditions	Intervention	Comparator	Study design (Allocation, Intervention/Observational model, Masking, Location, Primary purpose, Time perspective)	Country(s)	Status, Completion date
	X-linked Agammaglobulinaemia Hyperimmunoglobulin M Syndrome					
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	Anti-thymocyte globulin		Single-centre, Treatment	USA	Terminated, December 2002

Trial identifier	Conditions	Intervention	Comparator	Study design (Allocation, Intervention/Observational model, Masking, Location, Primary purpose, Time perspective)	Country(s)	Status, Completion date
	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	Busulfan Cyclophosphamide Cyclosporine Etoposide Methotrexate Methylprednisolone Prednisone Allogeneic bone marrow transplantation				

Trial identifier	Conditions	Intervention	Comparator	Study design (Allocation, Intervention/Observational model, Masking, Location, Primary purpose, Time perspective)	Country(s)	Status, Completion date
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

Trial identifier	Conditions	Intervention	Comparator	Study design (Allocation, Intervention/Observational model, Masking, Location, Primary purpose, Time perspective)	Country(s)	Status, Completion date
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			USA	Completed, July 2002

Trial identifier	Conditions	Intervention	Comparator	Study design (Allocation, Intervention/Observational model, Masking, Location, Primary purpose, Time perspective)	Country(s)	Status, Completion date
		ADA Umbilical Cord Blood Cells Transduced Lymphocytes				
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

Trial identifier	Conditions	Intervention	Comparator	Study design (Allocation, Intervention/Observational model, Masking, Location, Primary purpose, Time perspective)	Country(s)	Status, Completion date
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

Trial identifier	Conditions	Intervention	Comparator	Study design (Allocation, Intervention/Observational model, Masking, Location, Primary purpose, Time perspective)	Country(s)	Status, Completion date
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	Cyclosporine Mycophenolate Mofetil Allogeneic Bone Marrow Transplantation		Single Group Assignment, Open Label, Single-centre, Treatment	USA	Completed, December 2018

Trial identifier	Conditions	Intervention	Comparator	Study design (Allocation, Intervention/Observational model, Masking, Location, Primary purpose, Time perspective)	Country(s)	Status, Completion date
	Severe Combined Immunodeficiency Severe Combined Immunodeficiency With Absence of T and B Cells X-Linked Severe Combined Immunodeficiency					
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	Human T Lymphoid Progenitor (HTLP)		Single Group Assignment, Open Label, Single-centre, Treatment	France	Not yet recruiting, April 2024

Trial identifier	Conditions	Intervention	Comparator	Study design (Allocation, Intervention/Observational model, Masking, Location, Primary purpose, Time perspective)	Country(s)	Status, Completion date
	Cell Transplantation (HSCT)					
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

Trial identifier	Conditions	Intervention	Comparator	Study design (Allocation, Intervention/Observational model, Masking, Location, Primary purpose, Time perspective)	Country(s)	Status, Completion date
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

Trial identifier	Conditions	Intervention	Comparator	Study design (Allocation, Intervention/Observational model, Masking, Location, Primary purpose, Time perspective)	Country(s)	Status, Completion date
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

Trial identifier	Conditions	Intervention	Comparator	Study design (Allocation, Intervention/Observational model, Masking, Location, Primary purpose, Time perspective)	Country(s)	Status, Completion date
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	Hematopoietic stem cell transplantation		Non-RCT, Parallel Assignment, Open Label, Single-centre, Treatment	USA	Completed, August 2015

Trial identifier	Conditions	Intervention	Comparator	Study design (Allocation, Intervention/Observational model, Masking, Location, Primary purpose, Time perspective)	Country(s)	Status, Completion date
	Granuloma Wiskott-Aldrich Syndrome Chediak Higashi Syndrome Osteopetrosis Neutropenia Thrombocytopenia Hurler Disease Niemann-Pick Disease Fucosidosis					
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	Abatacept		Single Group Assignment, Open Label, Single-centre, Supportive care	USA	Completed, September 2019

