



**Australian Government**

**Department of Health**

# **Referral Form**

**Immunoglobulin use referred for HTA through MSAC**

**Review of Immunoglobulin use funded under the  
National Blood Agreement for**

***1592 PID - Primary Immunodeficiency diseases with antibody deficiency***

Disclaimer: There is a limit on the extent of research undertaken for this referral. Some elements are an expression of the NBA's general understanding which may or may not be fully comprehensive and accurate.

# REFERRER DETAILS AND SPECIFICATION OF THE SCOPE OF THE REFERRAL

## Referrer details (primary and alternative contacts)

Corporation / partnership details (where relevant): Statutory Authority  
Corporation name: National Blood Authority (a statutory authority forming part of the Commonwealth of Australia, established under the *National Blood Authority Act 2003* ('NBA Act'))  
ABN: 87 361 602 478  
Business trading name: National Blood Authority

### Primary contact name: REDACTED

Primary contact numbers  
Business: REDACTED  
Mobile: REDACTED  
Email: REDACTED

### Alternative contact name: REDACTED

Alternative contact numbers  
Business: REDACTED  
Mobile: REDACTED  
Email: REDACTED

## Overview of supply arrangements for publicly funded Immunoglobulin (Ig) in Australia

There are three frameworks which define the availability of publicly funded Ig products under the national blood arrangements. These arrangements are established under the National Blood Agreement and the *NBA Act*:

- a) TGA regulation
- b) policy decisions of all Australian Governments comprised in the *Criteria for the clinical use of immunoglobulin in Australia* (the Criteria), currently in force as Version 3, and
- c) supply arrangements implemented under national contracts established by the National Blood Authority.

Ig products are available as intravenous (IVIg) or subcutaneous (SCIg) formulations. Intramuscular (IMIg) formulations are also available but are treated as equivalent to SCIg formations for the purpose of these referrals. The potential use and availability of Ig differs for IVIg and SCIg, and these differences are identified where relevant throughout these referral.

Each of these frameworks is described briefly below.

### a) TGA regulation

Ig products for therapeutic use in Australia are regulated as prescription medicines under the *Therapeutic Goods Act 1989* and associated statutory instruments.

IVIg products are assessed for registration against the European Medicines Agency (EMA) EMA/CHMP/BPWP/94033/2007 rev.2 *Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg)* 22 July 2010, adopted by TGA effective 1 June 2014 (available from <http://www.tga.gov.au/clinical-efficacy-and-safety-guidelines#products>). This Guideline replaced CPMP/BPWG/388/95 Rev 1 (adopted by TGA 19 April 2001) (See [Attachment A](#)). This version has been included as some Ig products were registered on the Australian Register of Therapeutic Goods (ARTG) prior to the adoption of the updated Guideline and therefore assessed against this earlier version.

Under this regulatory guideline, IVIg products are considered to be registered indications in the following two categories: 'replacement therapy' and 'immunomodulatory effect'. The Guideline describes a range of conditions within each of these categories which are considered to be 'established', and others for which confirmatory data is required. Within this background, the Guideline describes a regulatory approach where certain lead indications are used as the proxy basis for establishment of efficacy for a range of other indications. The EMA approach is based on the regulatory approach adopted by the Federal Drug Administration in the USA.

In relation to primary immunodeficiency, section 7.3.1 provides as follows:

- Efficacy should be proven in an open clinical trial of one year duration in primary immunodeficiency syndromes. The patients selection should take into account statistical considerations (see below).
- At least 40 patients should be included; approximately half of these patients should be children and adolescents with an age distribution representative of this patient population. The patients should be followed over 12 months to avoid a seasonal bias (due to a greater rate of infections in the winter months).
- The recommended primary endpoint is the number of serious bacterial infections (less than 1.0 infection/subject/year). The protocol should prospectively provide specific diagnostic criteria for each type of serious infection to be included in the primary efficacy analysis. Serious bacterial infections include:
  - bacteraemia or sepsis,
  - bacterial meningitis,
  - osteomyelitis / septic arthritis,
  - bacterial pneumonia,
  - visceral abscess.
- Secondary endpoints are IgG trough levels, all other infections, antibiotic treatment, days lost from school/work, hospitalisations and fever episodes.

#### *Statistical considerations*

- The number of subjects to be included into the study might exceed 40 patients as the study should provide at least 80% power to reject the null-hypothesis of a serious infection rate greater or equal 1 by means of a one-sided test and a Type I error of 0.01.
- The secondary endpoints should be prospectively defined and their statistical analyses provided in the study protocol.
- The efficacy results from this study would apply to all types of primary immunodeficiency syndromes due to deficiency of functional IgG.

SCIg products are registered against the EMA document CHMP/BPWP/410415/2011 Rev.1 *Guideline on the clinical investigation of human normal immunoglobulin for subcutaneous and/or intramuscular administration (SCIg/IMIg)* 23 July 2015 adopted by TGA effective 2 February 2016 (available from <http://www.tga.gov.au/clinical-efficacy-and-safety-guidelines#products> ). This Guideline replaced EMEA/CPMP/BPWG/283/00 *Note for Guidance on the Clinical Investigation of Human Normal Immunoglobulin for Subcutaneous and Intramuscular Use* (adopted by TGA 12 March 2003), any SCIg products registered prior to the TGA adoption of the updated guidelines would have been assessed under this previous version.

The SCIg Guideline is read together with the IVIg Guideline above. Under the SCIg Guideline, SCIg products can be registered on an established basis for four replacement therapy indications, and any additional indications including CIDP are subject to a requirement for specific clinical data under para 5.3.4 .

#### b) *Criteria for the clinical use of immunoglobulin in Australia*

Under the National Blood Agreement, Australian Governments have determined that the basis for access to publicly funded Ig products under the National Blood Arrangements will be as specified in the Criteria for Clinical Use of Immunoglobulin in Australia (Criteria) available at This is confirmed in the *National Policy: Access to Government Funded Immunoglobulin Products in Australia* <https://www.blood.gov.au/national-policy-to-ig>.

Where an Ig product is not funded and supplied under the National Blood Arrangements, access to Ig for particular cases may still be available as a decision of a hospital drug committee or similar, or otherwise through direct order arrangements supported by some other source of funding.

Version 1 of the Criteria was issued in 2008, and partial review led to Version 2 issued in 2012. Version 2.1 was included in the national online system BloodSTAR from the time it was initially launched in 2016.

Version 3 of the Criteria has been developed through a comprehensive process of review managed by the NBA based on advice from Specialist Working Groups for Neurology, Immunology, Transplantation and the National Immunoglobulin Governance Advisory Group, and endorsed by all Governments through the Jurisdictional Blood Committee. The work on Version 3 commenced in 2014 and was completed in 2018. Version 3 of the Criteria more clearly articulates and standardises the diagnostic, qualifying and review criteria, initial and continuing authorisation periods, dosing controls and supporting evidence for access to Ig under the National Blood Agreement. These changes enhance consistency in access and further support the use of Ig products for clinically appropriate purposes, and for the treatment of patients whose health is most likely to be improved with Ig therapy.

Version 3 of the Criteria came into effect on 22 October 2018 and is available only in electronic form. It is primarily used for transactional authorisation of product access through the BloodSTAR system, and is available at <https://www.criteria.blood.gov.au/>.

In general, the Criteria follow the approach of TGA regulation and do not differentiate between individual brands of Ig products in relation to funded access under the National Blood Arrangements.

In relation to the availability of SCIg products under the National Blood Arrangements, governments have made a further policy decision that, in addition to access requirements applying generally under the Criteria, SCIg products are only approved for patients with a medical condition:

1. Where there is support for use cited in the Criteria, namely:

- primary immunodeficiency diseases with antibody deficiency
- specific antibody deficiency
- acquired hypogammaglobulinaemia secondary to haematological malignancies, or post-haemopoietic stem cell transplantation (HSCT)
- secondary hypogammaglobulinaemia unrelated to haematological malignancies, or post-haemopoietic stem cell transplantation (HSCT), and

2. Being treated by a clinical specialist within a hospital based SCIg program, where the hospital provides access to all resources and takes full accountability for the management and use of the SCIg product, at no additional cost to patients.

Further details on the requirements for access to SCIg products are available at <https://www.blood.gov.au/SCIg>. Note however, that the above hospital SCIg access model is scheduled for review in 2019 which may extend the range of ways in which patients can access SCIg. The policy decision of governments to fund access to SCIg products was supported by advice from the Medical Services Advisory Committee which can be found at <http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1334-public>

A detailed statement of the basis on which Ig is available under Version 3 of the Criteria for the condition in this referral is provided in Attachment B, which includes all evidence items which form part of the basis for access through the implementation of Version 3 of the Criteria in BloodSTAR. A summary of these criteria is provided at Attachment C. Evolution of the Criteria is expected to be a continuing process. For this reason any changes made to the Criteria V3 for the condition under this review, that occur during the assessment process that could potentially affect outcomes, will be communicated as an adjustment to this referral if and when the changes occur.

There could be differences in response rates between IVIg and SCIg for some of the selected outcomes (adverse events, disability, venous damage), and differences in health service consumption (e.g. outpatient, day-admission, hospital care v self-care). However, the product for both IVIg and SCIg is immunoglobulin (Ig) and for this reason it is recommended that Ig is the intervention and IVIg and SCIg are considered as different routes of administration.

c) *NBA supply arrangements*

The NBA has provided national supply of immunoglobulin products from Australian domestic arrangements for collection of plasma by the Australian Red Cross Blood Service and plasma fractionation by CSL Behring Pty Ltd and through imported product arrangements from a range of possible suppliers, since 2003.

NBA supply arrangements have evolved over that period with increasing demand for publicly funded Ig, with increasing numbers of Ig products registered for use in Australia on the ARTG, and with the addition of SCIg in addition to IVIg products under the National Blood Arrangements.

NBA supply arrangements do not simply fund all Ig products registered in Australia from time to time. To support supply security, good contract performance and value for money through competitive tendering, NBA arrangements currently include supply of multiple products from different sources and with some differing characteristics.

