Australian Government

Department of Health

Application 1592:

Review of immunoglobulin use for

PID – Primary Immunodeficiency Diseases with antibody deficiency

PICO Confirmation

(to guide a new application to MSAC)

Summary of PICO/PPICO criteria to define the question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

Component	Description
Patients	Patients with Primary Immunodeficiency Diseases (PID) with antibody deficiency who are currently eligible for immunoglobulin (Ig) treatment in Australia according to version 3.1 of the *Criteria for Clinical Use of Immunoglobulin in Australia*.
Intervention	The intervention to be investigated is immunoglobulin (Ig). This may be delivered in one of two forms: • Intravenous (IVIg) • Subcutaneous (SCIg)
Comparator	No Ig
Outcomes	*Safety Outcomes:* • Serious adverse events (e.g. antibiotic allergy, anaphylaxis, veno-occlusive events, risk of blood-borne infections) • Antibiotic resistance • Fevers • Headaches • Allergic reactions • Hives *Clinical effectiveness outcomes:* • Number of infections • Number of antibiotic treatments • Morbidity • Change in quality of life • Mortality • IgG trough levels • Bronchiectasis *Healthcare system resources utilisation*: • Ig products • Infusion equipment • Administrative and clinician time (e.g. resources associated with requesting and authorising access to Ig) • Nursing time (for initiation and monitoring IVIg) • For SCIg users, nursing time for education of users on how to administer SCIg at home • Hospitalisation (including use of hospital resources) • Medication to treat adverse events (e.g. analgesia or antihistamines) • Product dispensing and disposal of any unused product • Follow-up and/or monitoring visits, including regular immunologist visits

PICO rationale

Population

Patients with Primary Immunodeficiency Diseases (PID) with antibody deficiency who are currently eligible for immunoglobulin treatment in Australia according to the 'Criteria for Clinical Use of Immunoglobulin in Australia Version 3.1'[1] are the proposed population in this PICO Confirmation.

The Criteria for the Clinical Use of Immunoglobulin in Australia (herein referred to as '*the Criteria'*) is a framework describing the medical conditions and specific circumstances for which the use of immunoglobulin (Ig) is considered clinically appropriate and for which public funding is available.[1] This review is based on Version 3 which was published on 22 October 2018 and is available online.

According to '*the Criteria'* patients with PID with antibody deficiency who are eligible for publicly funded treatment with Ig are those with the following specific conditions, as diagnosed by an immunologist:

- Common Variable Immune Deficiency (CVID) - below normal serum IgG and IgA levels with or without below normal serum IgM levels
- Possible CVID - below normal serum IgG but normal serum IgA level with or without below normal serum IgM levels
- Transient hypogammaglobulinaemia of infancy
- 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. X-linked agammaglobulinemia)
- 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. CD40 ligand deficiency)
- Lymphoproliferative syndromes (e.g. XLP1, XLP2, CD27 deficiency).

The indications for Ig use for patients with PID with antibody deficiency, as defined in '*the Criteria*' are:

- Replacement therapy in CVID – European Society for Immunodeficiency Diseases (ESID) diagnostic criteria met
- Replacement therapy in possible 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 qualifying criteria for the above four indications that must be met for Ig therapy, as defined in '*the Criteria'*, are outlined in Table 1.

Table 1 Current qualifying criteria for the use of Ig in patients with PID with antibody deficiency according to the Criteria for Clinical Use of Immunoglobulin in Australia[1]

Indication: Replacement therapy in common variable immune deficiency (CVID) - ESID diagnostic criteria met

Note: if less than four years the request must be under the indication Transient hypogammaglobulinaemia of infancy (children aged less than four years)

- The patient is older than four years of age

AND

Blood samples for IgG and IgA testing should be taken on two occasions, at least one hour apart and at least one sample taken when the patient does not have an infection

- Evidence of a marked decrease of IgG and a marked decrease of IgA with or without low IgM levels and causes of secondary hypogammaglobulinaemia have been excluded

AND

- Documented failure of serum antibody response after vaccination with conjugated or unconjugated pneumococcal vaccine or following protein vaccine challenge

OR

- The patient's serum IgG is less than 2 g/L and a delay to providing Ig replacement (e.g. following an invasive bacterial infection) would present significant risk

OR

- The patient has absent haemagglutinins (if not blood group AB)

OR

- The patient has low switched memory B-cells (less than 70 percent of age-related normal value)

AND

- The patient has demonstrated an increased susceptibility to infection

OR

- The 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 six months and annually thereafter. Documentation of clinical effectiveness is necessary for continuation of Ig therapy.

Indication: Replacement therapy in possible common variable immune deficiency (CVID) – (below normal serum IgG but normal serum IgA level)

A low IgG (normal IgA with or without a low IgM) alone is not a sufficient indication for immunoglobulin replacement therapy. Many patients will be well despite the finding of a serum IgG below the normal range for age.

- The patient is older than four years of age

AND

Blood samples for IgG testing should be taken on two occasions, at least one hour apart and at least one sample taken when the patient does not have an infection

- Evidence of a marked decrease of IgG with normal IgA (with or without low IgM) levels and causes of secondary hypogammaglobulinaemia have been excluded

AND

- Documented failure of serum antibody response after vaccination with conjugated or unconjugated pneumococcal vaccine or following protein vaccine challenge

OR

- The patient's serum IgG less than 2 g/L and a delay to providing Ig replacement (e.g. following an invasive bacterial infection) would present significant risk

OR

- The patient has absent haemagglutinins (if not blood group AB)

OR

- The patient has low switched memory B-cells (less than 70 percent of age-related normal value)

AND

- The patient has demonstrated an increased susceptibility to infection

OR

- The patient has autoimmune manifestations, granulomatous disease, unexplained polyclonal lymphoproliferation or an affected family member with antibody deficiency

Initial review is required by an Immunologist at six months and ongoing reviews at least annually to assess clinical benefit. Documentation of clinical effectiveness is necessary for continuation of Ig therapy.

