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

1590 MMN - Multifocal motor neuropathy

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 multifocal motor neuropathy (MMN), paragraph 7.3.5 provides as follows:

> Published literature indicates a positive effect of IVIgs in some auto-immune disorders in particular multifocal motor neuropathy (MMN), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), and myasthenia gravis exacerbation. For these indications the efficacy in primary immunodeficiency syndromes and in ITP should be established. The applicant should also provide
>
> • An analysis of the existing literature and,
>
> • Confirmatory data with the applicant's IVIg (see also 'Guideline on Clinical Trials in Small Populations', CHMP/EWP/83561/2005), this should include a justification for the
>
> − scope of the confirmatory dataset (sample size, dose, time frame, patient population),
>
> − choice of the neurological scale and clinically meaningful differences within the chosen scale
>
> − comparator arm, or lack of comparator
>
> − wash-out period of previous medication and/or stable co-medication
>
> • The investigation of other auto-immune indications should be in accordance with the Paediatric Regulation (EC) No 1901/2006

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). This is confirmed in the *National Policy: Access to Government Funded Immunoglobulin Products in Australia*.

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 lead 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.

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. 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.

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 ARCBS 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 "Multifocal motor neuropathy".

Ig is used as immunomodulation therapy in MMN.

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

- First-line and maintenance therapy for multifocal motor neuropathy (MMN)
- Relapse of multifocal motor neuropathy (MMN) patients within six months of commencement of trial off immunoglobulin therapy

The specific condition within this medical condition is "Multifocal motor neuropathy with or without persistent conduction block".

This particular referral is for IVIg only. SCIg is not currently funded under the National Blood Arrangements for this condition. To the best of the NBA's knowledge, there are not currently any Phase 3 trials regarding the use of SCIg in MMN and there is no current Schedule 4 application to the NBA for a SCIg product for use in MMN. For these reasons, it is recommended that immunoglobulin administered intravenously (IVIg) is the intervention for this medical condition.

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?

TGA registered Ig products relevant to this referral

Table 1. Ig products registered on the ARTG for use in Australia

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

* Multifocal motor neuropathy with or without persistent conduction block

** Indicates that Ig is *currently* funded for MMN under the National Blood Arrangements. Note that tendering arrangements may change products funded in the future. Current National Product List with suppliers and prices. *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 MMN

	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.	Guidelines	Guidelines for the use of intravenous immunoglobulin in neurological diseases	These guidelines outline different indications for prescribing IVIg with research evidence and guidelines for monitoring patients on treatment.	Association of British Neurologists 2005, Guidelines for the use of intravenous immunoglobulin in neurological diseases, The Association, London.	2005
2.	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.	2004
3.	Handbook	The National Guideline Clearinghouse European Handbook of neurological management	Guideline for clinicians on management of neurological conditions.	The National Guideline Clearinghouse European Handbook of neurological management. 2nd Ed Vol 1 Oxford (UK); Wiley-Blackwell; 2011; p343-50.	2011
4.	Handbook	European Handbook of Neurological	Developed using a consensus approach, graded evidence and	Gilhus, NE, Barnes, MR, Brainin, M 2010, 'European Handbook of	2010