However, in general, NBA arrangements follow the approach of TGA regulation and the Criteria and do not differentiate between individual brands of Ig products in relation to funded access under the National Blood Arrangements. The most recent tender process for imported Ig products conducted by the NBA for supply from 1 January 2016 allowed for tenderers to put forward substantiated claims supporting the clinical fitness for purpose and utility of particular Ig products, which were then taken into account as one factor in the qualitative tender assessment process.

Currently Ig products supplied under the National Blood Arrangements are manufactured by the suppliers listed on the National Product List found at <https://www.blood.gov.au/national-product-list>.

Under NBA supply arrangements, all Ig product suppliers deliver products to the Australian Red Cross Blood Service (The Blood Service). The Blood Service operates as a secondary distributor of Ig products to hospitals and other health care facilities under a separate contract with the NBA.

**1. Provide a list of the medical condition/s and indications for which Immunoglobulin is funded under the National Blood Arrangements within the scope of this referral. Please indicate the specific Ig product(s) within the scope of this referral and the manner of administration (eg intravenous or subcutaneous)?**

This referral relates to the medical condition “Primary Immunodeficiency disease (PID) with antibody deficiency”.

Ig is used as immunoreplacement therapy in PID.

The indications for use under Version 3 (V3) of the Criteria are:

- Replacement therapy in common variable immune deficiency (CVID) – ESID diagnostic criteria met
- Replacement therapy in possible common variable immune deficiency (CVID) – (below normal serum IgG but normal serum IgA level)
- Replacement therapy in transient hypogammaglobulinaemia of infancy (children aged less than 4 years)
- Replacement therapy in recognised primary immunodeficiencies for which immunoglobulin replacement is universally indicated (e.g. SCID, Wiskott-Aldrich syndrome, etc.)

The specific conditions within this medical condition include:

- Severe combined immunodeficiency (SCID)
- Combined immunodeficiency generally less profound than SCID (e.g. thymoma)
- Combined immunodeficiency with associated or syndromal features (e.g. Wiskott Aldrich syndrome; ataxia telangiectasia)
- Severe reduction in all Ig isotypes with decreased or absent B-cells (e.g. XLA def)
- 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 (e.g. CD40L def)
- Transient hypogammaglobulinaemia of infancy
- Lymphoproliferative syndromes (e.g. XLP1, XLP2, CD27 def)
- Possible Common variable immune deficiency (CVID) - below normal serum IgG but normal serum IgA level

This particular referral is for Ig as a whole, as SCIg is currently funded under the National Blood Arrangements for this condition. As above, it is recommended that immunoglobulin is the intervention for this medical condition and IVIg and SCIg are considered as different routes of administration.

## INFORMATION ABOUT REGULATORY REQUIREMENTS

### 2. Has Ig been registered in the Australian Register of Therapeutic Goods (ARTG), for any of the medical condition/s and indications within the scope of this Referral?

*Table 1: Registered Ig products relevant to this referral*

Product name and company	Route of Administration	TGA indication for PID	NBA Funded for PID
Privigen 10% – CSL Behring Australia P/L (5g/50mL to 40g/400mL)	IV	Yes	Yes
Hizentra – CSL Behring Australia P/L (1g/5mL to 10g/50mL)	SC	Yes	Yes
Flebogamma 10% – Grifols Australia P/L (5g/50mL up to 40g/400mL)	IV	Yes	Yes
Evogam 16% – CSL Behring Australia P/L (0.8g/5mL or 3.2g/20mL)	SC	Yes	Yes
Intragam 10 – CSL Behring Australia P/L (2.5g/25mL to 20g/200mL)	IV	Yes	Yes
Flebogamma 5% - Grifols Australia P/L (0.5g/10mL to 20g/400mL)	IV	Yes	Yes
Cuvitru 20% - Shire Australia P/L	SC	Yes	No
Panzyga – Octaphama Australia P/L	IV	Yes	No
Gamunex 10% – Grifols Australia P/L	IV and SC	Yes	No
Hyqvia – Shira Australia P/L	SC	Yes	No
Intratect – Pfizer Australia P/L	IV	Yes	No
Intratect 5% – Pfizer Australia P/L	IV	Yes	No
Kiovig – Shira Australia P/L	IV and SC	Yes	No

\* Primary immunodeficiency diseases (PID)

\*\* Indicates that Ig is *currently* funded for PID funded under the National Blood Arrangements. Note that tendering arrangements may change products funded in the future. The current National Product List with suppliers and prices can be found at <https://www.blood.gov.au/national-product-list>. Please note that in the event of any discrepancy between Table 1 and the National Product List, the material from the National Product List should take precedence over any information in Table 1.

IV – intravenous  
SC – subcutaneous  
IM – intramuscular

An overview of the listings can be found at [Attachment D1](#) and the full listing of all indications for Ig products listed can be found at [Attachment D2](#).

## SUMMARY OF EVIDENCE

**3. Provide an overview of all key published journal articles or research related to Ig for any of the medical condition/s and indications within the scope of this review. Please do not attach full text articles; this is just intended to be a summary.**

Table 2. Overview of key published journal articles or research related to PID

Study No.	Type of study design	Title of journal article/research project (include trial identifier/study lead)	Short description of research (max 50 words)	Website link to journal article or research (or citation details if link not available)	Date of publication
1.	Literature review	'Summary data on conditions and papers', in A systematic literature review and report on the efficacy of intravenous immunoglobulin therapy and its risks	A systematic literature review of the efficacy and risks of IVIg. The results informed the development of evidence-based clinical practice guidelines for the use of IVIg in Australia.	Biotext 2004, 'Summary data on conditions and papers', in A systematic literature review and report on the efficacy of intravenous immunoglobulin therapy and its risks, commissioned by the National Blood Authority on behalf of all Australian Governments, pp. 218. Available from: <a href="https://www.blood.gov.au/system/files/A-systematic-literature-review-and-report-on-the-efficacy-of-IVIg-therapy-and-its-risks.pdf">https://www.blood.gov.au/system/files/A-systematic-literature-review-and-report-on-the-efficacy-of-IVIg-therapy-and-its-risks.pdf</a>	2004
2.	Guidelines	Practice parameter for the diagnosis and management of primary immunodeficiency	A practical guide for consultant allergists/immunologists for the clinical recognition and diagnosis of immunodeficiency, along with the general principles that guide management of primary immunodeficiency disorders.	Bonilla, FA, Bernstein, L, Khan, DA, et al 2005, 'Practice parameter for the diagnosis and management of primary immunodeficiency', Annals of Allergy, Asthma and Immunology, vol. 94, no. 5, suppl. 1, pp. S1–63.  <a href="https://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Practice%20and%20Parameters/PID-Nov-2015.pdf">https://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Practice%20and%20Parameters/PID-Nov-2015.pdf</a>	2005

<i>Study No.</i>	<i>Type of study design</i>	<i>Title of journal article/research project (include trial identifier/study lead)</i>	<i>Short description of research (max 50 words)</i>	<i>Website link to journal article or research (or citation details if link not available)</i>	<i>Date of publication</i>
3.	Guidelines	Chronic Suppurative Lung Disease and Bronchiectasis in children and adults in Australia and New Zealand – Clinical Practice Guideline	Guidelines for managing chronic suppurative lung disease (CSLD) and bronchiectasis in Australian and New Zealand children and adults updated (latest search date Oct 2013) based on systematic reviews, multi-disciplinary meetings and a modified Delphi process.	Chang, AB, Bell, SC, Torzillo, PJ, et al 2014, 'Thoracic Society of Australia and New Zealand Chronic Suppurative Lung Disease and Bronchiectasis in children and adults in Australia and New Zealand – Clinical Practice Guideline'. Available from: <a href="https://www.thoracic.org.au/journal-publishing/command/download_file/id/36/filename/TSANZ-ChronicSuppurativeLungDisease-Guidelines-2016-web.pdf">https://www.thoracic.org.au/journal-publishing/command/download_file/id/36/filename/TSANZ-ChronicSuppurativeLungDisease-Guidelines-2016-web.pdf</a> .	2014
4.	Textbook	Primary immune deficiency diseases		Cooper, MD & Schroeder, Jr HW 2005, 'Primary immune deficiency diseases', in DL Kasper, E Braunwald, AS Fauci, et al (eds), Harrison's Textbook of Medicine, 16th edn, McGraw-Hill, New York, pp. 1939–47.	2005
5.	Review of evidence	Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology	Reviews the basis for the FDA-approved indications for IGIV and will discuss other disease states in which IGIV has been used. Includes the review of 357 citations. Primary literature review on each subject was derived from searching the National Center for Biotechnology Information Pubmed database using the words 'IVIG', 'IGIV' and 'intravenous immunoglobulin'.	Orange, JS, Hossny, EM, Weiler, CR, et al 2006, 'Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology', Journal of Allergy and Clinical Immunology, vol. 117, no. 4, pp. S525–53.	2006



Study No.	Type of study design	Title of journal article/research project (include trial identifier/study lead)	Short description of research (max 50 words)	Website link to journal article or research (or citation details if link not available)	Date of publication
				<a href="https://www.jacionline.org/article/S0091-6749(06)00178-3/fulltext">https://www.jacionline.org/article/S0091-6749(06)00178-3/fulltext</a>	
6.	Report	Primary immunodeficiency diseases: an update on the classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency	An updated classification of PIDs presented in nine different tables of major groups. Each table lists the condition, its genetic defect if known, and the major immunological or non-immunological abnormalities associated with the disease.	Al-Herz, W, Bousfina, A, Casanova, J-L, et al 2014. 'Primary immunodeficiency diseases: an update on the classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency.' Frontiers in Immunology, Vol 5, article 162, pp1-33. doi: 10.3389/fimmu.2014.00162. Available from: <a href="http://journal.frontiersin.org/article/10.3389/fimmu.2014.00162/full">http://journal.frontiersin.org/article/10.3389/fimmu.2014.00162/full</a>	2014
7.	*Guidelines	Diagnostic Criteria PID	Developed to establish simple, objective and clear guidelines that ensure that different physicians and scientists are using the same definitions when they include patients in research studies.	European Society for Immunodeficiencies (ESID) Diagnostic Criteria PID 2019, found on 31/05/19 at <a href="https://esid.org/Education/Diagnostic-Criteria-PID">https://esid.org/Education/Diagnostic-Criteria-PID</a>	2019

*\* These guidelines have been updated since their inclusion in V3 of the Criteria. Both the 2014 and 2019 versions have been referenced in this referral.*

**4. Identify yet to be published research that may have results available in the near future that could be relevant in the consideration by MSAC Please do not attach full text articles; this is just intended to be a summary.**

The NBA is not currently associated with any research projects relating to PID.