Trial identifier	Conditions	Intervention	Comparator	Study design (Allocation, Intervention/Observational model, Masking, Location, Primary purpose, Time perspective)	Country(s)	Status, Completion date
	Severe Aplastic Anemia Thalassemia Major Hemophagocytic Lymphohistiocytosis Sickle Cell Disease					
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	Cyclophosphamide		Non-RCT, Single Group Assignment, Open Label, Treatment		Terminated, February 2014

Trial identifier	Conditions	Intervention	Comparator	Study design (Allocation, Intervention/Observational model, Masking, Location, Primary purpose, Time perspective)	Country(s)	Status, Completion date
	X-linked Lymphoproliferative Disease Metabolic Diseases					
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	Not yet recruiting

Trial identifier	Conditions	Intervention	Comparator	Study design (Allocation, Intervention/Observational model, Masking, Location, Primary purpose, Time perspective)	Country(s)	Status, Completion date
					Spain Korea DR	
ACTRN12618001502224	Auto-Immune Diseases	HL161BKN	Placebo	RCT	Australia	Terminated
ACTRN12618001394235	Lung Transplantation	Intravenous immunoglobulin	Placebo (Human Albumin)	RCT, Double-blind, treatment	Australia	Recruiting

REFERENCES

Guyatt, G, Oxman, AD, Sultan, S, Brozek, J, Glasziou, P, Alonso-Coello, P, Atkins, D, Kunz, R, Montori, V, Jaeschke, R, Rind, D, Dahm, P, Akl, EA, Meerpohl, J, Vist, G, Berliner, E, Norris, S, Falck-Ytter, Y & Schunemann, HJ 2013, 'GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes', *J Clin Epidemiol*, vol. 66, no. 2, Feb, pp. 151-157.

Aaaai. 2019. *Immunoglobulin (IgG) replacement therapy* [Online]. American Acedemy of Allergy, Asthma and Immunology. Available: https://www.aaaai.org/conditions-and-treatments/conditions-dictionary/immunoglobulin-(igg)-replacement-therapy [Accessed December 16 2019].

Abolhassani, H., Sadaghiani, M. S., Aghamohammadi, A., Ochs, H. D. & Rezaei, N. 2012. Home-based subcutaneous immunoglobulin versus hospital-based intravenous immunoglobulin in treatment of primary antibody deficiencies: systematic review and meta analysis. *J Clin Immunol,* 32**,** 1180-92.

Aghamohammadi, A., Farhoudi, A., Moin, M., Pourpak, Z., Rezaei, N., Nikzad, M., Movahedi, M., Gharagozlou, M., Atarod, L., Ahmadi Afshar, A., Bazargan, N., Abolmaali, K. & Mahmoudi, M. 2003. Adverse effects of intravenous immunoglobulin therapy in patients with antibody deficiency. *Iran J Allergy Asthma Immunol,* 2**,** 121-6.

Aghamohammadi, A., Farhoudi, A., Nikzad, M., Moin, M., Pourpak, Z., Rezaei, N., Gharagozlou, M., Movahedi, M., Atarod, L., Afshar, A. A., Bazargan, N. & Hosseinpoor, A. R. 2004. Adverse reactions of prophylactic intravenous immunoglobulin infusions in Iranian patients with primary immunodeficiency. *Ann Allergy Asthma Immunol,* 92**,** 60-4.

Aghamohammadi, A., Moazzami, K., Rezaei, N., Karimi, A., Movahedi, M., Gharagozlou, M., Abdollahzade, S., Pouladi, N., Kouhi, A. & Moin, M. 2008. ENT manifestations in Iranian patients with primary antibody deficiencies. *J Laryngol Otol,* 122**,** 409-13.

Aghamohammadi, A., Tavasoli, M., Abou Alhasani, H., Parvaneh, N., Moazami, K., Alahverdi, A., Mahdaviani, S., Atarod, L. & Rezaei, N. 2009a. Infectious and non-infectious complications among undiagnosed patients with common variable immunodeficiency.

Aghamohammadi, A., Tavassoli, M., Abolhassani, H., Parvaneh, N., Moazzami, K., Allahverdi, A., Mahdaviani, S. A., Atarod, L. & Rezaei, N. 2009b. Infectious and non-infectious complications among undiagnosed patients with common variable immunodeficiency. *Iranian Journal of Pediatrics,* 19**,** 367-375.