	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*
		Management	peer reviewed, these guidelines aim to guide clinicians on the treatment of neurological disorders.	Neurological Management', 2nd Edition, Volume 1, pp. 343-50, Oxford (UK), Wiley-Blackwell.	
5.	Randomised, double-blind, placebo-controlled study	Multifocal motor neuropathy improved by IVIg: randomized, double-blind, placebo-controlled study	This trial aimed to determine the effect of IVIg on neurologic function and electrophysiologic studies in MMN with conduction block. Included 16 patients.	Federico, P, Zochodne, DW, Hahn, AF, et al 2000, 'Multifocal motor neuropathy improved by IVIg: randomized, double-blind, placebo-controlled study', *Neurology*, vol. 55, no. 9, pp. 1256–62.	2000
6.	Literature review	The use of intravenous immunoglobulin in Australia. A report for the National Blood Authority, Part B: systematic literature review	A systematic literature review on the use of IVIg in Australia with the purpose of assisting clinicians in identifying those conditions and circumstances for which the use of IVIg is appropriate.	Frommer, M & Madronio, C, 2006, '*The use of intravenous immunoglobulin in Australia. A report for the National Blood Authority, Part B*: systematic literature review', Sydney Health Projects Group, University of Sydney, Sydney, pp. 35–7.	2006
7.	Observational study	A Modified Peripheral Neuropathy Scale: The Overall Neuropathy Limitations Scale	A study of the use of the ONLS and ODSS. Observation of 35 patients completing the tasks required for the different neurology assessment scales.	Graham, RC & Hughes, RA, 2006, 'A Modified Peripheral Neuropathy Scale: The Overall Neuropathy Limitations Scale', *Journal of Neurology, Neurosurgery and Psychiatry*, vol. 77,no. 8, pp. 973–976.	2006
8.	Controlled trial	A controlled trial of intravenous immunoglobulin in multifocal motor neuropathy	Trial which determined the effectiveness of IVIg in improving disability and muscles strength in 44 patients with MMN.	Hahn, AF, Beydoun, SR, Lawson, V, et al 2013, *'A controlled trial of intravenous immunoglobulin in multifocal motor neuropathy', Journal of the Peripheral Nervous System, vol. 18, no. 4, pp. 321-30.*	2013

	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*
9.	Consensus statements	Bringing consensus to the use of IVIg in neurology. Expert consensus statements on the use of IVIg in neurology	Consensus statements to support neurologists and clinicians in the use of IVIg in neurological practice.	Kornberg, AJ, for the Asia–Pacific IVIg Advisory Board, 2004, '*Bringing consensus to the use of IVIg in neurology. Expert consensus statements on the use of IVIg in neurology*', 1st edn, Asia–Pacific IVIg Advisory Board, Melbourne, pp. 30–4.	2004
10.	Review of evidence	Immunoglobulin (Ig) in multifocal motor neuropathy (MMN): update on evidence for Ig treatment in MMN	Review of current evidence to determine effectiveness of Ig therapy.	Leger JM 2014, 'Immunoglobulin (Ig) in multifocal motor neuropathy (MMN): update on evidence for Ig treatment in MMN', *Clinical and Experimental Immunology*, vol. 178, pp. 42–44. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4285485/	2014
11.	Retrospective study	Multifocal motor neuropathy: long-term clinical and electrophysiological assessment of intravenous immunoglobulin maintenance treatment	A long-term follow-up study of 11 patients with MMN who received maintenance treatment with IVIg.	Van den Berg-Vos, RM, Franssen, H, Wokke, JH, et al 2002, 'Multifocal motor neuropathy: long-term clinical and electrophysiological assessment of intravenous immunoglobulin maintenance treatment', *Brain*, vol. 125, no. 8, pp. 1875–86.	2002
12.	Guidelines	European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of multifocal motor neuropathy	Consensus guidelines on the definition, investigation and treatment of MMN.	Van Schaik, IN, Bouche, P, Illac, I, et al 2006, 'European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of multifocal motor neuropathy', *European Journal of Neurology*, vol. 13, pp. 802–8.	2006

	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*
13.	Cochrane review	Intravenous immunoglobulin for multifocal motor neuropathy	Cochrane review with the objective to systematically review the evidence from randomised controlled trials concerning the efficacy and safety of IVIg in MMN.	Van Schaik, IN, van den Berg, LH, de Haan, R, et al 2005, 'Intravenous immunoglobulin for multifocal motor neuropathy', (Cochrane Review) in *The Cochrane Library*, Issue 2, John Wiley & Sons, Ltd, Chichester, UK.	2005
14.	Guidelines*	European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of multifocal motor neuropathy. Report of a Joint Task Force of the European Federation of Neurological Societies and the Peripheral Nerve Society – first revision	An update to the Van Schaik et al 2006 consensus guidelines on the definition, investigation and treatment of MMN.	Joint Task Force of the EFNS and the PNS 2010, 'European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of multifocal motor neuropathy', *Journal of the Peripheral Nervous System*, vol. 15, pp. 295-301.	2010

**These guidelines have been updated since their inclusion in V3 of the Criteria. Both the 2006 and 2010 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 MMN.