*Table 3. Overview of yet to be published research related to PID*

<i>Study No.</i>	<i>Type of study design*</i>	<i>Title of journal article/research project (include trial identifier/study lead)</i>	<i>Short description of research (max 50 words)**</i>	<i>Website link to journal article or research (or citation details if link not available)</i>	<i>Relevant dates of research***</i>
.					

*\* Categorise study design, for example meta-analysis, randomised trial, non-randomised trial or observational study, etc.*

*\*\* Provide high level information including population numbers and whether patients are being recruited or in post-recruitment, including providing the trial registration number to allow for tracking purposes.*

*\*\*\* For example, research start date, expected research completion date, and expected publication date.*

# CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

## **5. List all appropriate professional bodies / organisations representing the groups of health professionals who are allowed to request Ig for the medical condition/s and indications within the scope of this referral:**

The Criteria V3 allows only an Immunologist to request Ig for PID.

Some professional bodies/organisations known to the NBA representing Immunologists are listed below:

- Australian Society for Clinical Immunology and Allergy (ASCIA)
- Australasian Society for Immunology
- The Thoracic Society of Australia and New Zealand
- Australasian Society for Infectious Diseases (ASID)
- Australian Antimicrobial Resistance Group
- Royal Australian College of Physicians

Please note that this may not be a comprehensive list and that further research may need to be undertaken.

## **6. List professional bodies / organisations that may be impacted by the use of Ig (i.e. those who provide a comparable product / device / service) within the scope of this Referral**

The possible comparable product for this condition is antibiotics as required. The providers of these products may be impacted.

Suppliers of Ig may also be impacted:

- CSL Behring
- Grifols
- Shire (Takeda)
- Octapharma
- Pfizer

## **7. List the consumer organisations relevant to the use of Ig within the scope of this Referral**

- Immune Deficiencies Foundation Australia (IDFA)
- Australian Primary Immunodeficiency Patient Support (AusPIPS)
- Lung Foundation Australia
- Rare Voices Australia
- Consumer Health Forum

## **8. Nominate the clinical experts who will be advising on the use of Ig within the scope of this Referral:**

Clinicians nominated by the Reference Group have been sent the targeted survey on the draft referral, however no prior agreement from specialist clinicians to provide advice was able to be obtained.

*Please note that the Department may also consult other referrers, procedural lists and disease specialists to obtain their insight.*

# POPULATION (AND PRIOR TESTS), INDICATION, COMPARATOR, OUTCOME (PICO) INFORMATION ABOUT THE PROPOSED POPULATION

## 9. Summarise the natural history of the medical condition/s within the scope of this referral, and a high level summary of associated burden of disease in terms of morbidity and mortality:

There are over 280 identified PIDs. Recognised PIDs for which immunoglobulin replacement is universally indicated are: X-linked agammaglobulinemia, severe combined immunodeficiency, Wiskott-Aldrich syndrome, X-linked lymphoproliferative syndrome, hyper IgM syndrome and severe T-cell immunodeficiency<sup>1</sup>.

Primary immune deficiencies usually present with signs and symptoms of infections that can be repetitive, severe, or refractory to therapy and caused by organisms of low virulence. Infection is by far the most common complication of PIDs and the most frequent problem that leads to medical evaluation. Infections in immunodeficient patients usually occur with pathogens that are prevalent in the community but are of unusual severity, frequency, and duration. They also tend to respond poorly to therapy. Children with invasive pneumococcal disease should undergo immunologic investigation because up to 26 percent of these patients older than two years have an identifiable PID. Autoimmune diseases and malignancies are complications of many PIDs<sup>2</sup>.

The revised European Society for Immunodeficiency Diseases (ESID 2014) diagnostic criteria for common variable immune deficiency (CVID)<sup>3</sup> require the diagnosis to be established after the fourth year of life (but symptoms may be present before) and at least one of the following:

- increased susceptibility to infection
- autoimmune manifestations
- granulomatous disease
- unexplained polyclonal lymphoproliferation
- affected family member with antibody deficiency.

AND

A marked decrease of immunoglobulin G (IgG) and marked decrease of IgA with or without low IgM levels (measured at least twice; less than the normal reference range for their age).

AND

At least one of the following:

- poor antibody response to vaccines (and/or absent isohemagglutinins); i.e. absence of protective levels despite vaccination where defined
- low switched memory B-cells (less than 70 percent of age-related normal value).

AND

Secondary causes of hypogammaglobulinemia have been excluded.

These 2014 ESID diagnostic criteria for PID have been used as a guide in the development of the qualifying criteria for Ig therapy in Australia.

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<sup>1</sup> Criteria for Clinical Use of Immunoglobulin in Australia V3

<sup>2</sup> Bonilla, FA, Bernstein, L, Khan, DA, et al 2005, 'Practice parameter for the diagnosis and management of primary immunodeficiency', *Annals of Allergy, Asthma and Immunology*, vol. 94, no. 5, suppl. 1, pp. S1–63

<sup>3</sup> European Society for Immunodeficiencies (ESID) Diagnostic Criteria PID 2014

The ESID 2019 diagnostic criteria for probable CVID<sup>4</sup> require the patient to have:

- an onset of immunodeficiency at greater than two years of age
- a marked decrease of IgG (at least 2 SD below the mean for age)
- a marked decrease in at least one of IgM or IgA
- absent isohemagglutinins and/or poor response to vaccines
- secondary causes of hypogammaglobulinaemia have been excluded.

Possible CVID is defined using the same above criteria as probable however requires only one isotype (IgG, IgM or IgA) to be markedly decreased.

Genetic diagnoses are continually being updated as described in the classification system for the International Union of Immunology Societies (IUIS). It is recognised that genetic diagnoses are not always possible<sup>5</sup>.

Patients with CVID are predisposed to chronic lung disease and pulmonary deterioration as a result of chronic or subclinical infection<sup>6</sup>. Most patients with CVID are recognised to have immunodeficiency in the second, third or fourth decade of life, after they have had several pneumonias; however children and older adults may also be affected. Viral, fungal and parasitic infections as well as bacterial infections may be problematic. Approximately 50 percent of patients have autoimmune manifestations. There is an increased risk of malignancy<sup>7</sup>.

In relation to X-linked agammaglobulinaemia, most patients develop recurrent bacterial infections, particularly otitis, sinusitis and pneumonia, in the first two years of life. Approximately 20 percent of patients present with an overwhelming infection, often with neutropenia<sup>5</sup>.

Severe combined immunodeficiency (SCID) is usually diagnosed within the first two years of life and most often results in failure to thrive, persistent diarrhoea, respiratory symptoms and/or thrush. Significant bacterial infections are common. SCID is fatal in the first two years of life unless the patient is treated with extremely restrictive isolation, hematopoietic stem cell transplant or therapy that replaces the abnormal gene or gene product<sup>6</sup>.

Further summaries of natural histories and burden of disease of 18 various PIDs with clearly established diagnostic criteria can be found at <https://esid.org/Education/Diagnostic-Criteria-PID>.

**10. Specify characteristics of patients with the medical condition/s within the scope of this referral who would be considered eligible for Ig therapy under the National Blood Arrangements, including details of how a patient is investigated, managed and referred within the Australian health care system in the lead up to being considered eligible for Ig therapy:**

How a patient with PID is investigated, managed and referred in the lead up to being considered eligible for Ig therapy is outside of the NBA's expertise. Expert clinical advice<sup>8</sup> from the Ig Reference Group explained that the process of patient investigations, diagnosis and management of people with PID with antibody deficiency is very complicated. This patient group includes a wide range of rare conditions and both paediatric and adult patients. Patients often present with atypical features, have an autoimmune disease as their primary presentation and therefore are on multiple therapies. Some PIDs are not antibody mediated and would therefore not be considered for Ig therapy.

The clinical expert immunologist advised that a number of tests are performed for diagnosis. These may include tests to measure antibody levels, assess the quality of the immune response (e.g. response to vaccine

<sup>4</sup> European Society for Immunodeficiencies (ESID) Diagnostic Criteria PID 2019, accessed 31/05/19 <https://esid.org/Education/Diagnostic-Criteria-PID>

<sup>5</sup> Criteria for Clinical Use of Immunoglobulin in Australia V3

<sup>6</sup> Orange, JS, Hossny, EM, Weiler, CR, et al 2006, 'Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology', Journal of Allergy and Clinical Immunology, vol. 117, no. 4, pp. S525–53.

<sup>7</sup> European Society for Immunodeficiencies (ESID) Diagnostic Criteria PID 2019, accessed 31/05/19 <https://esid.org/Education/Diagnostic-Criteria-PID>

<sup>8</sup> Clinical expert immunologist, Ig Review Reference Group Meeting 3, July 2019

challenge), genetic tests or response to therapies including Ig therapy. Genetic testing is not currently MBS funded.

Overall, given this patient group is so heterogeneous, the full work up of the patient and diagnostic tests varies widely.

An outline of the qualifying criteria to access Ig funded under the National Blood Arrangements for PID can be found at [Attachment C](#) or <https://www.criteria.blood.gov.au/MedicalCondition/View/2576> . For more detailed criteria refer to [Attachment B](#).