Alkan, G., Keles, S. & Reisli, I. 2017. Evaluation of clinical and immunological characteristics of children with common variable immunodeficiency. *Cogent Medicine. Conference: 9th Excellence in Pediatrics Conference, EIP,* 4.

Angel a Justiz-Vaillant and Christopher M Stang. 2019. *Lymphoproliferative disorders* [Online]. Available: https://www.ncbi.nlm.nih.gov/books/NBK537162/ [Accessed January 7 2020].

Ascia. 2019a. *Common variable immunodeficiency (CVID)* [Online]. Australasian Society of Clinical Immunology and Allergy. Available: https://allergy.org.au/patients/immunodeficiencies/common-variable-immune-deficiency-cvid [Accessed January 7 2020].

Ascia. 2019b. *Common variable immunodeficiency (CVID)* [Online]. Australasian Society of Clinical Immunology and Allergy, . Available:

https://allergy.org.au/patients/immunodeficiencies/common-variable-immune-deficiency-cvid [Accessed January 6 2020].
Ascia. 2019c. *Immunoglobulin Replacement Therapy in Primary Immunodeficiencies* [Online]. Australia: Australasian Society of Clinical Immunology and Allergy. Available: https://www.allergy.org.au/patients/immunodeficiencies/immunoglobulin-replacement-therapy [Accessed 1st October 2019].
Australian Bureau of Statistics. 2019. *3101.0 - Australian Demographic Statistics, Jun 2019* [Online]. Canberra. Available: https://www.abs.gov.au/AUSSTATS/abs@.nsf/Lookup/3101.0Main+Features1Jun%202019?OpenDocument [Accessed March 5 2020].
Ballow, M., Notarangelo, L., Grimbacher, B., Cunningham-Rundles, C., Stein, M., Helbert, M., Gathmann, B., Kindle, G., Knight, A. K., Ochs, H. D., Sullivan, K. & Franco, J. L. 2009. Immunodeficiencies. *Clin Exp Immunol,* 158 Suppl 1**,** 14-22.
Baris, S., Ercan, H., Cagan, H. H., Ozen, A., Karakoc-Aydiner, E., Ozdemir, C. & Bahceciler, N. N. 2011. Efficacy of intravenous immunoglobulin treatment in children with common variable immunodeficiency. *J Investig Allergol Clin Immunol,* 21**,** 514-21.
Baumgart, K. W., Britton, W. J., Kemp, A., French, M. & Roberton, D. 1997. The spectrum of primary immunodeficiency disorders in Australia. *Journal of allergy and clinical immunology,* 100**,** 415-423.
Bayrakci, B., Ersoy, F., Sanal, O., Kilic, S., Metin, A. & Tezcan, I. 2005. The efficacy of immunoglobulin replacement therapy in the long-term follow-up of the B-cell deficiencies (XLA, HIM, CVID). *Turk J Pediatr,* 47**,** 239-46.
Beaute, J., Levy, P., Millet, V., Debre, M., Dudoit, Y., Le Mignot, L., Tajahmady, A., Thomas, C., Suarez, F., Pellier, I., Hermine, O., Aladjidi, N., Mahlaoui, N. & Fischer, A. 2010. Economic evaluation of immunoglobulin replacement in patients with primary antibody deficiencies. *Clin Exp Immunol,* 160**,** 240-5.
Berger, M., Cunningham-Rundles, C., Bonilla, F. A., Melamed, I., Bichler, J., Zenker, O. & Ballow, M. 2007. Carimune NF Liquid is a safe and effective immunoglobulin replacement therapy in patients with primary immunodeficiency diseases. *J Clin Immunol,* 27**,** 503-9.
Bichuetti-Silva, D. C., Furlan, F. P., Nobre, F. A., Pereira, C. T., Goncalves, T. R., Gouveia-Pereira, M., Rota, R., Tavares, L., Mazzucchelli, J. T. & Costa-Carvalho, B. T. 2014. Immediate infusion-related adverse reactions to intravenous immunoglobulin in a prospective cohort of 1765 infusions. *Int Immunopharmacol,* 23**,** 442-6.
Bishu, S., Madhavan, D., Perez, P., Civitello, L., Liu, S., Fessler, M., Holland, S. M., Jain, A. & Pao, M. 2009. CD40 ligand deficiency: neurologic sequelae with radiographic correlation. *Pediatric neurology,* 41**,** 419-427.
Busse, P. J., Razvi, S. & Cunningham-Rundles, C. 2002. Efficacy of intravenous immunoglobulin in the prevention of pneumonia in patients with common variable immunodeficiency. *J Allergy Clin Immunol,* 109**,** 1001-4.
Chapel, H. M., Spickett, G. P., Ericson, D., Engl, W., Eibl, M. M. & Bjorkander, J. 2000. The comparison of the efficacy and safety of intravenous versus subcutaneous immunoglobulin replacement therapy. *J Clin Immunol,* 20**,** 94-100.
Conrad-Stoppler, M. 2018. *Thymoma* [Online]. Available: https://www.medicinenet.com/thymoma/article.htm#what_causes_thymoma_and_what_are_risk_factors_for_thymoma [Accessed January 6 2020].
Cunningham-Rundles, C. 1989. Clinical and immunologic analyses of 103 patients with common variable immunodeficiency. *J Clin Immunol,* 9**,** 22-33.
Dashti-Khavidaki, S., Aghamohammadi, A., Farshadi, F., Movahedi, M., Parvaneh, N., Pouladi, N., Moazzami, K., Cheraghi, T., Mahdaviani, S. A., Saghafi, S., Heydari, G., Abdollahzade, S. & Rezaei, N. 2009. Adverse reactions of prophylactic intravenous