Table 1 Current qualifying criteria for the use of Ig in patients with PID with antibody deficiency according to the Criteria for Clinical Use of Immunoglobulin in Australia[1]

Cessation of Ig therapy should be considered at least after each 12 months of treatment. If serum IgM and IgA levels are trending upwards and near normal, this may suggest recovery of the immune system and a trial might be considered if the patient is well. Once the patient has normal IgA and IgM levels, the IgG is also likely to be normal and a trial off 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 necessary to enable an accurate assessment. Prophylactic antibiotics may be considered to cover the period of cessation of immunoglobulin therapy.
Replacement therapy in transient hypogammaglobulinaemia of infancy (children aged less than 4 years)
The majority of young children with transient hypogammaglobulinaemia do not require immunoglobulin (Ig) therapy. However, if the patient has had recurrent suppurative infections that threaten organ function, review by an immunologist is recommended for consideration of Ig therapy. Some patients may require treatment during the winter months only and others will benefit from more prolonged treatment. Blood samples for IgG testing should be taken on two occasions, at least one hour apart and at least one sample taken when the patient does not have an infection. • Younger than four years of age at diagnosis **AND** • Evidence of a marked decrease of IgG and causes of secondary hypogammaglobulinemia have been excluded **AND** • The patient has demonstrated an increased susceptibility to infection Initial review is required by an Immunologist, at six months, and ongoing reviews at least annually to assess clinical benefit. Documentation of clinical effectiveness is necessary for continuation of Ig therapy. Cessation of Ig therapy should be considered at least after 24 months of treatment. [a] If serum IgM and IgA levels are trending upwards and close to normal, this may suggest recovery of the immune system and a trial might be considered if the patient is well. Once the patient has normal IgA and IgM levels, the IgG is also likely to be normal and a trial off therapy should 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. When the child is four years old, a decision must be made regarding a trial off treatment or qualification may be appropriate under a different indication such as possible or confirmed CVID.
Replacement therapy in recognised primary immunodeficiencies for which immunoglobulin replacement is universally indicated (e.g. SCID, Wiskott-Aldrich syndrome, etc.)
Blood samples for IgG testing should be taken on two occasions, at least one hour apart and at least one sample taken when the patient does not have an infection. • Confirmed or suspected diagnosis of primary immunodeficiency **AND** • Evidence of hypogammaglobulinaemia[b] Initial review by an Immunologist is required at six months, with reviews annually thereafter. Documentation of clinical effectiveness is necessary for continuation of IVIg therapy. Where a diagnosis has initially been suspected, confirmation will be required for access to continuing Ig therapy.

Source: The Criteria for Clinical Use of Immunoglobulin in Australia (version 3.1)[1]

Abbreviations: CVID: Common Variable Immune Deficiency; ESID: European Society for Immunodeficiencies; PID: Primary Immunodeficiency Diseases; SCID: Severe Combined Immunodeficiency

Notes: [a] This sentence should be interpreted as 'after 24 months of treatment, a trial of cessation could be considered', not that a trial of cessation is required. [b] Not all patients with recognised primary immunodeficiencies who are eligible for IVIg will have hypogammaglobulinaemia (e.g. patient's with Wiskott Aldrich syndrome).

Also outlined in '*the Criteria'* are factors which would exclude a person from receiving Ig therapy under this condition.[1] These are:

- Acquired hypogammaglobulinaemia secondary to haematological malignancy or post haematopoietic stem cell transplantation (HSCT)
- Specific antibody deficiency
- IgG subclass deficiency
- Secondary hypogammaglobulinaemia unrelated to haematological malignancy or HSCT.

Note: these patients may be eligible to receive Ig under a separate medical condition.

Background

Immunodeficiencies are a group of disorders characterised by a defect in the immune system. They are classified into two types; PID and secondary immunodeficiencies. Secondary immunodeficiencies are usually caused as a result of another disease or illness or due to certain medications or infections, whilst PID, those of relevance to this PICO, are mostly caused by inherited defects of genes that control the immune system.[2]

The term PID encompasses a group of more than 400 disorders. They may present at any age; however, more severe forms, such as severe combined immunodeficiency (SCID), generally become apparent early in life whilst other PID, such as CVID, are more commonly diagnosed in adults.[2]

People with PID have an increased susceptibility to infection. Whilst anyone is susceptible to infection, in people with PID the infections are unusually persistent, recurrent or resistant to treatment, very severe, or due to unusual germs.[3] The Australasian Society of Clinical Immunology and Allergy (ASCIA) describes the early warning signs of PID as:[2]

- An unusually large number of infections requiring treatment (e.g. infections of the middle ear, sinus, pneumonia, chronic suppurative sinus or lung disease in adults)
- Infections caused by unusual or opportunistic types of organisms
- Infections in unusual places (e.g. perianal or organ abscesses)
- Infections that do not respond to treatment as normally expected
- A child that does not respond to treatment as normally expected or weight loss in adults
- A family history of immunodeficiency or abnormal infections
- Any other unusual symptoms related to infection (e.g. persistent diarrhoea)
- Other features of PID (autoimmune cytopenias, granuloma formation at any site, chronic enteropathy unresponsive to gluten withdrawal from diet, unexplained hepatomegaly, unexplained splenomegaly, lymphoid pneumonitis).

PID are generally classified according to the part of the immune system that is primarily affected and include: antibody deficiencies, combined immunodeficiencies, phagocytic cell deficiencies, immune dysregulation and complement deficiencies.[4] Those PID that are relevant to this PICO (listed in '*the Criteria*' and thus publicly funded for treatment with Ig) are described below.

Antibody deficiencies

Common Variable Immunodeficiency (CVID)

Common Variable Immunodeficiency (CVID) is one of the most common PID. It can occur at any age; however, many people are not diagnosed until they are adults.[5] It results from

hypogammaglobulinemia; an inability of the body's B-cells to produce a sufficient number of functional circulating antibodies (immunoglobulins).[6] People with CVID may have decreased levels of:

- All three major types of Ig (IgG, IgA and IgM)
- IgG and IgA, or
- Only IgG[5]

People with CVID have frequent infections of the ears, sinuses, nose and/or lungs due to their reduced antibody responses. They may also experience conjunctivitis and persistent diarrhoea.[5] If left untreated these infections can result in organ damage such as sinusitis and bronchiectasis.[5]

It should be noted that '*the Criteria'* specifies that IVIg is indicated for use in CVID in which the European Society for Immunodeficiencies (ESID) diagnostic criteria have been met and also in possible CVID (below normal serum IgG but normal serum IgA level).

Transient hypogammaglobulinaemia of infancy

Development of immunoglobulins follows a predictable pattern in infancy and early childhood. With transient hypogammaglobulinaemia (THI) production of immunoglobulins in infants and young children is delayed.[2] The most common symptoms of children with THI include upper and lower respiratory tract infections, allergic disorders and gastrointestinal problems.[7]

Combined immunodeficiencies

In people with combined immunodeficiencies, both B and T-cell function are affected.[3]

Severe Combined Immunodeficiency (SCID)

SCID is the most serious form of combined immunodeficiency which has a high mortality if diagnosis is delayed.[2] Without treatment it is usually fatal within the first two years of life, requiring a haematopoietic stem cell transplant to survive.[2] Infants affected by SCID generally appear well at birth but generally become symptomatic within the first few months of life. Symptoms, as defined by the ASCIA[2], include:

- Recurrent severe infections
- Chronic diarrhoea
- Poor growth and failure to thrive
- Recurrent or persistent oral thrush, viral respiratory and gastrointestinal infections
- Opportunistic infections, particularly *Pneumocystis jiroveci* pneumonia (PJP) or disseminated Bacillus Calmette-Guérin (BCG)
- Extensive skin rashes such as erythroderma or eczema
- Absent lymphoid tissue.