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)*	*Relevant dates of research****

** 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 a Neurologist to request Ig for MMN.

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

- Australian and New Zealand Association of Neurologists (ANZAN)
- Royal Australian College of Physicians (RACP)

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

Suppliers of Ig may 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

- The Inflammatory Neuropathy Support Group of Victoria
- Brain Foundation
- NSW CIDP Group (is this the GBS Association of NSW?)
- Guillain-Barre syndrome (GBS)/chronic inflammatory demyelinating neuropathy (CIDP) Foundation International (include caveat to feedback is relevant to Australian setting only)
- Consumers Health Forum (CHF)
- Rare Voices Australia (RVA)

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:

The Criteria V3[1] describes MMN as a relatively rare disorder characterised by slowly progressive, asymmetric, predominately distal limb weakness without sensory impairment. Weakness often begins in the arms and the combination of weakness, wasting, cramps and fasciculation may mimic motor neuron disease. However, clinical examination may demonstrate that the pattern of weakness follows the distribution of individual nerves rather than a spinal segmental pattern. The European Guidelines on management of MMN[2] suggest diagnostic criteria to include an age of onset between 20 and 65.

Investigations will typically show conduction block on nerve conduction studies. IgM anti-GM-1 antibodies have been reported in a large number of patients with MMN and provide confirmatory evidence but are not essential for the diagnosis[1,3]. Conduction block is persistent for prolonged periods, months or years[3].

MMN causes prolonged periods of disability[4] which may ultimately result in severe wasting[3].The aim of treatment is to reduce the motor deficit, reverse or improve the motor conduction block and limit ongoing axonal degeneration, which leads to irreversible functional impairment[5]. Remission in MMN is very uncommon, even with treatment[6].

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 MMN is investigated, managed and referred in the lead up to being considered eligible for Ig therapy is outside of the NBA's expertise. Clinical expert advice from the Ig Review Reference Group advised that while the diagnosis would always be made by a neurologist, the referral pathways to a neurologist are variable. While some patients may be referred by a GP, others are likely to have seen a range of specialists (e.g. rheumatologist, orthopaedic surgeon) before being referred to a neurologist.

The investigations likely to be undertaken in these patients include neurophysiology, magnetic resonance imaging (MRI) and blood tests. Some patients may have lumbar puncture. Genetic testing may be considered to rule out the main differential diagnosis, motor neuron disease, however this is not currently funded on the MBS[7].

It should be noted that there may be a considerable delay between the onset of symptoms and diagnosis.

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[1] The Criteria for Clinical Use of Immunoglobulin in Australia V3

[2] Van Schaik, IN, Bouche, P, Illac, I, et al 2006, 'European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of multifocal motor neuropathy', *European Journal of Neurology*, vol. 13, pp. 802–8

[3] Kornberg, AJ, for the Asia–Pacific IVIg Advisory Board, 2004, '*Bringing consensus to the use of IVIg in neurology. Expert consensus statements on the use of IVIg in neurology*', 1st edn, Asia–Pacific IVIg Advisory Board, Melbourne, pp. 30–4.

[4] Van Schaik, IN, van den Berg, LH, de Haan, R, et al 2005, 'Intravenous immunoglobulin for multifocal motor neuropathy', (Cochrane Review) in *The Cochrane Library*, Issue 2, John Wiley & Sons, Ltd, Chichester, UK

[5] Leger JM 2014, 'Immunoglobulin (Ig) in multifocal motor neuropathy (MMN): update on evidence for Ig treatment in MMN', *Clinical and Experimental Immunology*, vol. 178, pp. 42–44.

[6] Van den Berg-Vos, RM, Franssen, H, Wokke, JH, et al 2002, 'Multifocal motor neuropathy: long-term clinical and electrophysiological assessment of intravenous immunoglobulin maintenance treatment', *Brain*, vol. 125, no. 8, pp. 1875–86.