immunoglobulin; a 13-year experience with 3004 infusions in Iranian patients with primary immunodeficiency diseases. *J Investig Allergol Clin Immunol,* 19**,** 139-45.
De Gracia, J., Vendrell, M., Alvarez, A., Pallisa, E., Rodrigo, M. J., De La Rosa, D., Mata, F., Andreu, J. & Morell, F. 2004. Immunoglobulin therapy to control lung damage in patients with common variable immunodeficiency. *Int Immunopharmacol,* 4**,** 745-53.
Elsink, K., Van Montfrans, J. M., Van Gijn, M. E., Blom, M., Van Hagen, P. M., Kuijpers, T. W. & Frederix, G. W. J. 2020. Cost and impact of early diagnosis in primary immunodeficiency disease: A literature review. *Clin Immunol,* 213**,** 108359.
Fernandez, J. 2019. *Wiskott-Aldrich Syndrome* [Online]. Available: https://www.msdmanuals.com/professional/immunology-allergic-disorders/immunodeficiency-disorders/wiskott-aldrich-syndrome [Accessed January 6 2020].
Fu, L. W., Song, C., Isaranuwatchai, W. & Betschel, S. 2018. Home-based subcutaneous immunoglobulin therapy vs hospital-based intravenous immunoglobulin therapy: A prospective economic analysis. *Ann Allergy Asthma Immunol,* 120**,** 195-199.
Garbett, N. D., Currie, D. C. & Cole, P. J. 1989. Comparison of the clinical efficacy and safety of an intramuscular and an intravenous immunoglobulin preparation for replacement therapy in idiopathic adult onset panhypogammaglobulinaemia. *Clin Exp Immunol,* 76**,** 1-7.
Gardulf, A., Bjorvell, H., Gustafson, R., Hammarstrom, L. & Smith, C. I. 1993. The life situations of patients with primary antibody deficiency untreated or treated with subcutaneous gammaglobulin infusions. *Clin Exp Immunol,* 92**,** 200-4.
Gathmann, B., Mahlaoui, N., Gerard, L., Oksenhendler, E., Warnatz, K., Schulze, I., Kindle, G., Kuijpers, T. W., Van Beem, R. T., Guzman, D., Workman, S., Soler-Palacin, P., De Gracia, J., Witte, T., Schmidt, R. E., Litzman, J., Hlavackova, E., Thon, V., Borte, M., Borte, S., Kumararatne, D., Feighery, C., Longhurst, H., Helbert, M., Szaflarska, A., Sediva, A., Belohradsky, B. H., Jones, A., Baumann, U., Meyts, I., Kutukculer, N., Wagstrom, P., Galal, N. M., Roesler, J., Farmaki, E., Zinovieva, N., Ciznar, P., Papadopoulou-Alataki, E., Bienemann, K., Velbri, S., Panahloo, Z. & Grimbacher, B. 2014. Clinical picture and treatment of 2212 patients with common variable immunodeficiency. *J Allergy Clin Immunol,* 134**,** 116-26.
Gholami, K., Laali, E., Abolhassani, H., Ahmadvand, A., Mohebbi, N., Javadi, M. R., Aghamohammadi, A. & Rezaei, N. 2017. Costs of Hospital Admission on Primary Immunodeficiency Diseases. *Iran J Public Health,* 46**,** 342-350.
Guo, Y., Tian, X., Wang, X. & Xiao, Z. 2018. Adverse Effects of Immunoglobulin Therapy. *Front Immunol,* 9**,** 1299.
Health Quality Ontario 2017. Home-Based Subcutaneous Infusion of Immunoglobulin for Primary and Secondary Immunodeficiencies: A Health Technology Assessment. *Ont Health Technol Assess Ser,* 17**,** 1-86.
Healtline. 2019. *Immunodeficiency Disorders* [Online]. Available: https://www.healthline.com/health/immunodeficiency-disorders [Accessed December 10 2019].
Idf. 2013. *FDA Safety Communication: New boxed warning for thrombosis related to human immune globulin products.* [Online]. Immune Deficiency Foundation. Available: https://primaryimmune.org/fda-safety-communication-new-boxed-warning-for-thrombosis-related-to-human-immune-globulin-products [Accessed 2 March 2020].
Idf. 2019. *Severe combined immune deficiency and combined immune deficiency* [Online]. Immune Deficiency Foundation,. Available: https://primaryimmune.org/about-primary-immunodeficiencies/specific-disease-types/severe-combined-immune-deficiency-and-combined-immune-deficiency/ [Accessed January 6 2020].