Combined immunodeficiency with associated or syndromal features

Combined immunodeficiencies with associated or syndromal features are a group of over 30 conditions that have a characteristic group of phenotypic or laboratory abnormalities (e.g. Wiskott-Aldrich syndrome, Ataxia telangiectasia (Louis-Bar's syndrome), DiGeorge Syndrome).[8, 9]

Immune dysregulation

Lymphoproliferative syndromes

Disorders of immune dysregulation are PID associated with autoimmune disease, whereby the body's immune system reacts against its own cells.[4] In many of these disorders lymphocytes may be present but dysfunctional.[4] One type of immune dysregulation, characterised by an abnormal increase in lymphocytes, is autoimmune lymphoproliferative syndrome.[10] There are a range of lymphoproliferative diseases, classified according to their genetic defect and presumed pathogenesis.[9] They vary in their clinical presentation, severity, timing of onset and treatment.[10]

Diagnosis

The investigation, management and referral of patients with PID within the Australian healthcare system is complicated owing to the wide range of rare conditions and both paediatric and adult patients (Referral Form, page 13). Patients may present with atypical features or require multiple therapies. Diagnosis may include measures of antibody levels, vaccine challenge tests and Ig therapy tests, with wide variation owing to the heterogenous nature of the patient group (Referral Form, page 14).

The Central Adelaide Local Health Network (CALHN) and Southern Adelaide Local Health Network (SALHN) have published outpatient GP referral guidelines, outlining the criteria and investigations required for referral of a patient to their allergy/clinical immunology service if PID is suspected.[11, 12] Details are provided of the SALHN guidelines in Table 2.

Table 2 SALHN outpatient GP referral guidelines for referring a patient to an allergy/immunology service for suspected PID[11]

Referral criteria* **1 or more of the following:**	**Investigations required†**
4 or more new ear infections within the 1 year	Full blood count (with differentials)
2 or more serious sinus infections within the 1 year	Liver function tests including albumin/protein
2 or more months of antibiotics with little effect	Immunoglobulins (IgG, IgA and IgM)
Failure of an infant to gain weight or grow normally	Lymphocyte surface markers
Recurrent, deep skin or organ abscesses	C4
Persistent thrush in mouth or fungal infection on skin	Chest X-ray (if history of chest infections)
Need for intravenous antibiotics to clear infection	
2 or more deep-seated infections including septicaemia	
A family history of primary immune deficiency	

*The CALHN referral criteria are slightly different

†The CALHN guidelines differ in that they do not stipulate liver function test, lymphocyte surface markers or C4 but require IgE immunoglobulins in addition to IgG, IgA and IgM

GP: general practitioner; PID: primary immunodeficiency disease; SALHN: Southern Adelaide Local Health Network

'The Criteria' stipulate that a diagnosis of PID with antibody deficiency must be made by an immunologist and outlines the diagnostic criteria for determining eligibility of PID patients for publicly funded Ig treatment.[1] It notes that the revised ESID (2014) diagnostic criteria[1] were used as a guide in the development of the qualifying criteria for Ig therapy in Australia and that a low IgG alone is not a sufficient indication for Ig replacement.

[1] The ESID (2014) diagnostic criteria have subsequently been revised. However, at the time the Referral was developed, the ESID (2014) was the version used as the basis for developing the qualifying criteria in *'the Criteria'*.

For CVID, the most common PID, the revised ESID diagnostic criteria 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 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 isohaemagglutinins); 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.

The latest version (published January 22, 2019) of the ESID registry of 'Working Definitions for Clinical Diagnosis of PID' is available online. This version contains criteria for clinical diagnosis of all other forms of PID with antibody deficiency conditions listed in '*the Criteria*'.[13]

Prevalence of PID with antibody deficiency

The prevalence of PID is variable and depends on the specific disorder. ASCIA state that the overall prevalence of PID is 1 in 1200; however, IgA deficiency, the most common PID, is estimated to occur in 1 in 500 people, whilst other rarer PID occur in 1 in 10,000 to 1 in 1,000,000 people.[2]

As Ig is already funded in Australia, robust figures about the use of Ig to treat PID with antibody deficiency, for those conditions that are eligible to receive it, are available. Information relevant to this PICO Confirmation has been published in the 'National Report on the Issue and Use of Immunoglobulin (Ig) Annual Report 2015-16' released by the National Blood Authority.[14] This report provides an overview of the number of PID patients receiving Ig therapy in Australia. The report states that per diagnostic group, PID accounted for 13.3 per cent of the total Ig use, making it the third highest Ig using diagnostic group behind Acquired Hypogammaglobulinaemia secondary to haematological malignancies (highest user) and Chronic Inflammatory Demyelinating Polyneuropathy (second highest user). Data on the number of patients and usage of Ig for 2015-2016 for some of the PID with antibody deficiency conditions listed in '*the Criteria*' are provided in Table 3. Based on Ig usage data, ASCIA estimate the prevalence of CVID Disease is 7.2 per 100,000

population, ranging from 3.7 to 16.0 per 100,000 population across Australian states and territories.[14]

Table 3 National Ig supply figures and number of patients with different PID antibody deficiency conditions between 2015 to 2016[14]

Condition	Patients (n)	Grams Ig	Grams Ig/Episode	Grams Ig per 1,000
Common Variable Immunodeficiency Disease	1,724	580,964	21	24
Other Primary Immunodeficiency	121	32,072	13	1
Severe Combined Immunodeficiency	39	8,636	13	<1
Wiskott-Aldrich Syndrome	5	1,176	11	<1

Source: National report on the issue and use of immunoglobulin (Ig), Annual Report 2015-16.[14]

More recent data on Ig use per episode provided by the Applicant is detailed in Table 4 (Referral Form, page 29). The Applicant notes that when considering the data, the meaning of the term 'episode' has evolved over the development of the dataset, with the definition more closely related to a dispensing episode or event. They also state that "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".

Table 4 Ig dosing and frequency between 2016-2017 and 2017-2018 for PID and CVID

	PID Total		CVID	
	2016-17	2017-2018	2016-17	2017-2018
Treatment episodes	32,207	33,108	27,680	28,872
Average treatment episodes per year	15	14	15	15
Average Ig gms/kg/episode	0.48	0.47	0.47	0.44

Source: Referral Form page 29. Produced from internal National Blood Authority Data.
Abbreviations: CVID: Combined Variable Immunodeficiency Disease; PID: primary immunodeficiency disease

Rationale

The population as stated in the Referral Form is broad and encompasses several subpopulations, which have a unique natural history, burden of disease and management strategy.

CVID is the most common of the PIDs included in the population for this PICO and it is also associated with the highest Ig usage (Table 3).