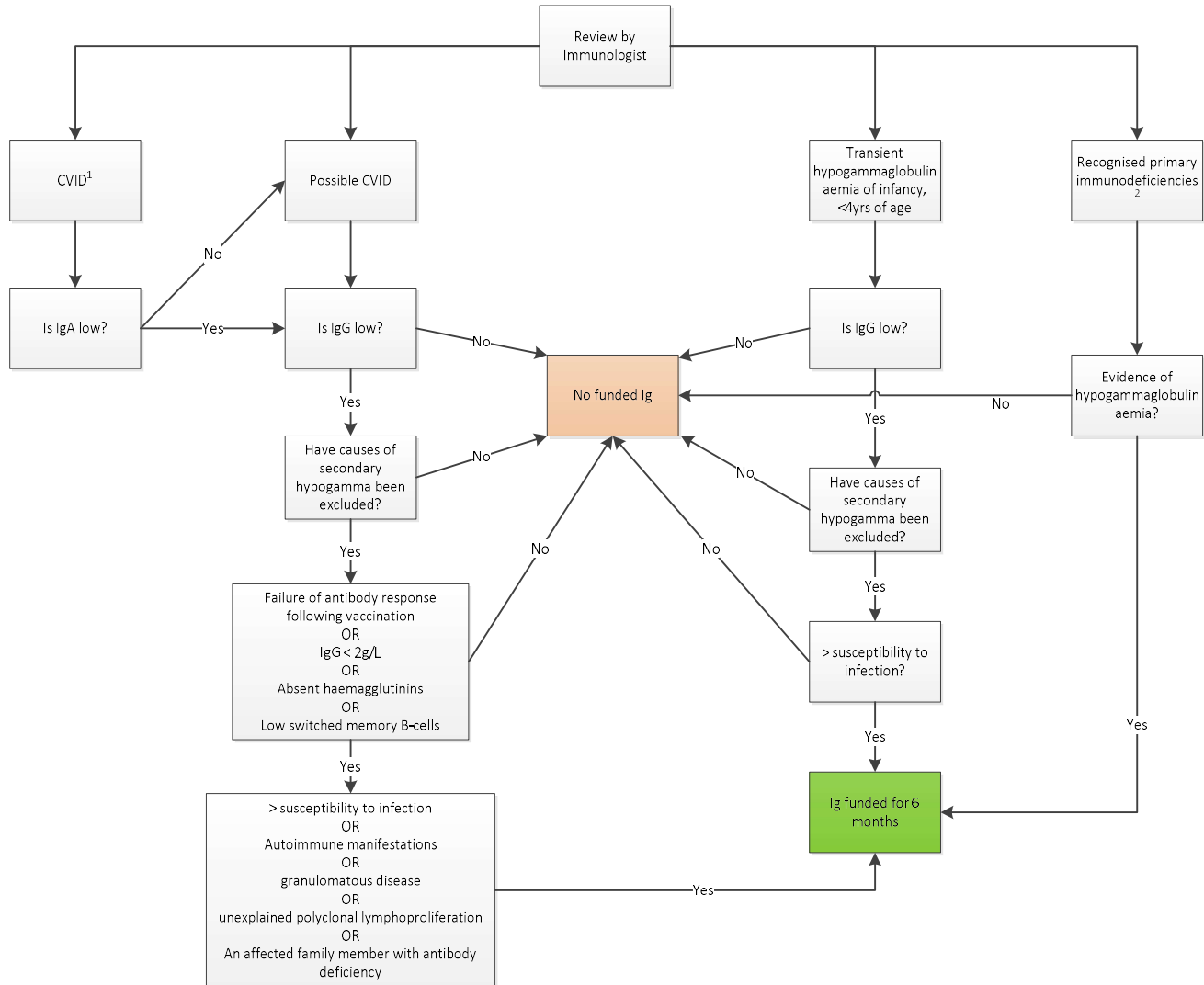
**11. Define and summarise the current clinical management pathways (algorithm) for patients who are eligible for Ig therapy (supplement this summary with an easy to follow flowchart depicting the current clinical management pathways leading up to being considered eligible for Ig therapy):**

For a patient to access government funded Ig for PID they must meet the criteria for one of four indications listed below and described in detail at [Attachment B](#).

- Replacement therapy in common variable immune deficiency (CVID) – ESID diagnostic criteria met
- Replacement therapy in possible common variable immune deficiency (CVID) – (below normal serum IgG but normal serum IgA level)
- Replacement therapy in transient hypogammaglobulinaemia of infancy (children aged less than 4 years)
- Replacement therapy in recognised primary immunodeficiencies for which immunoglobulin replacement is universally indicated (e.g. SCID, Wiskott-Aldrich syndrome, etc.)

*Please note that in the event of any discrepancy between Figure 1 and Q10 , the material from the Criteria provided in Q10 should take precedence over any interpretation taken in Figure 1.*

**FIGURE 1 –Initial access to Ig funded under the National Blood Arrangements as per this Referral – Algorithm**



1. ESID diagnostic criteria met

2. Must be a recognised PID for which Ig replacement is universally indicated

**12. If applicable, advise which health professionals primarily manage the patient receiving the Ig product within the scope of this referral:**

Under V3 of the Criteria, only an AHPRA registered immunologist may diagnose and review a patient with PID for the purpose of requesting Ig. If a patient is not being cared for by an immunologist they will need to be referred to one for access to Ig Funded under the National Blood Arrangements.

# INFORMATION ABOUT THE INTERVENTION

## 13. Describe the key components (including administering health professionals) and clinical steps involved in delivering Ig therapy to eligible patients within the scope of this referral:

If Ig therapy is delivered by intravenous infusion, patients will attend hospital for a day procedure to be infused. Depending on the dose, which may be split over several days, they may (or may not) be required to attend for a 'day procedure' on a number of days (usually consecutive) each month.

Intravenous infusion involves:

- identification check to ensure the right patient is receiving the right product at the right dose and at the right time. This check is done by two health professionals – usually one must be a doctor or a registered nurse and the other can be either a doctor, registered nurse or an enrolled nurse;
- preparation of equipment (Ig vial/bottle, vented line, aseptic dressing pack, cannula);
- the procedure is explained to the patient and consent is obtained;
- cannula is inserted using aseptic technique by a credentialed nurse or doctor;
- the IV line is inserted directly into the Ig vial/bottle and the IV line is primed with Ig product (without dilution) and hung in accordance with the local hospital's protocol;
- the patient is monitored for any reactions and the infusion is slowed or stopped depending on the patient's response.

If the Ig therapy is delivered subcutaneously, the patient or carer will be educated about how to administer the product at home. They will undertake more frequent subcutaneous infusions (usually twice weekly) at home. This requires:

- storing the product in accordance with the manufacturer's advice;
- insertion of a butterfly subcutaneous cannula using aseptic techniques into subcutaneous layer just under the skin of the abdomen or thigh;
- drawing up the required dose into a syringe;
- connection of the syringe to the subcutaneous line;
- pushing the dose into the abdomen at the required rate which will vary depending on the dose size and the patient's response.
- 

## 14. Specify how long the delivery of Ig therapy typically takes to perform within the scope of this referral:

The timeframe to administer an Ig infusion is dependent on the:

- dose required;
- the patient's weight (as dosing is in grams/kg);
- the product's advised infusion rate and hospital's protocol which determines the infusion rate used at that location (which may differ from the product's Product Information Sheet);
- the patient's response during the infusion. If the patient experiences a reaction such as a headache, the rate of infusion will be slowed or stopped depending on the severity of the reaction;
- whether administration is intravenous or subcutaneous.

### **Typical IVIg delivery time for PID**

The dose could be administered over the course of a few hours for an 80 Kg person (including day admission, identification, cannulation and set-up, infusion, post infusion monitoring) (e.g. 0.4g/kg for an 80Kg person = 32g). Applying the infusion rate provided in the Product Information sheet provided for Intragam 10 is set out below. This table indicates a minimum total infusion time of 100 minutes for a patient of 80kg. The infusion rate could reduce for various reasons, e.g. adverse events. Please note that this is only one of the products funded for PID and that other products may have different infusion rates.



Table 4: 80Kg person @ 0.4g/Kg = 32grams of a 10% Ig product

Minutes	Rate ml/min	grams	Mls	Mls remaining
Starting	0	0	0	320
15	1	1.5	15	305
15	3	4.5	45	260
15	3	4.5	45	215
15	4	6	60	155
15	4	6	60	95
15	4	6	60	35
10	4	4	40	-5

**Typical SCIg delivery time for PID**

The Product Information sheet for Hizentra<sup>[1]</sup> states that the recommended initial infusion rate should not exceed 15 mL/hour/site. If well-tolerated, the infusion rate can then gradually increase to 25 mL/hour/site. Applying this infusion rate and assuming only one site is used at a time, the minimum administration time for a patient of 80kg on a dose of 0.1g/kg (0.5mL/kg) per week would be approximately 1 hour and 48 minutes (note that the 'gradual increase' of rate may be interpreted and implemented differently, see table 5 for interpretation in this example). It is advised that if the dose is above 25mL that multiple injection sites be used. The infusion rate could reduce for various reasons, e.g. adverse events. Please note that this is only one of the products funded for PID and that other products may have different infusion rates. There are also likely to be multiple infusion devices available for SCIg which may increase or decrease the rate of infusion.

Table 5: 80Kg person @ 0.1g/Kg = 8grams = 40mL Hizentra

Minutes	Rate ml/min	Mls	Mls remaining
Starting	0	0	40
15	0.25	3.75	36.25
15	0.3	4.5	31.75
15	0.35	5.25	26.5
15	0.42	6.3	20.2
15	0.42	6.3	13.9
15	0.42	6.3	7.6
18	0.42	6.3	0

[1] Product information for AusPAR Hizentra Normal Human Immunoglobulin CSL Behring Ltd 2013-00301-2-2 Final 25 June 2014. Accessed 7 August 2019 from <https://www.tga.gov.au/sites/default/files/auspar-normal-human-immunoglobulin-140625-pi.pdf>

**15. If applicable, are there any limitations on provision of the various Ig product to the relevant patient groups within the scope of this referral (i.e. accessibility, dosage, quantity, duration or frequency):**

In addition to the 'Criteria' outlined above:

- Patients receiving (or carers administering) subcutaneous immunoglobulin will require training and sufficient aptitude and capability to administer the product at home. SCIg also requires the appropriate infusion equipment as appropriate for the particular product. SCIg programs are not available at all hospitals. This varies depending on the local jurisdiction's policy, and the local hospital's capacity.
- IV administration of Ig requires good venous access and availability of a day hospital with IV infusion facilities.
- The following dosing parameters are set in the Criteria V3:
  - Maximum dose
  - Minimum dose
  - Dose frequency
  - Whether divisions are allowed

While higher doses can be accessed, doctors must provide a rationale for requiring a higher dose. Criteria V3 encourages dosing at the lowest effective dose by defaulting to the minimum dose and frequency.