Idf. 2020a. *Specific Disease Types* [Online]. Immune Deficiency Foundation. Available: https://primaryimmune.org/about-primary-immunodeficiencies/specific-disease-types/ [Accessed January 20 2020].
Idf. 2020b. *Transient Hypogammaglobulinemia of Infancy* [Online]. Immune Deficiency Foundation. Available: https://primaryimmune.org/about-primary-immunodeficiencies/specific-disease-types/transient-hypogammaglobulinemia-of-infancy/ [Accessed January 15 2020].
Igarashi, A., Kanegane, H., Kobayashi, M., Miyawaki, T. & Tsutani, K. 2014. Cost-minimization analysis of IgPro20, a subcutaneous immunoglobulin, in Japanese patients with primary immunodeficiency. *Clin Ther,* 36**,** 1616-24.
Ihe. 2012. *Development of a quality appraisal tool for case series studies using a modified Delphi technique* [Online]. Institute of Health Economics. Available: https://www.ihe.ca/research-programs/rmd/cssqac/cssqac-info [Accessed 3 March 2020].
Immunodeficiency Australia. 2019. *Types of immunodeficiency disease* [Online]. Available: https://www.immunodeficiency.com.au/content/types-immunodeficiency-disease [Accessed December 18 2019].
Jones, G. L., Vogt, K. S., Chambers, D., Clowes, M. & Shrimpton, A. 2018. What Is the Burden of Immunoglobulin Replacement Therapy in Adult Patients With Primary Immunodeficiencies? A Systematic Review. *Front Immunol,* 9**,** 1308.
Joshi, A. Y., Iyer, V. N., Hagan, J. B., St Sauver, J. L. & Boyce, T. G. 2009. Incidence and temporal trends of primary immunodeficiency: a population-based cohort study. *Mayo Clinic proceedings,* 84**,** 16-22.
Kirkpatrick, P. & Riminton, S. 2007a. Primary Immunodeficiency Diseases in Australia and New Zealand. *Journal of Clinical Immunology,* 27**,** 517-524.
Kirkpatrick, P. & Riminton, S. 2007b. Primary immunodeficiency diseases in Australia and New Zealand. *J Clin Immunol,* 27**,** 517-24.
Knutsen, A. P. 2019. *Transient hypogammaglobulinemia of infancy* [Online]. Available: https://emedicine.medscape.com/article/888706-overview#a5 [Accessed January 7 2020].
Lee, J. L., Mohamed Shah, N., Makmor-Bakry, M., Islahudin, F. H., Alias, H., Noh, L. M. & Mohd Saffian, S. 2020. A Systematic Review and Meta-regression Analysis on the Impact of Increasing IgG Trough Level on Infection Rates in Primary Immunodeficiency Patients on Intravenous IgG Therapy. *J Clin Immunol*.
Lingman-Framme, J. & Fasth, A. 2013. Subcutaneous immunoglobulin for primary and secondary immunodeficiencies: an evidence-based review. *Drugs,* 73**,** 1307-19.
Martin, A., Lavoie, L., Goetghebeur, M. & Schellenberg, R. 2013. Economic benefits of subcutaneous rapid push versus intravenous immunoglobulin infusion therapy in adult patients with primary immune deficiency. *Transfus Med,* 23**,** 55-60.
Martinez Garcia, M. A., De Rojas, M. D., Nauffal Manzur, M. D., Munoz Pamplona, M. P., Compte Torrero, L., Macian, V. & Perpina Tordera, M. 2001. Respiratory disorders in common variable immunodeficiency. *Respir Med,* 95**,** 191-5.
Mccusker, C., Upton, J. & Warrington, R. 2018. Primary immunodeficiency. *Allergy, asthma, and clinical immunology : official journal of the Canadian Society of Allergy and Clinical Immunology,* 14**,** 61-61.
Menzin, J., Sussman, M., Munsell, M. & Zbrozek, A. 2014. Economic impact of infections among patients with primary immunodeficiency disease receiving IVIG therapy. *Clinicoecon Outcomes Res,* 6**,** 297-302.
National Blood Authority. *Criteria for Clinical Use of Immunoglobulin in Australia* [Online]. Available: https://www.criteria.blood.gov.au/DoseCalculator [Accessed 3 March 2020].