Noting the likely paucity of comparative evidence and very heterogeneous population of patients with PID with antibody deficiency, the Ig Review Reference Group advised that the most appropriate approach to the evidence collection would be to consider the comparative evidence on safety and effectiveness for all PIDs for patients eligible for Ig therapy in Australia under Version 3 of the Criteria, but limit identification of observational studies to CVID. The Reference Group advised that the systematic literature search should also seek data on the natural history of CVID, noting that a naïve comparison may need to be made. The Reference Group further noted that a full critical appraisal of the literature may not be required, but instead a narrative review focusing on the most informative studies may be more appropriate.

The Reference Group suggested that the HTA evaluators also search for more recent evidence to support when it is clinically appropriate to trial off or discontinue Ig therapy. The detailed Criteria attached to the Referral provides recommendations to guide clinicians as to when a trial off may be considered.

The Reference Group advised that a staged approach to the development of the assessment report was required, so that the available evidence could be considered before a decision was made on the approach to be taken for development of the economic model or cost analysis. The Reference Group noted that if an economic model were developed for CVID, it would not be equitable or appropriate to extrapolate from this model to other PIDs given their different natural histories.

Intervention

The intervention under review is Ig for immunoreplacement therapy in people with PID with antibody deficiency (Referral Form, page 5). It should be noted that Ig can be delivered intravenously (IVIg) or subcutaneously (SCIg). The Applicant recommends that for this PICO, Ig should be the intervention and IVIg and SCIg considered as different routes of administration (Referral Form, page 6). Ig replacement therapy is used in people with PID with antibody deficiency to treat new infections, prevent new infections from occurring and prevent long-term damage from chronic infections.[15] Ig therapy does not cure the antibody deficiency or reverse long-term organ damage from chronic infections.[15]

In Australia, '*the Criteria*' specifies which PID with antibody deficiency conditions IVIg has an established therapeutic role, and IVIg use is currently publicly funded for under the National Blood Arrangements. Currently a range of PID with antibody deficiency conditions are listed in '*the Criteria'* (see Population section above). It is reported in the Referral Form (page 4) that "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." Only imported IVIg is available for purchase for indications not listed in '*the Criteria*'. It can be accessed directly from the supplier at the same price negotiated by the National Blood Authority and must be paid in full by the recipient (health service or individual patient).[16] In addition to PID with antibody deficiency, Ig use in Australia is currently publicly funded for a range of other medical conditions. These are all described in '*the Criteria'.*[1]

In the Referral Form (page 22) it is reported that long-term antibiotic therapy might be required in addition to Ig replacement for preventing infection in antibody-deficient patients. It is noted by the Applicant; however, that "…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" (Referral Form, page 22).

Immunoglobulin products approved for the treatment of PID with antibody deficiency

In Australia, Ig products are funded and supplied under the National Blood Arrangements. The Ig products are sourced domestically, from plasma collected 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 (Referral Form, page 5).

A range of Ig products are listed on the Australian Register of Therapeutic Goods (ARTG). However, not all Ig products registered in Australia are funded for use under the Arrangements. A competitive tendering process is used for imported products to ensure good contract performance, value for money and supply security (Referral Form, page 5). Those Ig products currently funded under the Arrangements are listed on the National Product List.

Not all Ig products listed on the ARTG or National Product list are indicated for PID with antibody deficiency. Based on Table 1 from the Referral Form (page 6) there are currently 13 Ig products on the ARTG that are indicated for PID and of these 6 funded for PID under the National Blood Arrangements (Table 5).

Table 5 TGA and NBA listings of Ig indicated for PID. Those products which are both TGA indicated and NBA funded for PID are highlighted in grey.

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	Yes IV only
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
Octagam 10% - Octapharma	IV	Yes	No
Gammanorm - Octapharma	SC	Yes	No

Source: Table 1, page 6 of the Referral Form

Abbreviations: IV: intravenous; NBA: National Blood Arrangement; PID: Primary Immunodeficiency Diseases; SC: Subcutaneous; TGA: Therapeutic Goods Administration

Dosage and duration of use

In addition to stipulating the PID with antibody deficiency indications for which Ig use is approved, '*the Criteria'* outlines the approved dosage for each indication (Table 6) and the review criteria for determining the duration of each authorisation.[1] The Criteria states that the aim for each indication is to use the lowest possible dose that achieves the appropriate clinical outcome for each patient. The Applicant notes that doses higher than the parameters provided in *'the Criteria'* can be accessed, but a doctor must provide a rationale for needing it, which may or may not be approved (Referral Form, page 18). They also note that the dose may need to be adjusted for excessive infections (poor clinical response), growth or weight change, or other processes such as enteric loss or increased metabolism (Referral Form, page 18).

As outlined in '*the Criteria'*, for each of the indications listed in Table 6, an initial review is required by an immunologist at six months and annual reviews thereafter. Documentation of clinical effectiveness is necessary for continuation of Ig therapy.[1] For CVID, '*the Criteria*' stipulates that cessation of Ig therapy should be considered at least after each 12 months of treatment, whilst for transient hypogammaglobulinaemia of infancy, cessation of Ig therapy should be considered at least after 24 months of treatment.[1]

The Applicant notes that the majority of patients will have more than one authorisation; however, the average duration for PID is unknown and is likely to vary between specific conditions due to

varying underlying causes (Referral Form, page 29). A clinical expert on the Ig Reference Group advised that patients may or may not respond to Ig therapy, but confirmed that patients who do respond will be on the treatment for life as it is replacement therapy. They further stated that weaning off Ig therapy may be trialled in some paediatric patients if it is suspected that their immune system has recovered (Referral Form, page 29).

Table 6 Approved Ig dosage for patients with PID with antibody deficiency according to the Criteria for Clinical Use of Immunoglobulin in Australia[1]