- Duration of access to Ig is determined by the 'authorisation period' determined in the Criteria V3. Access to Ig cannot exceed the 'authorisation period'. To access further treatment the doctor must reapply and demonstrate the patient meets the 'criteria' (see Attachment B: V3 Proforma for PID).

The frequency of monitoring depends on age (more frequent monitoring is advisable in younger growing children) and the clinical considerations of the individual patient. A minimum of every 6 to 12 months is standard. The adequacy of IgG replacement is determined by the trough (preinfusion) or steady-state IgG level in association with the clinical course. The dose might need to be adjusted for excessive infections (poor clinical response), growth or weight change, or other processes, such as enteric loss or increased metabolism. The steady-state IgG level is also useful for monitoring adherence of patients receiving SCIg infusions<sup>9</sup>.

**16. If applicable, identify any healthcare resources or other medical services that need to be delivered at the same time as the Ig products within the scope of this referral):**

The patient's vital signs will be monitored during the course of the infusion (blood pressure, pulse, temperature) by a nurse or enrolled nurse. Patients may require analgesia or antihistamine to manage a reaction e.g. headaches, flushes, rash.

As an example; in all patients receiving Flebogamma, IVIg administration requires:

- adequate hydration prior to the initiation of the infusion of IVIg;
- monitoring of urine output;
- monitoring of serum creatinine levels;
- avoidance of concomitant use of loop diuretics<sup>10</sup>.

**17. If applicable, advise whether delivering Ig therapy could be delegated or referred by the health professional primarily responsible for managing the patient to another professional for delivery including any limitations on who might deliver it:**

The diagnosis and management of the patient cannot be delegated. Intravenous administration of Ig requires a treating doctor to determine the dose. However, the doctor who diagnoses the condition may not be the same doctor to reviews treatment. The administration of Ig intravenously delivered Ig is undertaken by nursing staff or possibly a junior doctor and cannot be delegated. The intravenous infusion is overseen by the hospital

<sup>9</sup> Bonilla, FA, Bernstein, L, Khan, DA, et al 2005, 'Practice parameter for the diagnosis and management of primary immunodeficiency', *Annals of Allergy, Asthma and Immunology*, vol. 94, no. 5, suppl. 1, pp. S1-63

<sup>10</sup> Therapeutic Goods Administration 2019. Australian Product Information, Flebogamma 10% DIF (Human Normal Immunoglobulin [IVIg] 100mg/ml) solution for infusion. Found at <https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2013-PI-01254-1&d=201905201016933>

medical staff with overarching responsibility held by the treating clinician. The NBA understands that in very rare circumstances, IVIg has been administered by the patient or by a 'hospital in the home' nurse.

If Ig is administered at home via subcutaneous administration, the administration of the product can be delegated to the patient or their carer. A nurse or technician has responsibility for ensuring the patient or carer is trained in subcutaneous administration. Ongoing support is generally provided by a registered nurse. Access to, and protocols and processes for, SCIg programs vary across the country.

**18. If applicable, advise what type of training or qualifications are required to deliver Ig therapy as well as any accreditation requirements to support its delivery:**

BloodSTAR requires any medical officer registered as an immunologist with the Australian Health Practitioner Regulation Agency (AHPRA) to diagnose and review a patient with PID.

Local hospital policies will vary. Nursing qualifications are required to commence and monitor an IVIg infusion.

As this procedure requires cannulation, training should be provided and competence determined and monitored for this procedure which may be done by a doctor or a nurse depending on the institution.

For subcutaneous administration, the patient/carer must be trained in the procedure by a qualified nurse or technician.

All sites that administer blood or blood products should be accredited under the National Safety and Quality Health Service Standard for Blood Management.

**19. Indicate the proposed settings in which Ig therapy is delivered (select all relevant settings):**

- Inpatient private hospital
- Inpatient public hospital (as a private patient)
- Inpatient public hospital (as a public patient)
- Outpatient clinic
- Consulting rooms
- Day surgery centre (as an admitted private patient)
- Day surgery centre (as an outpatient)
- Residential aged care facility
- Patient's home
- Laboratory
- Other – please specify below 'Private same day infusion facility unattached to a hospital'

**20. Please describe the rationale for and proportion of delivery in each setting (to enable a judgement about the settings that are important enough to fall within the scope of the clinical and economic evaluations in the review):**

**Inpatient – private hospital.** Patient requires admission due to dose required over multiple days, comorbidities/advanced age, has private medical insurance and a preference to be in a private facility and is managed by a neurologist who is able to support the patient's preference.

**Inpatient - public hospital (as a private patient).** Patient requires admission due to dose required over multiple days, comorbidities/advanced age, has private medical insurance and a preference to be admitted as a private patient and is managed by a neurologist who is able to support the patient's preference.

**Inpatient - public hospital (as a public patient).** Patient requires admission due to dose required over multiple days, comorbidities/advanced age, and does not have medical insurance or has a preference to be admitted as a public patient.

**Outpatient clinic (as an outpatient).** Patient has regular maintenance infusions and does not require admission to hospital.

**Patient's home** –SCIg is available under the National Blood Arrangements for PID and may be available to be administered in the patient's home where: the patient or carer has a preference for SCIg, the patient has access to a hospital participating in a suitable SCIg program, the doctor prescribes SCIg, SCIg service/training is available, the patient/carer has received training. NBA advises that in 2017-18, around 8.3 percent of all *treatment episodes* of Ig therapy used SCIg, of which 67 percent were for PID. In the same year, approximately

3.4 percent of *total Ig grams* issued were for SCIg. Of these, 65 percent were for PID. While the initial infusions are administered in the public hospital outpatient setting to train the patient or the carer, SCIg is subsequently administered in the patient's home. SCIg use at home is expected to increase.

**Private same day infusion facility** (e.g. private infusion facility where chemotherapy or other infusion/venesection procedures are conducted). These would be pre-arranged infusions.

NBA data held for the 2017-18 financial year on CVID indicate around 74 percent of patients are treated in the public setting than in the private setting (see Table 6). Of all specific conditions in the Criteria V3, CVID and possible CVID account for 82 percent of Ig issued for PID.

*Table 6: 2017-18 Public and private patients receiving Ig for CVID: sourced from the National Report on the Issue and Use of Immunoglobulin (Ig) (publication forthcoming, date to be confirmed)*

	Public n (%)	Private n (%)	Total N (%)
Patients	1464 (74%)	504 (26%)	1,968 (100%)
Grams	484,500 (76%)	154,138 (24%)	638,638 (100%)

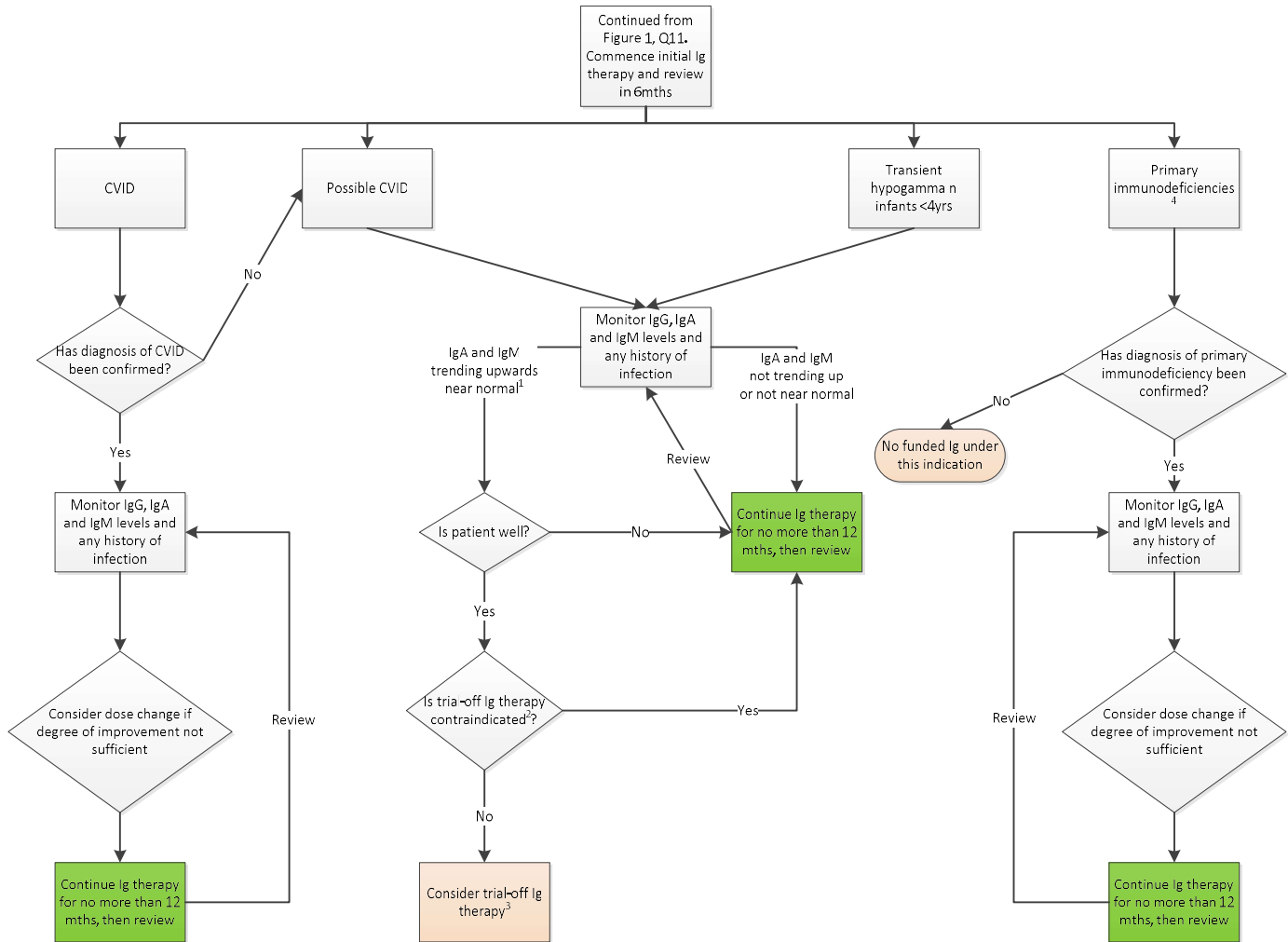
**21. Define and summarise the current clinical management pathways (algorithm) from the point of initiating Ig therapy within the scope of this referral, including provision of health care resources (supplement this summary with an easy to follow flow chart, including health care resources):**

The current basis for ongoing access to Ig products for PID under Version 3 of the Criteria under the National Blood Arrangements is described at <https://www.criteria.blood.gov.au/MedicalCondition/View/2576> or in detail at [Attachment B](#) (V3 Condition Proforma). If there is a discrepancy between the information contained from the weblink and the detailed proforma at Attachment B, the web-link should take precedence.