Nba. 2017-18. *National Report on the Issue and Use of Immunoglobulin (Ig)* [Online]. National Blood Authority Australia,. Available: https://www.blood.gov.au/system/files/Report-on-the-Issues-and-Use-of-Ig-2017-18%20FINAL.pdf [Accessed December 18 2019].
Nba. 2018. *Criteria for the clinical use of immunoglobulin in Australi (the Criteria)* [Online]. Available: https://www.criteria.blood.gov.au/MedicalCondition/View/2603 [Accessed December 10 2019].
Nba. 23 Decemebr 2020 2019. *RE: Phase 2 HTA conditions data.*
Ness, S. 2019. Differentiating characteristics and evaluating intravenous and subcutaneous immunoglobulin. *Am J Manag Care,* 25**,** S98-s104.
Niaid. 2019. *Severe combined immunodeficiency (SCID)* [Online]. National Institute of Allergy and Infectious Diseases, . Available: https://www.niaid.nih.gov/diseases-conditions/severe-combined-immunodeficiency-scid [Accessed January 6 2020].
Nlm. 2019a. *Ataxia-telangiectasia* [Online]. US National Library of Medicine,. Available: https://ghr.nlm.nih.gov/condition/ataxia-telangiectasia#genes [Accessed January 6 2020].
Nlm. 2019b. *X-linked agammaglobulinemia* [Online]. US National Library of Medicine. Available: https://ghr.nlm.nih.gov/condition/x-linked-agammaglobulinemia [Accessed January 6 2020].
Nlm. 2020. *Common variable immune deficiency* [Online]. US National Library of Medicine. Available: https://ghr.nlm.nih.gov/condition/common-variable-immune-deficiency [Accessed January 15 2020].
Nolte, M. T., Pirofsky, B., Gerritz, G. A. & Golding, B. 1979. Intravenous immunoglobulin therapy for antibody deficiency. *Clin Exp Immunol,* 36**,** 237-43.
Orange, J. S., Grossman, W. J., Navickis, R. J. & Wilkes, M. M. 2010. Impact of trough IgG on pneumonia incidence in primary immunodeficiency: A meta-analysis of clinical studies. *Clin Immunol,* 137**,** 21-30.
Palabrica, F. R. R., Kwong, S. L. & Padua, F. R. 2013. Adverse events of intravenous immunoglobulin infusions: a ten-year retrospective study. *Asia Pacific allergy,* 3**,** 249-256.
Perraudin, C., Bourdin, A., Spertini, F., Berger, J. & Bugnon, O. 2016. Switching Patients to Home-Based Subcutaneous Immunoglobulin: an Economic Evaluation of an Interprofessional Drug Therapy Management Program. *J Clin Immunol,* 36**,** 502-10.
Pollock, R. F. & Meckley, L. M. 2018. An evaluation of the budget impact of a new 20% subcutaneous immunoglobulin (Ig20Gly) for the management of primary immunodeficiency diseases in Switzerland. *Clinicoecon Outcomes Res,* 10**,** 223-229.
Pourpak, Z., Aghamohammadi, A., Sedighipour, L., Farhoudi, A., Movahedi, M., Gharagozlou, M., Chavoshzadeh, Z., Jadid, L., Rezaei, N. & Moin, M. 2006. Effect of regular intravenous immunoglobulin therapy on prevention of pneumonia in patients with common variable immunodeficiency. *J Microbiol Immunol Infect,* 39**,** 114-20.
Quinti, I., Soresina, A., Agostini, C., Spadaro, G., Matucci, A., Sfika, I., Martini, H., Borghese, F., Guerra, A., Alessandra, V., Visentini, M., Plebani, A. & Fiorilli, M. 2008. Prospective study on CVID patients with adverse reactions to intravenous or subcutaneous IgG administration. *J Clin Immunol,* 28**,** 263-7.
Quinti, I., Soresina, A., Spadaro, G., Martino, S., Donnanno, S., Agostini, C., Claudio, P., Franco, D., Maria Pesce, A., Borghese, F., Guerra, A., Rondelli, R. & Plebani, A. 2007. Long-term follow-up and outcome of a large cohort of patients with common variable immunodeficiency. *J Clin Immunol,* 27**,** 308-16.
Sadeghi, B., Abolhassani, H., Naseri, A., Rezaei, N. & Aghamohammadi, A. 2015. Economic burden of common variable immunodeficiency: annual cost of disease. *Expert Rev Clin Immunol,* 11**,** 681-8.