Replacement therapy in common variable immune deficiency (CVID) - ESID diagnostic criteria met
• **Loading Dose** - One loading dose of 0.4 g/kg in the first month of therapy (in addition to the maintenance dose) is permitted if the serum IgG level is <4 g/L. • **Disseminated Enterovirus dose** - One dose of 2g/kg at any stage is permitted (in addition to the maintenance dose) in the management of disseminated enterovirus infection. • **Maintenance Dose** - 0.4-0.6 g/kg every four weeks (IVIg) or 0.1-0.15 g/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. The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient. Refer to the current product information sheet for further information on dose, administration and contraindications.
Replacement therapy in possible common variable immune deficiency (CVID) – (below normal serum IgG but normal serum IgA level)
• **Loading Dose** - One loading dose of 0.4 g/kg in the first month of therapy (in addition to the maintenance dose) is permitted if the serum IgG level is <4 g/L. • **Dissemination Enterovirus Dose** - One dose of 2 g/kg at any stage is permitted (in addition to the maintenance dose) in the management of disseminated enterovirus infection. • **Maintenance Dose** - 0.4-0.6 g/kg every four weeks (IVIg) or 0.1-0.15 g/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 9 g/L is permitted if chronic suppurative lung disease is not adequately controlled at an IgG trough level at the lower limit of the age-specific serum IgG reference range. A total dose of up to 1 g/kg may be given over any four-week period. The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient. Refer to the current product information sheet for further information on dose, administration and contraindications.
Replacement therapy in transient hypogammaglobulinaemia of infancy (children aged less than 4 years)
• **Loading Dose** - One loading dose of 0.4 g/kg in the first month of therapy (in addition to the maintenance dose) is permitted if the serum IgG level is <4 g/L. • **Maintenance Dose** - 0.4-0.6 g/kg every four weeks (IVIg) or 0.1-0.15 g/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 9 g/L is permitted if chronic suppurative lung disease is not adequately controlled at an IgG trough level at the lower limit of the age-specific serum IgG reference range. A total dose of up to 1 g/kg may be given over any four-week period. The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient. Refer to the current product information sheet for further information on dose, administration and contraindications
Replacement therapy in recognised primary immunodeficiencies for which immunoglobulin replacement is universally indicated (e.g. SCID, Wiskott-Aldrich syndrome, etc.)

Replacement therapy in common variable immune deficiency (CVID) - ESID diagnostic criteria met
• Loading Dose - One loading dose of 0.4 g/kg in the first month of therapy (in addition to the maintenance dose) is permitted if the serum IgG level is <4 g/L. • Disseminated Enterovirus Dose - One dose of 2 g/kg at any stage is permitted (in addition to the maintenance dose) in the management of disseminated enterovirus infection. • Maintenance Dose - 0.4 g/kg every four weeks (IVIg) or 0.1-0.15 g/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 9 g/L is permitted if chronic suppurative lung disease is not adequately controlled at an IgG trough level at the lower limit of the age-specific serum IgG reference range. A total dose of up to 1 g/kg may be given over any four-week period. The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient. Refer to the current product information sheet for further information on dose, administration and contraindications.

Source: The Criteria for Clinical Use of Immunoglobulin in Australia (version 3.1)[1]
Abbreviations: CVID: Common Variable Immune Deficiency; ESID: European Society for Immunodeficiencies; PID: Primary Immunodeficiency Diseases; SCID: Severe Combined Immunodeficiency

Delivery time for Ig infusion

The Applicant (Referral Form, page 16) has noted that the timeframe to administer Ig is dependent on:

- The dose required
- The patient's weight
- 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 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.

IVIg infusion rates

Infusion rates for four IVIg products that are currently ARTG listed and NBA funded for PID, as recommended in the IVIg Clinical Practice Guideline produced by the Victorian Department of Health, are outlined in Table 7.[17] As noted by the Applicant (Referral Form, page 16), administration times may vary between hospitals owing to different IVIg protocols. ASCIA also has published guidelines on standardised infusion rates for IVIg replacement therapy.[18]

Table 7 Rates of infusion for four IVIg products NBA funded for PID with antibody deficiency as outlined in Clinical Practice Guidelines produced by the Victorian Department of Health[17]

Intragam®10	Privigen®	Flebogamma 5% DIF	Flebogamma 10% DIF
The infusion should be commenced at a rate of 1 mL/minute. After 15 minutes the rate may be gradually increased to a maximum of 3–4 mL/minute over a further 15 minutes **Maximum infusion rate = 4 mL/minute (240 mL/hr)** **Paediatrics:** Consideration should be given to running IVIg at slower rates for paediatric/neonatal patients	The initial infusion rate is 0.3 mL/kg/hr. If well tolerated, the rate of administration may gradually be increased to 4.8 mL/kg/hr. **Maximum infusion rate = 4.8 mL/kg/hr** **Maximum rate for patients with ITP is 2.4 mL/kg/hr as per product information**	Flebogamma 5% DIF should be infused intravenously at an initial rate of 0.01–0.02 mL/kg/min for the first 30 minutes. If well tolerated the rate of administration may gradually be increased to a maximum of 0.1 mL/kg/min. **Maximum infusion rate = 6 mL/kg/hr**	Initial rate of 0.01 mL/kg/min for the first 30 minutes. If tolerated advance to 0.02 mL/kg/min for the second thirty minutes. If tolerated advance to 0.04 mL/kg/min for the third 30 minutes. If tolerated advance to 0.06 mL/kg/min for the fourth thirty minutes. If tolerated advance to a maximum rate of 0.08 mL/kg/min for the fifth thirty minutes.

Intragam®10	Privigen®	Flebogamma 5% DIF	Flebogamma 10% DIF
			Maximum infusion rate = 4.8 mL/kg/hr

Source: adapted from Appendix A of IVIg Clinical Practice Guideline Template, Victorian Department of Health.[17]
Abbreviations: ITP: Immune Thrombocytopenic Purpura

The Applicant reports that for an 80 kg person, with a dosage of 0.4 g/kg (32 g in total of a 10% Ig product), the dose could be administered over the course of a few hours, including day-admission, identification, cannulation and set-up, infusion and post-infusion monitoring. Using infusion rates outlined in the product information sheet for Intragam 10 a minimum total infusion time of 100 minutes for an 80 kg person is calculated. However, the Applicant notes that the infusion rate could be reduced for various reasons, e.g. adverse events (Referral Form, page 16).

SCIg infusion rates

Infusion rates for the two SCIg products that are currently ARTG listed and NBA funded for PID, as recommended in the Subcutaneous immunoglobulin (SCIg) Clinical Practice Guidance Principles document produced by the Victorian Department of Health, are outlined in Table 8.[19]

Table 8 Rates of infusion for the two SCIg products NBA funded for PID with antibody deficiency as outlined in a Clinical Practice Guidance document produced by the Victorian Department of Health[19]

Evogam®	Hizentra®
Evogam® dose and dosage interval must be individualised from each patient based on serum IgG trough levels and clinical response Dosage guideline: 0.2–0.6 g/kg/body weight monthly	Hizentra® loading dose of at least 0.2–0.5 g/kg body weight may be required. Maintenance dose of 0.4–0.8 g/kg of body weight depending on patient's clinical response and serum IgG trough levels.
Recommended initial infusion rate is 10 mL/hr gradually increased to 20 mL/hr	Initial infusion rate depending on patient needs should not exceed 15 mL/hr/site. If well tolerated infusion rate can be gradually increased to 25 mL/hr/site
If large doses are given > 20 mL/site administration via multiple sites is recommended	If larger doses are given > 25 mL/site administration via multiple sites is recommended

Source: adapted from Appendix A of SCIg Clinical Practice Guidance Principles, Victorian Department of Health[19]

The Applicant has provided a typical infusion delivery time for the SCIg product Hizentra for an 80 kg person using infusion rates recommended in the product information sheet for this product (Referral Form, page 17). This is one of the SCIg products that is ARTG listed and NBA funded for PID. Based on an initial infusion rate not exceeding 15 mL/hour/site and then a gradual increase to 25 mL/hour/site, and assuming only one site is used at a time, they estimate the minimum administration time for an 80 kg patient on a dose of 0.1 g/kg (0.5 mL/kg) per week would be approximately 108 minutes. They note that the infusion rate could be reduced for various reasons, e.g. adverse event.