A schematic summary of the basis for ongoing access to Ig therapy for PID, is provided at Figure 2.

Please note that in the event of any discrepancy between Figure 2 and the BloodSTAR weblink, the material from the BloodSTAR weblink should take precedence over any interpretation taken in Figure 2.

**FIGURE 2—Continuing access to Ig funded under the National Blood Arrangements as per this Referral – Algorithm. NOTE: this algorithm is a representation only, not all conditions are able to be captured in one flowchart.**



<sup>1</sup> 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.

<sup>2</sup> 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.

<sup>3</sup> 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.

<sup>4</sup> Recognised PIDs for which Ig is universally indicated.

## INFORMATION ABOUT THE COMPARATOR(S)

### 22. Nominate the appropriate comparators for Ig therapy, i.e. how would the eligible populations be managed if they cannot receive Ig therapy (including identifying health care resources that are delivered at the same time as the comparator product or service):

Standard therapy for PIDs may include Ig, hematopoietic stem cell transplant (HSCT) and/or gene therapy. Treatment of underlying cause may include splenectomy, thymectomy, chemotherapy, immunomodulation, antivirals prophylactically or as needed, plasmapheresis, Rituximab and Cytokine inhibitors or supplements. Aggressive and prolonged antimicrobial therapy should be considered for immunodeficient patients. Long-term antibiotic therapy might be required in addition to Ig replacement for preventing infection in antibody-deficient patients<sup>11</sup>. However, the Thoracic Society of Australia and New Zealand Clinical Practice Guideline suggested that long-term oral antibiotics should not be prescribed routinely for patients with chronic suppurative lung disease and bronchiectasis<sup>12</sup>.

The Ig Reference Group agreed that given the heterogeneous patient group, 'no Ig' is the most appropriate comparator for this condition. Best supportive care may or may not include antibiotic treatment, prophylactic antibiotics, and antimicrobials.

Table 7: Sensitivities for comparator

Diagnosis	IgG	HSCT	Gene therapy	Other treatments
<b>CIDs</b>				
SCID (IL2RG, ADA)	Yes	Yes	Yes	<ul style="list-style-type: none"> <li>• Avoid live vaccines: all</li> <li>• PCP prophylaxis: all SCID, CD40, CD40L</li> <li>• Antimicrobials as needed</li> <li>• Blood products irradiated, CMV-: all</li> <li>• ADA: PEG-ADA</li> <li>• CD40, CD40L: G-CSF</li> </ul>
SCID (other)	Yes	Yes	No	
CD40L deficiency	Yes	Yes	No	
Other CID	Yes	Many	No	
<b>Immunodeficiency syndromes</b>				
WAS	Yes	Yes	Yes	<ul style="list-style-type: none"> <li>• Avoid live vaccines: many</li> <li>• Multidisciplinary care: many</li> <li>• WAS: splenectomy</li> <li>• DGS: thymus transplantation</li> <li>• Immunomodulation as needed</li> <li>• Chemotherapy as needed</li> </ul>
AT	Some	No	No	

<sup>11</sup> Bonilla, FA, Bernstein, L, Khan, DA, et al 2005, 'Practice parameter for the diagnosis and management of primary immunodeficiency', Annals of Allergy, Asthma and Immunology, vol. 94, no. 5, suppl. 1, pp. S1-63

<sup>12</sup> Chang, AB, Bell, SC, Torzillo, PJ, et al 2014, 'Thoracic Society of Australia and New Zealand Chronic Suppurative Lung Disease and Bronchiectasis in children and adults in Australia and New Zealand – Clinical Practice Guideline'.

<i>Diagnosis</i>	<i>IgG</i>	<i>HSCT</i>	<i>Gene therapy</i>	<i>Other treatments</i>
DGS	Some	No	No	
Other syndromes	Some	Some	No	
<b>Antibody deficiency</b>				
Agammaglobulinaemia	Yes	No	No	<ul style="list-style-type: none"> <li>• Avoid live vaccines: agammaglobulinaemia, CVID</li> <li>• Antibiotics: all</li> <li>• Splenectomy: CVID</li> <li>• Immunomodulation: CVID</li> <li>• Chemotherapy: CVID</li> <li>• Pneumococcal vaccine: SIGAD, IGGSD, SAD</li> </ul>
CVID	Yes	Rare	No	
Other antibody deficiency	Yes	No	No	
<b>Immune dysregulation</b>				
Other than FHL, ALPS, IPEX or APECED	Some	Some	No	<ul style="list-style-type: none"> <li>• Antimicrobials as needed</li> <li>• Chemotherapy as needed</li> <li>• Immunomodulators as needed</li> </ul>
<b>Phagocytic cell defects</b>				
HIES type 1	Some	Rare	No	<ul style="list-style-type: none"> <li>• Avoid live bacterial vaccines</li> <li>• Antimicrobial prophylaxis</li> </ul>
<b>Innate immune defects</b>				
NEMO deficiency, other NF-KB defects	Yes	Yes	No	<ul style="list-style-type: none"> <li>• Avoid live vaccines: NF-KB</li> <li>• PCP prophylaxis: NF-KB</li> <li>• Antimicrobial prophylaxis: NF-KB</li> <li>• G-CSF: WHIM syndrome</li> </ul>
WHIM syndrome	Yes	Some	No	
Cytokine autoantibody-mediated disorders	Possible	No	No	<ul style="list-style-type: none"> <li>• Plasmapheresis</li> <li>• Rituximab</li> <li>• Cytokine supplement</li> </ul>

The above table is a modification of "TABLE VI. Summary of therapeutic considerations for primary immunodeficiencies and their complications"<sup>13</sup>, noting that PIDs for which IgG is not included as standard of care have been removed

**23. Do the products or alternative service that are nominated as the comparator have existing MBS items or PBS listings?**

<sup>13</sup> Bonilla, FA, Bernstein, L, Khan, DA, et al 2005, 'Practice parameter for the diagnosis and management of primary immunodeficiency', Annals of Allergy, Asthma and Immunology, vol. 94, no. 5, suppl. 1, pp. S1-63

- Yes (please provide all relevant MBS items or PBS listings)
- No

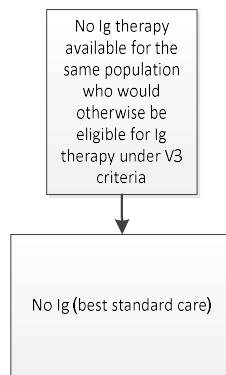
*Table 8: PBS listing for comparator products*

Generic Name	PBS subsidised for <i>insert condition name</i>	PBS unrestricted or Authority required	PBS item numbers and presentations if available
.			
.			
.			

**24. Define and summarise the comparator clinical management pathways (algorithm) that patients would follow after they first receive the products or alternative services nominated as the comparator (supplement this summary with an easy to follow flow chart, including health care resources):**

In circumstances where Ig is not an option, a schematic summary of the treatment pathway is suggested for the purpose of this review as follows:

**Figure 3 – Treatment pathway when Ig is not an option.**



**25. (a) Are there additional products or services used with the nominated comparators**

- Yes
- No

**(b) If yes, please identify these products or services and outline the extent to which each additional product / device is used with the nominated comparators:**



# INFORMATION ABOUT THE CLINICAL OUTCOMES

## 26. Summarise the clinical claims of Ig therapy, against the nominated comparators, in terms of consequences for health outcomes (comparative benefits and harm):

Ig is used as antibody replacement therapy in PIDs.

Among the immunodeficiencies, the clearest indication for IVIg is for patients who produce no antibody, which can occur because of the absence of functionally mature B cells. However, common variable immunodeficiency (CVID) is the highest user of Ig in the PID group in Australia. Studies of IVIg in this indication have shown that it reduces the incidence of infection, including pneumonia and progression of lung disease. The historical evidence and existing studies are compelling enough to indicate this therapy to prevent recurrent infection in the setting of CVID. The review of evidence that came to this conclusion categorised the recommendation for use of Ig in PID as:

- definitely beneficial in primary immune defects with absent B cells
- definitely beneficial in primary immune defects with hypogammaglobulinaemia and impaired specific antibody production
- probably beneficial in primary immune defects with normogammaglobulinaemia and impaired specific antibody production
- unlikely to be beneficial in isolated IgA deficiency
- unlikely to be beneficial in isolated IgG4 deficiency<sup>14</sup>.