Salehzadeh, M., Aghamohammadi, A. & Rezaei, N. 2010. Evaluation of immunoglobulin levels and infection rate in patients with common variable immunodeficiency after immunoglobulin replacement therapy. *J Microbiol Immunol Infect,* 43**,** 11-7.

Salzer, E., Daschkey, S., Choo, S., Gombert, M., Santos-Valente, E., Ginzel, S., Schwendinger, M., Haas, O. A., Fritsch, G., Pickl, W. F., Förster-Waldl, E., Borkhardt, A., Boztug, K., Bienemann, K. & Seidel, M. G. 2013. Combined immunodeficiency with life-threatening EBV-associated lymphoproliferative disorder in patients lacking functional CD27. *Haematologica,* 98**,** 473-478.

Shabaninejad, H., Asgharzadeh, A., Rezaei, N. & Rezapoor, A. 2016. A Comparative Study of Intravenous Immunoglobulin and Subcutaneous Immunoglobulin in Adult Patients with Primary Immunodeficiency Diseases: A Systematic Review and Meta-Analysis. *Expert Rev Clin Immunol,* 12**,** 595-602.

Shabaninejad, H., Asgharzadeh, A., Rezapour, A. & Rezaei, N. 2017. Cost-effectiveness analysis of subcutaneous immunoglobulin replacement therapy in Iranian patients with primary immunodeficiencies. *Med J Islam Repub Iran,* 31**,** 94.

Shrestha, P., Karmacharya, P., Wang, Z., Donato, A. & Joshi, A. Y. 2019a. Impact of IVIG vs. SCIG on IgG trough level and infection incidence in primary immunodeficiency diseases: A systematic review and meta-analysis of clinical studies. *The World Allergy Organization journal,* 12**,** 100068-100068.