Setting

According to the Applicant (Referral Form, page 19), Ig therapy may be delivered in the following settings:

- Inpatient – private hospital
- Inpatient – public hospital (as a private patient)
- Inpatient – public hospital (as a public patient)

- Outpatient clinic
- Patient's home
- Private same day infusion facility.

The Applicant noted that for CVID, the largest PID user group of Ig, NBA data from the 2017-18 financial year indicated around 74 per cent of patients were treated in the public setting (Referral Form, page 20).

Limitations/barriers to access

To access Ig therapy under the National Blood Arrangements a patient with PID must be diagnosed and reviewed by an immunologist registered with the Australian Health Practitioner Regulation Agency (Referral Form, page 19). Sites that administer blood or blood products need to be accredited under the National Safety and Quality Health Service Standard for Blood Management. To infuse IVIg, specific nursing qualifications are required (Referral Form, page 19). SCIg can only be accessed from hospitals participating in national SCIg programs. A list of hospitals in each state with SCIg programs can be accessed from the NBA website. It should be noted that in some states, such as South Australia, hospitals participating in SCIg programs are only situated in the capital city. This would result in a significant travel burden to some patients. The Applicant also notes that for SCIg administration, the patient/carer must be trained in the procedure by a qualified nurse or technician (Referral Form, page 19).

Contraindications/Exclusion criteria

'The Criteria' outlines exclusion criteria for Ig therapy for PID with antibody deficiency.[1] These are:

- Acquired hypogammaglobulinaemia secondary to haematological malignancy or post HSCT
- Specific antibody deficiency (SAD)
- IgG subclass deficiency
- Secondary hypogammaglobulinaemia (including iatrogenic immumodeficiency).

A general contraindication to IVIg is patients who are allergic and have an anaphylactic response to human immunoglobulin. In addition, there are specific contraindications relating to each Ig product which are outlined in the product information sheets (e.g. Flebogamma 5% and 10% are contraindicated in patients with hereditary fructose intolerance as the stabiliser used for this product is sorbitol).[17]

Comparator

The Ig 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 (Referral Form, page 22). They further noted that best supportive care may or may not include antibiotic treatment, prophylactic antibiotics and antimicrobials.

When commenting on the PICO Confirmation, the Ig Review Reference Group confirmed that there are no active comparators to IVIg for the treatment of PIDs available in Australia. As noted above, the Reference Group considered that evidence on the natural history of CVID should be sought, as

the likely paucity of comparative studies may mean that a naïve comparison may be the most appropriate way to approach the evidence evaluation.

Rationale

In the Referral Form it was reported (page 22) by the Applicant that:

"Standard therapy for PID may include Ig, haematopoietic stem cell transplant and/or gene therapy. Treatment of the 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."

In their clinical update on primary immunodeficiencies the ASCIA list the following as specific therapies for PID[2]:

- Prophylactic antibiotics, antifungals, antivirals
- Immunoglobulin replacement therapy
- Immune modulatory drugs
- Gamma interferon
- Haematopoietic stem cell transplant (HSCT)
- Bone marrow transplantation
- Gene therapy
- Others – granulocyte colony stimulating factor (G-CSF), polyethylene glycol-conjugated adenosine deaminase (PEG-ADA).

They note that the therapies need to be individualised according to the type of PID.

A consensus guideline by the ASCIA Transplantation and Primary Immunodeficiency (TAPID) group, specifically on the diagnosis and management of patients with SCID, states that the current standard of care for definitive correction of SCID is HSCT. They note that this must be performed urgently, as outcomes are best when performed at an early age with no active infection.[20]

Evidence-based practice parameters for the diagnosis and management of PID have been published by the American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy, Asthma and Immunology.[21] Included in this publication is a summary table of the therapeutic considerations for PID. A modified version of this table, including only those PID for which Ig is indicated as a therapeutic consideration is included below (Table 9).

Table 9 Summary of therapeutic considerations for primary immunodeficiencies

Category of immunodeficiency	IVIG	BMT	Gene therapy	Other treatments
Humoral immunodeficiency				Avoidance of live vaccines: all except SIGAD, IGGSD, THI Antibiotics: all Immunomodulators: CVID, SIGAD, IGGSD Splenectomy: CVID Chemotherapy: CVID Pneumoccocal vaccines: SAD
XLA, ARA, AICDA, UNG, ICOS, CVID, SAD, hypogam	Yes	No	No	
IGGSD, SIGAD, THI	?	No	No	
Combined immunodeficiency				
SCID (IL-2RG, ADA)	Yes	Yes	Yes	Avoidance of live vaccines: all (partial DGS?) Avoidance of nonirradiated blood or products: all Avoidance of CMV-positive blood or cells: all Antibiotics: all Pneumocystis prophylaxis: all SCID, TNFSF5, TNFRSF5 PEG-ADA: ADA Splenectomy: WAS Anti-inflammatory: WAS G-CSF: TNFSF5, TNFRSF5, WHIM syndrome GM-CSF: WHIM syndrome Chemotherapy: XLP, GS Thymus transplantation: DGS Multidisciplinary care: DGS, A-T
SCID (JAK3, IL-2RA, IL7RA, RAG1/2, CD45, MHC 1/11, CD3, ZAP70, Artemis, NP (unknown))	Yes	Yes	No	
WAS, A-T, NBS, DGS, TNFSF5, XLP, GS, NEMO, WHIM, syndrome caspase 8, Unknown	Yes	Yes	No	

Source: Adapted from Bonilla et al (2015)[21]. Only those immunodeficiency categories for which IVIG was considered a therapy were included.