The Biotext systematic review<sup>15</sup> rated the level of evidence for the use of IVIg in those PIDs that were subject to literature review as 2a (some RCTs and/or case studies, possible benefit – research needed). The Biotext systematic review suggested that the efficacy of IVIG as replacement IgG therapy in primary and secondary immunodeficiency syndromes probably relates to the provision of a broad spectrum of antibodies against endemic pathogens. It reported that the frequency of adverse reactions ranged from 1 to 15 percent, but was usually less than 5 percent. Most reported adverse reactions were mild, immediate generalised reactions which manifested as:

- pyrogenic reactions (marked by high temperature and systemic symptoms)
- minor systemic reactions (headache, myalgia, fever, chills, light-headedness, nausea and/or vomiting)
- vasomotor or cardiovascular manifestations (changes in blood pressure and tachycardia, possibly associated with shortness of breath and chest tightness).

These generalised reactions were usually self-limiting, and often alleviated by reducing the rate or volume of infusion, or by premedication with an analgesic or antihistamine. Less frequently, delayed generalised reactions can arise a few days after infusion.

Headache was the most commonly reported immediate adverse reaction with IVIG. Other adverse reactions reported included thrombophlebitis (associated with prolonged administration), positive direct antiglobin tests and red cell haemolysis and neutropenia. Acute renal dysfunction and acute renal failure have been reported rarely, and hypersensitivity reactions very rarely<sup>13</sup>.

## 27. Please advise if the overall clinical claim is:

- Superiority  
 Non-inferiority

<sup>14</sup> Orange, JS, Hossny, EM, Weiler, CR, et al 2006, 'Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology', *Journal of Allergy and Clinical Immunology*, vol. 117, no. 4, pp. S525–53.

<sup>15</sup> Biotext 2004, 'Summary data on conditions and papers', in A systematic literature review and report on the efficacy of intravenous immunoglobulin therapy and its risks, commissioned by the National Blood Authority on behalf of all Australian Governments, pp. 218.

**28. Please list the health outcome types that need to be specifically measured in assessing the clinical claim of Ig therapy versus the comparator within the scope of this referral, prioritising the major health outcomes first:**

Outcomes	<p><i>The outcomes identified pre assessment and considered in scope are:</i></p> <p><i>Safety Outcomes:</i></p> <ul style="list-style-type: none"> <li>• Serious adverse events (e.g. antibiotic allergy, anaphylaxis, veno-occlusive events)</li> <li>• Antibiotic resistance</li> </ul> <p><i>Clinical effectiveness outcomes:</i></p> <ul style="list-style-type: none"> <li>• IgG trough levels (increased)</li> <li>• Number of antibiotic treatments (decreased)</li> <li>• Number of infections (decreased)</li> <li>• Quality of life</li> <li>• Morbidity</li> <li>• Mortality</li> </ul> <p><i>Healthcare system resources utilisation:</i></p> <ul style="list-style-type: none"> <li>• Changes in health system resource utilisation associated with the intervention             <ul style="list-style-type: none"> <li>○ Ig products</li> <li>○ Infusion equipment</li> <li>○ Administrative and clinician time (e.g. resources associated with requesting, and authorising, access to Ig)</li> <li>○ Nursing time (for initiation and monitoring if IVIg)</li> <li>○ Hospitalisation (including use of hospital resources)</li> <li>○ Medication to treat adverse events (e.g. analgesia or antihistamines)</li> <li>○ Product dispensing and disposal of any unused product</li> <li>○ Follow-up and/or monitoring visits, including regular immunologist visits</li> </ul> </li> <li>• Change in health system resource utilisation associated with the comparator(s)</li> </ul>
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## INFORMATION ABOUT ESTIMATED UTILISATION

### 29. Estimate the prevalence and/or incidence of the proposed populations within the overall medical condition:

Primary immunodeficiencies occur in as many as 1:2000 live births and a prevalence of 1:10,000 in the general population. The male/female ratio of PIDs is approximately 5:1 in infants and children but approaches 1:1 in adults<sup>16</sup>. Australia's population as at 31 December 2017 was reported by the Australian Bureau of Statistics as 24,775,400<sup>17</sup>. Assuming a prevalence of 1:10,000 this equates to 2478 patients with PID in Australia. NBA data in Table 9 indicates 2324 patients treated with Ig for PIDs in 2017-18 financial year.

More than 280 primary immunodeficiency diseases (PIDs) have been identified. Many of these cause antibody deficiency. In some cases, antibody deficiency is associated with B-cell deficiency (e.g. X-linked agammaglobulinaemia), while in others, B-cells are present. Antibody deficiency can be the only manifestation of PID, or there can be other defects as well (e.g. T-cell deficiency, autoimmunity). Not all PIDs cause antibody defects and, therefore, Ig replacement is not always indicated<sup>18</sup>. The Criteria V3 requires qualifying patients to have a confirmed or suspected PID and susceptibility to infection (in the case of those PIDs for which immunoglobulin replacement is universally indicated this may be represented by hypogammaglobulinaemia only) as many patients will be well despite the finding of a serum IgG below the normal range for age<sup>15</sup>.

### 30. Provide data on the use of Ig therapy over recent years for the medical condition/s within the scope of this referral:

Table 9: Data on the use of Ig therapy over recent years for PID (NBA internal data)

	2013-14	2014-15	2015-16	2016-17	2017-18
New patients	266	275	223	IVIg 232 SCIg 51 Total 283	IVIg 218 SCIg 39 Total 257
Total patients	1822	1941	1999	IVIg 1825 SCIg 334 Total 2159	IVIg 1851 SCIg 473 Total 2324
Grams	558,617	614,781	660,816	IVIg 599,555 SCIg 102,075 Total 701,630	IVIg 596,588 SCIg 128,798 Total 725,386
Average grams per patient	307	317	331	IVIg 329 SCIg 306	IVIg 322 SCIg 272

Distribution of the specific conditions under V3 of the Criteria can be seen in the chart below. Note that the data obtained for this chart is limited to a short time-frame - from the implementation of V3 (22 October 2018) to 31 December 2018. This has been done due to the change in specific conditions between V2 and V3 of the Criteria.

<sup>16</sup> Bonilla, FA, Bernstein, L, Khan, DA, et al 2005, 'Practice parameter for the diagnosis and management of primary immunodeficiency', Annals of Allergy, Asthma and Immunology, vol. 94, no. 5, suppl. 1, pp. S1-63.

<sup>17</sup> Australian Bureau of Statistics, 3101.0 – Australian Demographic Statistics, released 20 June 2019, accessed from <https://www.abs.gov.au/ausstats/abs@.nsf/0/D56C4A3E41586764CA2581A70015893E?Opendocument> on 7 August 2019

<sup>18</sup> Criteria for Clinical Use of Immunoglobulin in Australia V3

Figure 4: Distribution of grams of Ig by specific condition V3 (NBA internal data)

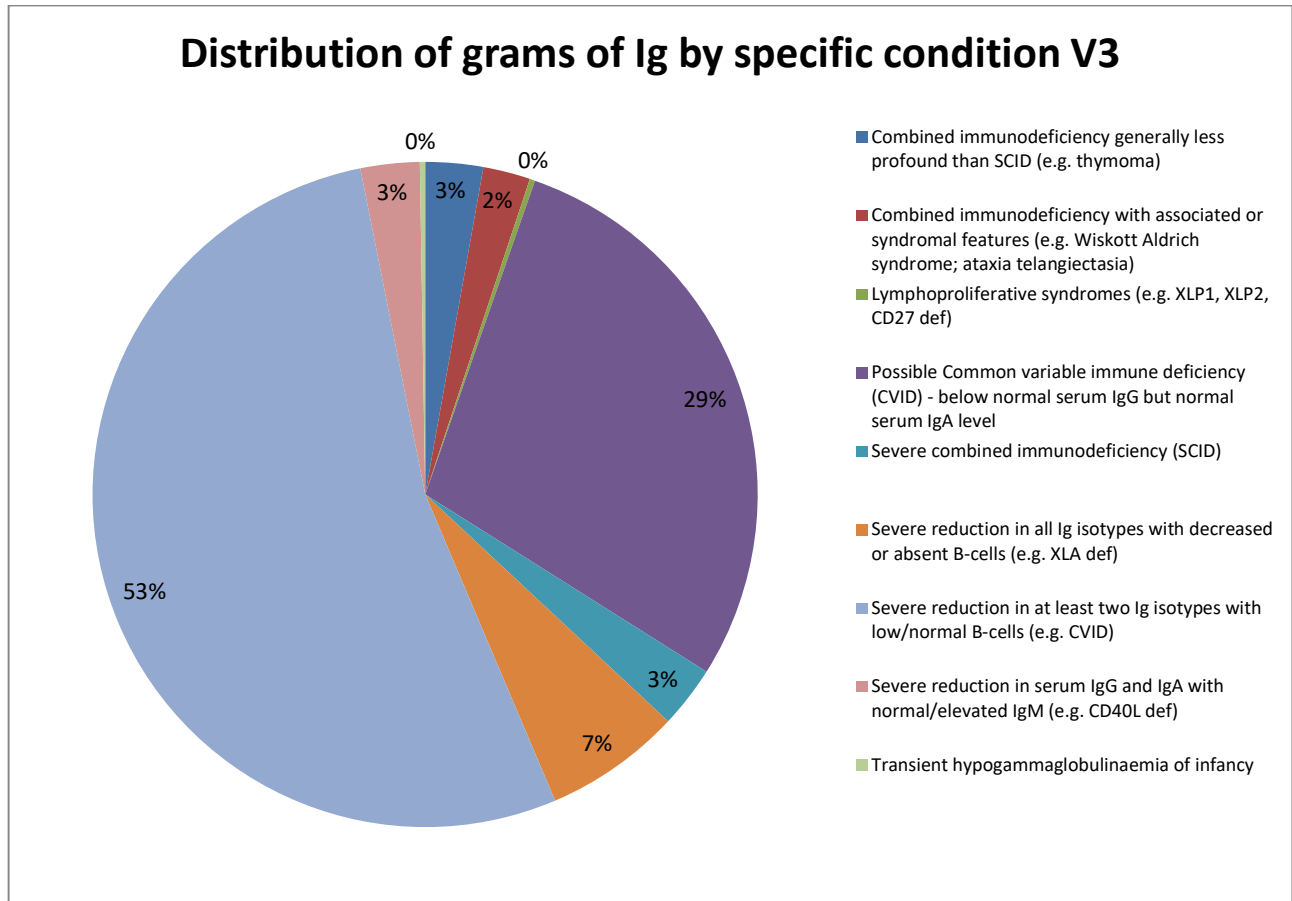
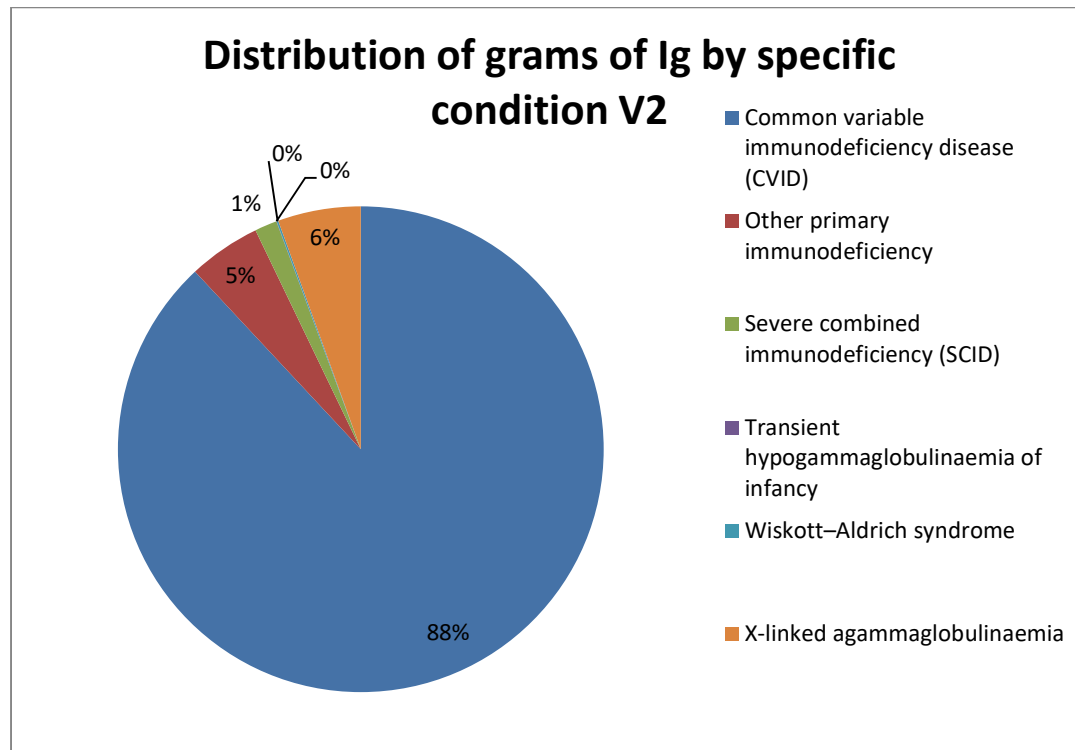