[7] Clinical expert advice, Ig Review Reference Group 2019

An outline of the qualifying criteria to access Ig funded under the National Blood Arrangements for MMN can be found at Attachment C or https://www.criteria.blood.gov.au/MedicalCondition/View/2558 . For more detailed criteria refer to Attachment B.

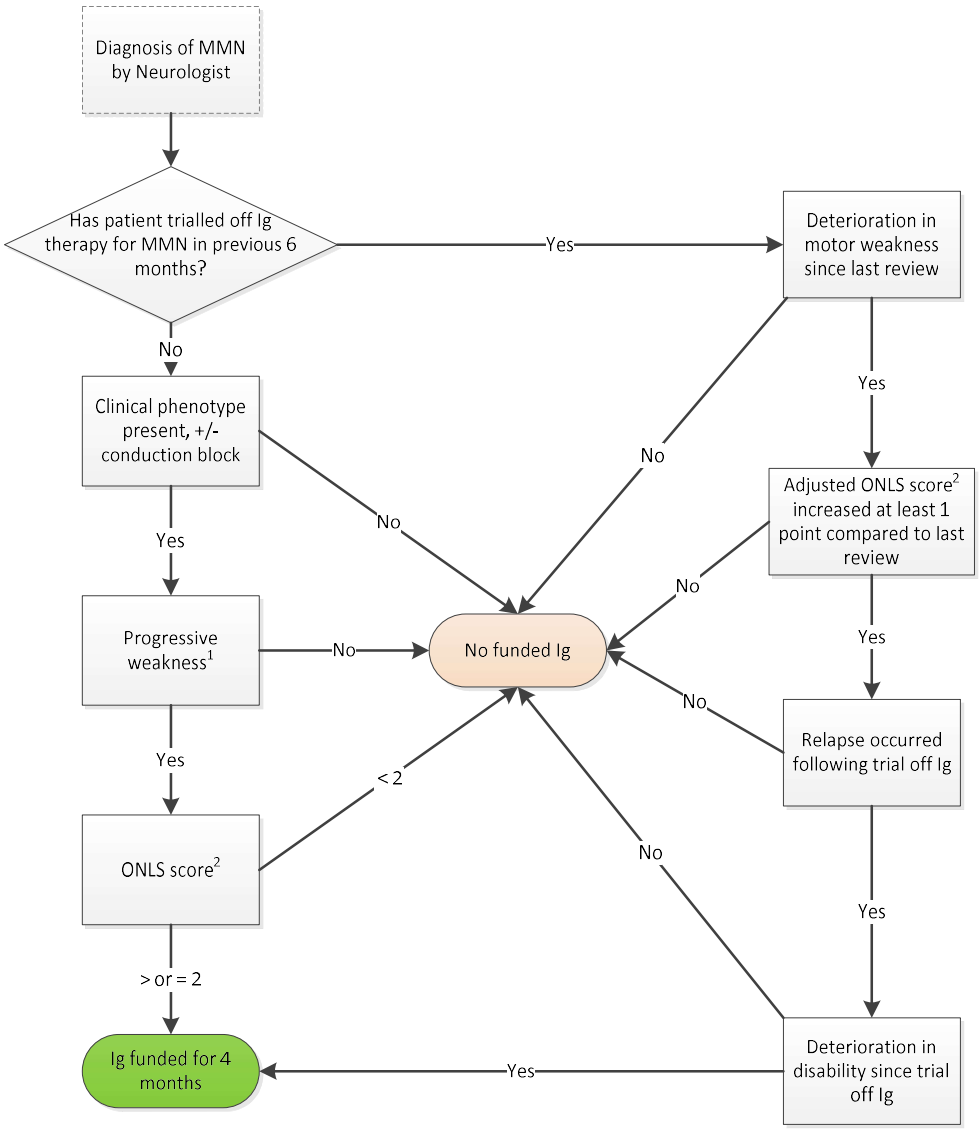
11. Define and summarise the current clinical management pathways (algorithm) for patients who are eligible for Ig therapy (supplement this summary with an easy to follow flowchart depicting the current clinical management pathways leading up to being considered eligible for Ig therapy):

For a patient to access government funded Ig for MMN they must meet the criteria for one of two indications listed below and described in detail at Attachment B.