Abbreviations: A-T: ataxia-talangiectasia; ADA: adenosine deaminase; AICDA: activation-induced cytidine deaminase; ARA: autosomal recessive agammaglobulinemia; BMT: bone marrow transplantation; CVID: common variable immunodeficiency; hypogam: hypogammaglobulinemia; DGS: DiGeorge Syndrome; G-CSF: granulocyte colony-stimulating factor; GM-CSF: granulocyte-macrophage colony stimulating factor; ICOS: inducible T-cell costimulator; IGGSD: IgG subclass deficiency; IL: interleukin; IVIG: intravenous immunoglobulin; GS: Griscelli syndrome; MHC: major histocompatibility complex; NBS: Nijmegen breakage syndrome; NEMO: nuclear factor of $_{\kappa}$B essential modifier; NP: nucleoside phosphorylase; PEG: polyethylene glycol; SAD: specific antibody deficiency; SCID: severe combined immunodeficiency; SIGAD: selective IgA deficiency; THI: transient hypogammaglobulinemia of infancy; TNFSF5: tumor necrosis factor superfamily member 5; TNFRSF5: tumor necrosis factor receptor superfamily member 5; UNG: uracil nucleoside glycosylase; WAS: Wiskott-Aldrich syndrome; WHIM: warts, hypogammaglobulinemia, immunodeficiency and myelokathexis; XLA: x-linked agammaglobulinaemia

ASCIA note that neither gene therapy nor thymic transplantation are available for patients in Australia or New Zealand and therefore these treatments should not be included as comparators.[20]

Outcomes

The outcomes identified by the Applicant (Referral Form, page 26) are as follows:

Patient relevant

Safety outcomes:

Adverse events associated with Ig treatment and with comparator and supportive care measures; including:

- Serious adverse events (e.g. antibiotic allergy, anaphylaxis, veno-occlusive events, acute renal failure)
- Antibiotic resistance

- Blood-borne infections
- Headaches
- Fever
- Hives
- Chills
- Arthralgia
- Vomiting
- Nausea
- Low blood pressure
- Moderate low back pain
- Thrombophlebitis
- Acute renal dysfunction.

Clinical effectiveness outcomes:

- Number of antibiotic treatments
- Number of infections
- Quality of life
- Morbidity
- Mortality
- IgG trough levels.

The outcomes listed are those identified in the development of the PICO. Additional or more specific outcomes identified during the evaluation process that are considered relevant to the intervention or comparator treatment may be addressed in the evaluation report (Contracted Assessment).

After considering public feedback on the Referral, the Ig Review Reference Group agreed that prevention of bronchiectasis should be included as a clinical effectiveness outcome, noting that further discussion may be required on whether and how this evidence should be incorporated into the evaluation.

Broadly, the outcomes identified pre-assessment and considered in scope are:

Healthcare system resources utilisation

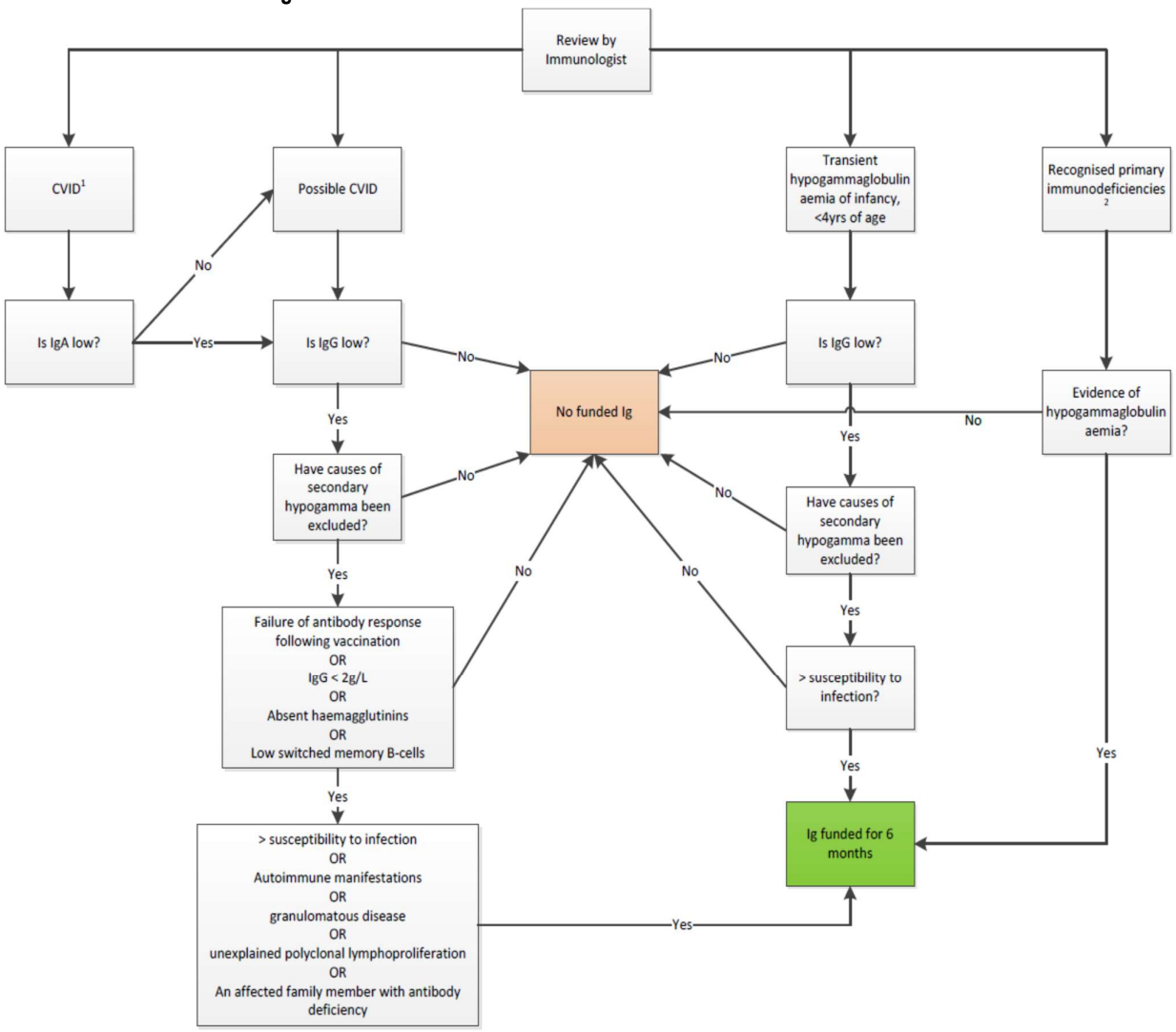
Changes in health system resource utilisation associated with the intervention include:

- Ig products
- Infusion equipment
- Administrative and clinician time (e.g. resources associated with requesting and authorising access to Ig)
- Nursing time (for initiation and monitoring of IVIg)
- Hospitalisation (including use of hospital resources)
- Medication to treat adverse events (e.g. analgesia or antihistamines)
- Product dispensing and disposal of any unused product
- Follow-up and/or monitoring visits, including regular immunologist visits
- For SCIg users, nursing time for education of users on how to administer SCIg at home.

The Applicant notes that there could be differences in health service consumption (e.g. outpatient, day-admission, hospital care versus self-care) between patients on IVIg versus those on SCIg (Referral Form, page 4).