Shrestha, P., Karmacharya, P., Wang, Z., Donato, A. & Joshi, A. Y. 2019b. Impact of IVIG vs. SCIG on IgG trough level and infection incidence in primary immunodeficiency diseases: A systematic review and meta-analysis of clinical studies. *World Allergy Organ J,* 12**,** 100068.

Singh, Y. N., Khare, S. D. & Malaviya, A. N. 1994. Common variable immunodeficiency (CVID) in northern India. *Asian Pac J Allergy Immunol,* 12**,** 169-72.

Staples, E. R., Mcdermott, E. M., Reiman, A., Byrd, P. J., Ritchie, S., Taylor, A. M. R. & Davies, E. G. 2008. Immunodeficiency in ataxia telangiectasia is correlated strongly with the presence of two null mutations in the ataxia telangiectasia mutated gene. *Clinical and experimental immunology,* 153**,** 214-220.

Sterne, J. A., Hernán, M. A., Reeves, B. C., Savović, J., Berkman, N. D., Viswanathan, M., Henry, D., Altman, D. G., Ansari, M. T., Boutron, I., Carpenter, J. R., Chan, A.-W., Churchill, R., Deeks, J. J., Hróbjartsson, A., Kirkham, J., Jüni, P., Loke, Y. K., Pigott, T. D., Ramsay, C. R., Regidor, D., Rothstein, H. R., Sandhu, L., Santaguida, P. L., Schünemann, H. J., Shea, B., Shrier, I., Tugwell, P., Turner, L., Valentine, J. C., Waddington, H., Waters, E., Wells, G. A., Whiting, P. F. & Higgins, J. P. 2016. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. 355**,** i4919.

Stiehm, E. R. & Fudenberg, H. H. 1966. Serum levels of immune globulins in health and disease: a survey. *Pediatrics,* 37**,** 715-27.

Strober, W. & Chua, K. 2000. Common variable immunodeficiency. *Clin Rev Allergy Immunol,* 19**,** 157-81.

Su, H. C. 2014. *Combined immune deficiencies* [Online]. Available: https://www.sciencedirect.com/topics/immunology-and-microbiology/combined-immunodeficiencies [Accessed January 6 2020].

Tga. 2020. *Database of Adverse Event Notifications (DAEN)* [Online]. Australian Government Department of Health, Therapeutic Goods Administration. Available: https://www.tga.gov.au/database-adverse-event-notifications-daen [Accessed 4 March 2020].

Van Montfrans, J. M., Hoepelman, A. I. M., Otto, S., Van Gijn, M., Van De Corput, L., De Weger, R. A., Monaco-Shawver, L., Banerjee, P. P., Sanders, E. a. M., Jol-Van Der Zijde, C. M., Betts, M. R., Orange, J. S., Bloem, A. C. & Tesselaar, K. 2012. CD27

deficiency is associated with combined immunodeficiency and persistent symptomatic EBV viremia. *The Journal of allergy and clinical immunology,* 129**,** 787-793.e6.

Viti, R., Marcellusi, A., Capone, A., Matucci, A., Vultaggio, A., Pignata, C., Spadaro, G., Vacca, A., Marasco, C., Agostini, C. & Mennini, F. S. 2018. Direct and Indirect Costs of Immunoglobulin Replacement Therapy in Patients with Common Variable Immunodeficiency (CVID) and X-Linked Agammaglobulinemia (XLA) in Italy. *Clin Drug Investig,* 38**,** 955-965.

Waniewski, J., Gardulf, A. & Hammarstrom, L. 1994. Bioavailability of gamma-globulin after subcutaneous infusions in patients with common variable immunodeficiency. *J Clin Immunol,* 14**,** 90-7.

Windegger, T. M., Nghiem, S., Nguyen, K. H., Fung, Y. L. & Scuffham, P. A. 2020. Primary immunodeficiency disease: a cost-utility analysis comparing intravenous vs subcutaneous immunoglobulin replacement therapy in Australia. *Blood Transfus,* 18**,** 96-105.