- First-line and maintenance therapy for multifocal motor neuropathy (MMN)
- Relapse of multifocal motor neuropathy (MMN) patients within six months of commencement of trial off immunoglobulin therapy

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. Progressive weakness as demonstrated in the distribution of individual peripheral nerves
2. Overall Neuropathy Limitations Scale

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

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 neurologist may diagnose and review a patient with MMN for the purpose of requesting Ig. If a patient is not being cared for by a neurologist 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 the 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.

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), and
- 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.

Typical Ig delivery time for MMN

- 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[8] 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 MMN and that other products may have different infusion rates.

[8] Australian Product Information Intragam 10 (Human normal immunoglobulin) 2018.

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

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:

- 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 V3 Criteria:
  - Maximum dose
  - Minimum dose
  - Dose frequency
  - Whether divisions are allowed

While higher doses can be accessed in exceptional circumstances, doctors must provide a rationale for requiring a higher dose. V3 Criteria 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 V3 Criteria. 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 *MMN*).
-

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[9].

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 who reviews treatment. The administration of 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 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.

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 a Neurologist with the Australian Health Practitioner Regulation Agency (AHPRA) to diagnose and review a patient with MMN.

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.

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 (note: administration in this setting would be rare and should therefore not be included in the economic evaluation for this condition)
☐ 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.

[9] Therapeutic Goods Administration 2019. Australian Product Information, Flebogamma 10% DIF (Human Normal Immunoglobulin [IVIg] 100mg/ml) solution for infusion.

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.

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 MMN indicate around 70 percent of patients are treated in the public setting than in the private setting (see Table 5).

Table 5: *2017-18 Public and private patients receiving Ig for MMN: 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	406 (70%)	176 (30%)	582 (100%)
Grams	247,736 (70%)	106,698 (30%)	354,434 (100%)

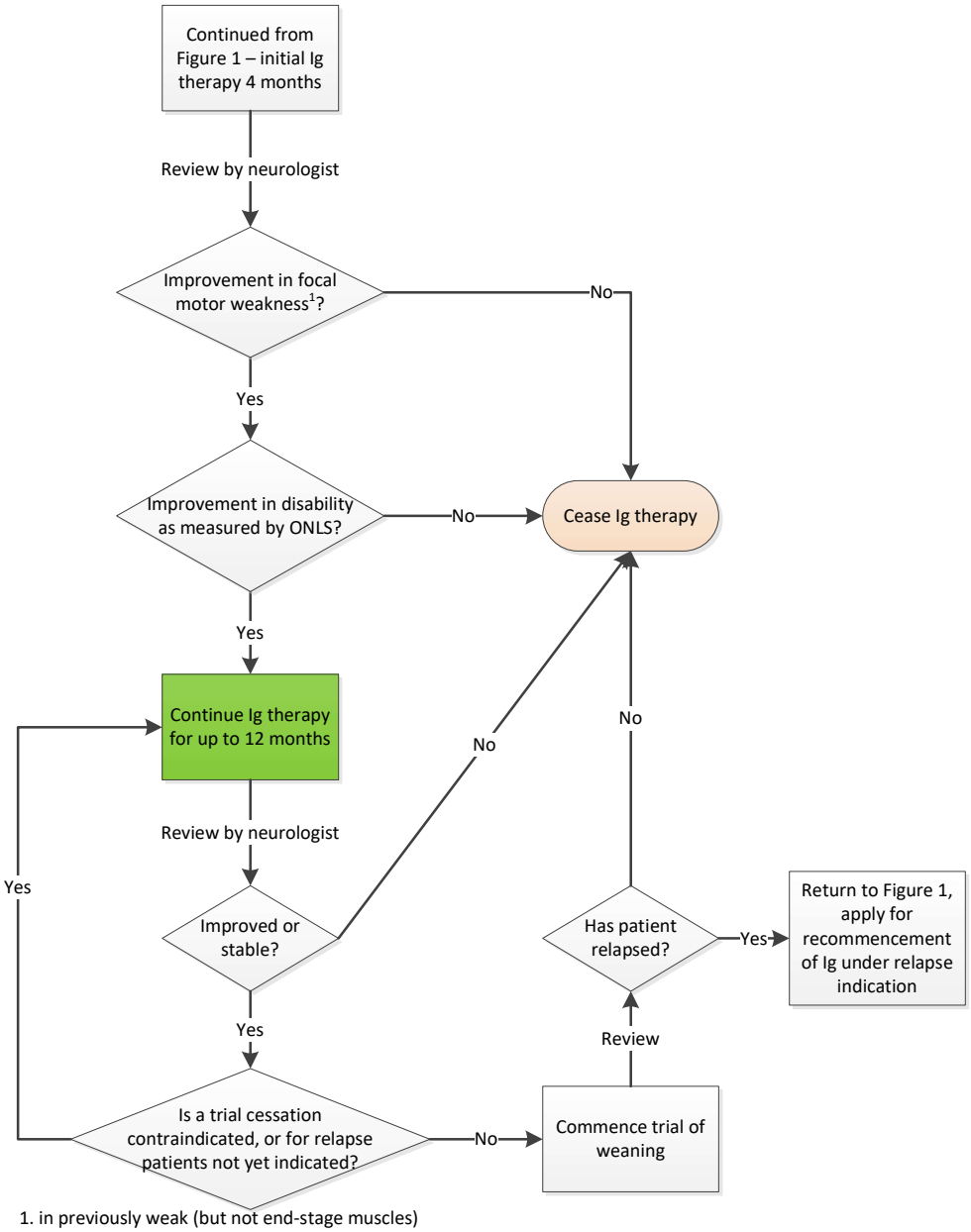
21. Define and summarise the current clinical management pathways (algorithm) from the point of initiating Ig therapy within the scope of this referral, including provision of health care resources (supplement this summary with an easy to follow flow chart, including health care resources):