Current clinical management algorithm when IVIg is used

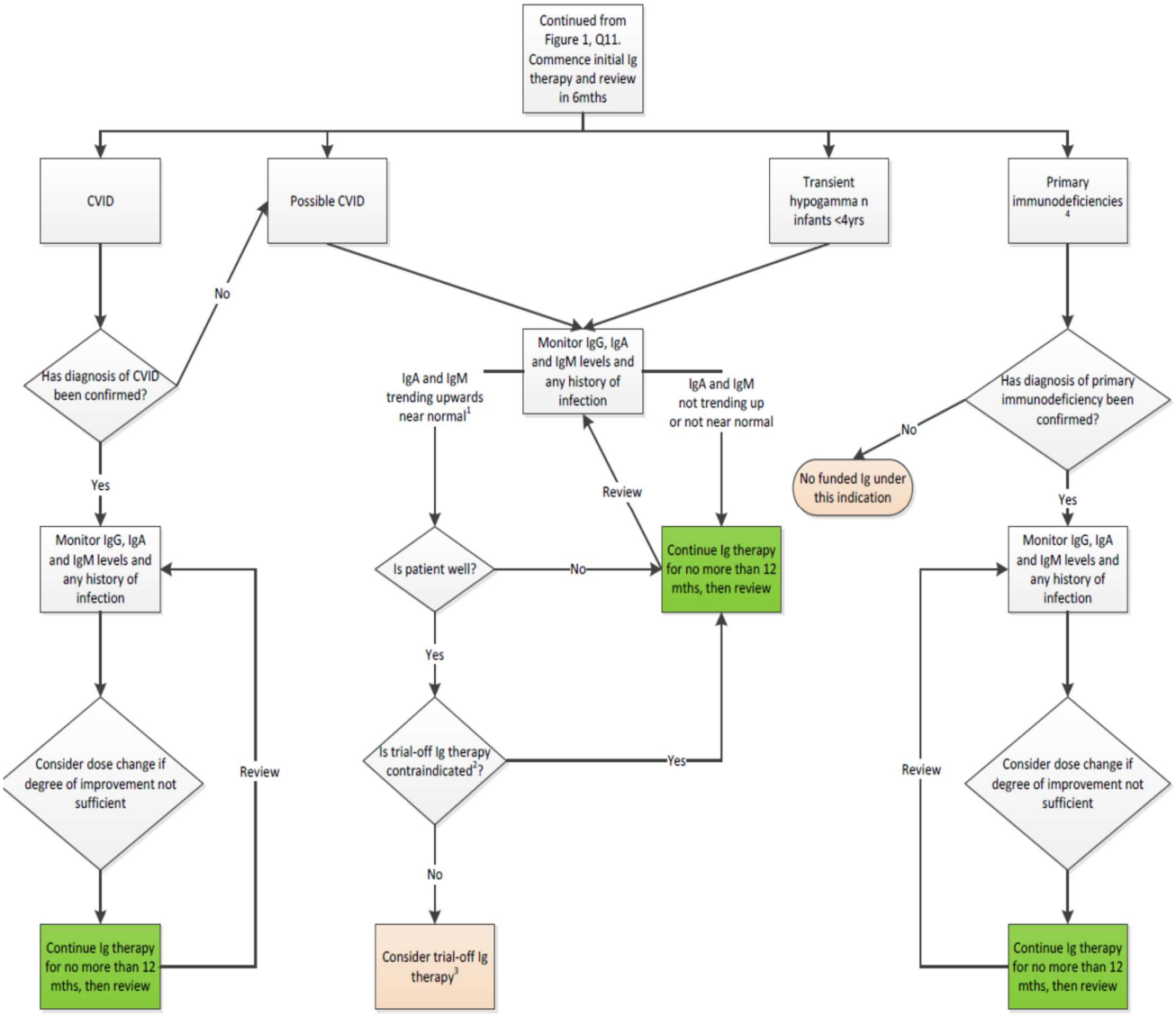
Figure 1 Current algorithm for PID with antibody deficiency patients' initial access to Ig funded under the National Blood Arrangements



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 Immune Deficiency; ESID: European Society for Immunodeficiencies; Ig: Immunoglobulin; PID: Primary Immunodeficiency Diseases

Figure 2 **Current algorithm for PID with antibody deficiency patients' continuing access to Ig funded under the National Blood Arrangements. Note: this algorithm is a representation only, not all conditions are able to be captured in one flowchart.**



[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.

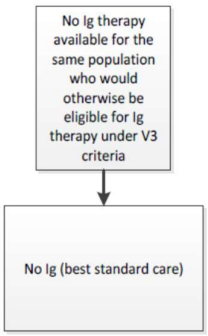
[4] Recognised PIDs for which Ig is universally indicated.

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

Clinical management algorithm when IVIg is not a treatment option

Note: this algorithm may also be applicable for any patient not/no longer eligible for IVIg under version 3 of '*the Criteria*' or for patients in whom IVIg is contraindicated.

Figure 3 Proposed algorithm for treatment of PID with antibody deficiency patients 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

Proposed economic evaluation

Ig is claimed to have superior effectiveness (Referral Form, page 25) and inferior safety compared to no Ig.

Assuming superior effectiveness and inferior safety, a cost effectiveness or cost-utility analysis is appropriate as shown in Table 10. The decision on how to best proceed with the economic evaluation will be made by the Reference Group based on the breadth and quality of the literature identified in the literature searches.

Table 10 Guide to appropriate economic evaluation

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

Source: Table produced by Adelaide Health Technology Assessment (AHTA) and included with permission on Reference Group advice (advice pending at draft stage).

X = health forgone (at cost). An economic evaluation is not warranted and continued use of Ig should not occur in this circumstance unless there are other supportive factors.
F = undertake a full economic evaluation. These may take the form of cost-utility analyses (CUA) (preferred if adequate data are available) or cost effectiveness analyses (CEA) in terms of clinically relevant outcome(s).
? = high levels of uncertainty will occur in an economic evaluation (if it is feasible to construct one). A cost analysis (partial economic evaluation) could be performed.
$ = cost minimisation analysis (partial economic evaluation that explicitly assumes no significant differences in health outcomes, associated with either effectiveness or safety, and analyses cost-differences only).
[a] where the conclusions with respect to effectiveness and safety are not congruent, then analyses identifying all relevant health consequences (i.e., effectiveness and safety outcomes in opposing directions of benefit) need to be presented. If a CUA is presented, this should capture effectiveness and safety collectively. If a CUA is not possible, then a single CEA may

not capture all health consequences adequately and so a cost consequence analysis (CCA) is likely to be required. Where possible, the CCA should be quantitative, but in the absence of adequate data, a minimum qualitative identification of consequences should be presented.

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

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

Proposed item descriptor

Public funding is not sought through the MBS for Ig treatment of PID with antibody deficiency. Ig treatment for specific PID with antibody deficiency conditions, as listed in '*the Criteria*'[1], is already publicly funded under the National Blood Arrangements.

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