Figure 5: Distribution of grams of Ig by specific condition V2 (NBA internal data)



**31. Estimate the dose of Ig and the number of times Ig is delivered to a patient per year for the medical condition/s within the scope of this referral:**

Table 10: Ig dosing and frequency for PID (NBA internal data).

Note: The meaning of term ‘episode’ has evolved over the course of the development of this administrative dataset. The definition of the term is more closely related to a ‘dispensing episode or event’. As there may be more than one ‘dispense episode or event’ in a single course of treatment, the true number of courses of treatment during any period is highly likely to be fewer than the number of ‘episodes’ recorded in BloodSTAR and STARS.

	PID Total		CVID	
	2016-17	2017-18	2016-17	2017-18
Treatment episodes	32,207	33,108	27,680	28,872
Average treatment episodes per year	15	14	15	15
Average Gms/Kg/Episode	0.48	0.47	0.47	0.44

**32. How many years is Ig required for the patient with the medical condition/s within the scope of the referral?**

This condition is usually life-long, however the need for Ig therapy can be acute, chronic or transient. The usual length of an authorisation for maintenance therapy is one year at which point a review is required to assess ongoing need for further Ig therapy. Continuing therapy is allowed so can exceed one year and can be ongoing. The majority of patients have more than one authorisation. The average duration of Ig therapy for PIDs is unknown and is likely to vary between specific conditions due to varying underlying causes.

The clinical expert on the Ig Reference Group<sup>19</sup> advised that patients may or may not respond to Ig therapy but confirmed that patients who do respond to Ig will be on the treatment for life as this is replacement therapy. However, weaning off Ig therapy may be trialled in some paediatric patients if it is suspected that their immune system has recovered.

**33. Provide commentary on risk of ‘leakage’ to populations with the medical condition/s not targeted by Ig therapy (outside the population indicated in V3 Criteria):**

The most significant leakage risk is associated with patients receiving ongoing Ig therapy for an unconfirmed PID and after recovery of the immune system.

To manage this risk, the Criteria encourages cessation of Ig therapy to be considered at least after each 12 months of treatment for those patients treated under the indication ‘Replacement therapy in possible CVID (below normal serum IgG but normal serum IgA level), unless contraindicated. If serum IgM and IgA levels are trending upwards and near normal, this may suggest recovery of the immune system and a trial might be considered if the patient is well. Once the patient has normal IgA and IgM levels, the IgG is also likely to be normal and a trial off Ig therapy may be undertaken. Ig therapy should be extended as required to enable cessation of therapy in September/October, with repeat clinical and/or immunological evaluation before re-commencement of therapy. This should particularly be considered in patients who do not have active bronchiectasis and/or suppurative lung disease. An immunoglobulin washout period of four to six months is

<sup>19</sup> Clinical expert immunologist, Ig Review Reference Group Meeting 3, July 2019

necessary to enable an accurate assessment. Prophylactic antibiotics may be considered to cover the period of cessation of immunoglobulin therapy<sup>20</sup>. If patients do require further Ig therapy after trialling off, a new request may be made.

For those patients with a suspected PID for which Ig replacement is universally indicated, evidence of hypogammaglobulinaemia is required for initial Ig treatment and confirmation of diagnosis is required for access to continuing treatment.

The Criteria also encourages cessation of Ig therapy at least after 24 months for infants with transient hypogammaglobulinaemia should IgM and IgA levels be trending upwards and close to normal, and if the patient is well. This indication has a low risk of leakage regardless due to the small amounts of Ig used in infants.

For those patients with confirmed CVID or other recognised PID for which Ig replacement is universally indicated, treatment is likely to be ongoing. To mitigate the risk of patients with unconfirmed diagnosis, the Criteria utilises the ESID diagnostic criteria to ensure CVID is confirmed for access under this indication. A clinical or genetic diagnosis must be provided for ongoing treatment in patients with recognised PIDs.

Another risk of leakage for consideration is in dosing. Some patients may be on higher doses of Ig than required. BloodSTAR mitigates this risk somewhat by defaulting to the lowest recommended dose when Ig is requested. The prescriber can then increase the dose if required. A higher dose than the maximum cited in the Criteria may be requested but is likely to only be approved in exceptional circumstances.

Jurisdictional data for 2015-16 on number of patients, grams, grams/episode and grams/1,000 population in the relevant state or territory and nationally are provided below. These data indicate substantial variation in practice between jurisdictions.

*Table 11: Jurisdictional differences in Ig prescribing for CVID (NBA Annual Report 2015-16)*

CVID	NSW	VIC	QLD	SA	WA	TAS	NT	ACT	National	Fold Vari*
Patients	920	320	350	111	100	28	5	69	1,876	
Grams	311,301	107,889	124,577	30,967	32,192	8,463	1,810	21,440	638,638	
Grams/Episode	20	24	27	22	23	27	50	23	22	
Grams/1,000 population	40	17	26	18	13	16	7	53	26	3.1

\* Fold vari = Fold variation calculated by dividing the largest grams/1000 population by the smallest g/1000 population using only data from the five largest states (NSW, VIC, QLD, SA and WA).

<sup>20</sup> Criteria for Clinical Use of Immunoglobulin in Australia V3

## COST INFORMATION

### 34. Indicate the current cost of providing Ig therapy within the medical condition/s. Where possible, please provide overall and breakdown costs:

The cost of Ig for PID funded under National Blood Arrangements for domestic Ig products was \$85,259,890 (\$78,377,751 IVIg and \$6,882,138 SCIg) in 2017-18. This equates to an average cost per patient of \$36,686.

Table 12: Breakdown of product costs for PID (NBA internal data)

Product category	Cost (ex GST)
*Domestic IVIg cost	\$ 78,377,751.67
Imported IVIg cost	\$ 1,875,135.74
*Domestic SCIg	\$ 6,882,138.89
Imported SCIg	\$ 3,650,282

\*Domestic costs include the cost of plasma collection and fractionation.

Costs associated with the following have not been included in the above estimate:

- MBS costs: i.e. doctor visits
- Costs associated with requesting access to Ig product
- Hospital costs: nursing time, infusion centre administration, patient/carer training costs
- IV and SCIg infusion equipment costs
- Authorisation costs: cost to contract Blood Service to conduct authorisations
- Product dispensing costs
- Product wastage (e.g. discarding unused portion of product)
- Criteria review and update costs

Table 13: Ig product issued 2017-18: sourced from the National Report on the Issue and Use of Immunoglobulin (Ig) (publication forthcoming, date to be confirmed)

Primary immunodeficiency	IVIg					SCIg	
	Flebogamma 5 percent	Flebogamma 10 percent	* Intragam P	Intragam 10	Privigen 10 per cent	SCIg Evogam	SCIg Hizentra
Ig product issued in grams	10,978	7,145	7,620	547,861	22,985	48,775	80,023
NBA current price per gram in \$	45	45	58.49	58.49	45	58.49	59.15
**Total cost by product in \$	494,010	321,525	445,694	32,044,390	1,034,325	2,852,849	4,733,360

\*Intragam P no longer available

\*\*Note that product issued data is from 2017-18 and the price listed is current as at 14 June 2019. Prices and allocation of products change over time. Costs are for product only and domestic costs do not include plasma collection or fractionation.