The current basis for ongoing access to Ig products for MMN under Version 3 of the Criteria under the National Blood Arrangements is described at https://www.criteria.blood.gov.au/MedicalCondition/View/2558 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 weblink should take precedence.

A schematic summary of the basis for ongoing access to Ig therapy for MMN, 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



1. in previously weak (but not end-stage muscles)
2. Improvement must be indicated by an reduction of at least one point in the ONLS compared to the qualifying score
3. Improved or stable focal muscle weakness (slow deterioration may occur over several years in stable patients, and the same or reduced ONLS compared to previous review
4. A trial off should be considered if patient is stable, an avenue to return to Ig treatment is defined for relapse within 6 months of trial commencement

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):

Literature indicates that, at present, there is no therapeutic alternative to IVIg therapy[10].

The EFNS/PNS guidelines for the treatment of MMN[11] stated that if IVIg is not sufficiently effective then immunosuppressive treatment may be considered. However, no agent has shown to be beneficial in a clinical trial and data from case series are conflicting. Toxicity makes cyclophosphamide a less desirable option. For these reasons immunosuppressants should not be considered a comparator and that best supportive care was most appropriate.

Therefore, the appropriate comparator for MMN to be consistent with previous referrals is best referred to as 'no Ig'.

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

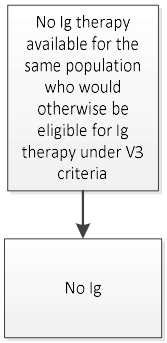
☐ Yes (please provide all relevant MBS items or PBS listings)
☐ No

Generic Name	PBS subsidised for *insert condition name*	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

[10] Van den Berg-Vos, RM, Franssen, H, Wokke, JH, et al 2002, 'Multifocal motor neuropathy: long-term clinical and electrophysiological assessment of intravenous immunoglobulin maintenance treatment', *Brain*, vol. 125, no. 8, pp. 1875–86.

[11] Joint Task Force of the EFNS and the PNS 2010, 'European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of multifocal motor neuropathy', *Journal of the Peripheral Nervous System*, vol. 15, pp. 295-301.

(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):

The aim of treatment in MMN is to reduce the motor deficit, reverse or improve the motor conduction block and limit ongoing axonal degeneration, which leads to irreversible functional impairment. However, current therapeutic options for MMN are limited, as patients do not respond to corticosteroids or plasma exchange and may eventually worsen under these treatments[12]. As the comparator is no Ig, the long term costs, including quality of life, associated with functional impairment and disability should be considered.

The EFNS/PNS Guidelines recommend IVIg as first line treatment for MMN that is severe enough to warrant treatment. Maintenance Ig therapy dosing should be guided by patient response[13].

A Cochrane review[15] found that IVIg treatment improved strength significantly more often than placebo. Evidence from four randomised controlled trials showed that people treated with IVIg had significant improvements in strength. Improvement in disability was also seen but was not significant. However, the EFPN Guidelines state that as weakness is the only determinant of disability in patients with MMN, it is to be expected that in patients whose muscle strength improves after IVIg treatment, disability will improve as well[14]. Side effects were common but were mild and transient. Muscle strength improved spontaneously in 1 out of 27 cases (4%), but treatment with IVIg increased this chance of improvement to 78% (21 out of 27 patients)[14].

Van den Berg[15] states that the effect of IVIg treatment lasts only several weeks. Although IVIg maintenance treatment does not prevent a mild global decrease in muscle strength and does not induce remission of MMN, it was found that IVIg maintenance treatment had a beneficial long-term effect on muscle strength, upper limb disability and electrophysiological variables in nerves with conduction block, and that treatment was well tolerated. In this study of 11 patients with MMN who received IVIg maintenance treatment for 4–8 years, it was found that muscle strength and upper limb disability scores were significantly better at the last follow-up examination than before IVIg treatment.

According to Leger[13], as at 2014, studies investigating Ig therapy in the treatment of MMN had only looked at short-term therapy, and options for the long-term treatment for MMN remained unclear. No long-term, placebo-controlled trials investigating the use of IVIg in MMN had been carried out. Although there were no RCTs investigating the long-term effects of IVIg in the treatment of MMN, there was data from retrospective trials showing that IVIg could be an effective long-term therapy in MMN. Some patients did not respond to IVIg, while others required progressively more frequent doses to maintain remission.

The Criteria V3[16] describes MMN as a condition for which IVIg has an established therapeutic role with clear evidence of benefit, however states that IVIg is not recommended for patients:

- with presence of upper motor neuron signs
- with marked bulbar involvement
- with significant sensory impairment without an adequate alternative explanation
- with diffuse symmetric weakness during the initial weeks
- without typical clinical or electrophysiological features, who are likely to have motor neuron disease (MND).

[12] Leger JM 2014, 'Immunoglobulin (Ig) in multifocal motor neuropathy (MMN): update on evidence for Ig treatment in MMN', *Clinical and Experimental Immunology*, vol. 178, pp. 42–44.
[13] Joint Task Force of the EFNS and the PNS 2010, 'European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of multifocal motor neuropathy', *Journal of the Peripheral Nervous System*, vol. 15, pp. 295-301.
[14] Van Schaik, IN, van den Berg, LH, de Haan, R, et al 2005, 'Intravenous immunoglobulin for multifocal motor neuropathy', (Cochrane Review) in *The Cochrane Library*, Issue 2, John Wiley & Sons, Ltd, Chichester.
[15] Van den Berg-Vos, RM, Franssen, H, Wokke, JH, et al 2002, 'Multifocal motor neuropathy: long-term clinical and electrophysiological assessment of intravenous immunoglobulin maintenance treatment', *Brain*, vol. 125, no. 8, pp. 1875–86.
[16] The Criteria for Clinical Use of Immunoglobulin in Australia V3.

The Therapeutic Goods Administration (TGA) maintains a reporting service for adverse events or defects in medicines in Australia.

The Product Information for Flebogamma in Australia[17] advises: Certain severe adverse reactions to the medicinal product may be related to the rate of infusion. The recommended infusion rate and method of administration must be closely followed. Patients must be closely monitored and carefully observed for any symptoms throughout the infusion period.

Certain adverse reactions may occur more frequently:

- in case of high rate of infusion
- in patients with hypo- or agammaglobulinaemia with or without IgA deficiency
- in patients who receive human normal immunoglobulin for the first time, or in rare cases, when the human normal immunoglobulin product is switched or when there has been a long interval since the previous infusion.

True hypersensitivity reactions are rare. They can occur in the very seldom cases of IgA deficiency with anti-IgA antibodies. Rarely, human normal immunoglobulin can induce a fall in blood pressure with anaphylactic reaction. Very rarely, thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism, deep vein thromboses have been observed with human normal immunoglobulin.

Cases of acute renal failure have been reported in patients receiving IVIg therapy. In most cases, risk factors have been identified, such as pre-existing renal insufficiency, diabetes mellitus, hypovolemia, overweight, concomitant nephrotoxic medicinal products or age over 65.

27. Please advise if the overall clinical claim is:

☒ Superiority
☐ Non-inferiority

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	***The outcomes identified pre assessment and considered in scope are:***
	Safety Outcomes:
	• Serious adverse events (e.g. anaphylaxis, veno-occlusive events)
	
	Clinical effectiveness outcomes:
	• Change in focal motor muscle weakness
	• Change in disability (e.g. as measured by the Overall Neuropathy Limitations Scale [ONLS])
	• Change in quality of life
	
	Healthcare system resources utilisation:
	• Changes in health system resource utilisation associated with either the intervention or comparator
	  ○ Ig products
	  ○ Infusion equipment
	  ○ Administrative and clinician time (e.g. resources associated with requesting, and authorising, access to Ig)

[17] Therapeutic Goods Administration. Australian Product Information, Flebogamma 10% DIF (Human Normal Immunoglobulin [IVIg] 100mg/ml) solution for infusion. Accessed May 2019.

	○ Nursing time (for initiation and monitoring if 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 neurology visits ○ Increase in use of disability support services ○ Increased home nursing and support needs ○ Increased hospital admissions

INFORMATION ABOUT ESTIMATED UTILISATION

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

Almost 80 percent of people with MMN are between 20 and 50 years of age at onset of the disease. Men are more frequently affected than women with a ratio of 2.6:1. The prevalence is estimated to be one to two per 100,000[18]. Australia's population as at 31 December 2017 was reported by the Australian Bureau of Statistics as 24,775,400[19]. Assuming a prevalence of 1.5/100,000 this equates to 372 patients in Australia, a prevalence of 2/100,000 indicates a population of 496 patients with MMN. NBA data in Table 7 indicates 560 patients in 2017-18 financial year.

Clinical expert advice[20] from the Ig Reference Group indicated that there are likely two groups of patients being treated for MMN with Ig. The first group would be those who truly have MMN and respond to treatment with Ig. Of those with MMN, less than 10 percent of patients are likely to not require Ig therapy at a given time due to the condition being mild. The other group includes patients with motor neuron disease (MND) who have been incorrectly started on Ig. A placebo effect may be seen in some patients with MND and cause treatment with Ig to continue and the differential diagnosis not be recognized for some period of time. This may account for the discrepancy between the prevalence calculation above and the data held by the NBA.

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

Table 7: Data on the use of Ig therapy over recent years for MMN (NBA internal data)

	2013-14	2014-15	2015-16	2016-17	2017-18
New patients	127	105	137	126	125
Total patients	438	444	496	527	560
Grams	239,791	256,041	293,458	331,147	354,434
Average grams per patient	546	577	592	628	633

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:

The treatment episodes for MMN in 2017-18 were 8,258 for a total patient count of 560. This equates to an average of 14.7 episodes per patient (sourced from NBA internal data). 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.

Table 8: Ig grams per kg weight per episode for MMN (Report on the Issues and Use of Ig 2017-18)(publication forthcoming, date to be confirmed)

Specific Condition	<=0.4 g/kg/ episode n (%)	0.4 – 0.99 g/kg/ episode n (%)	1 – 2 g/kg/ episode n (%)	>2 g/kg/ episode n (%)	No weight Data n(%)	Ig Average g/kg/ episode

[18] Van Schaik, IN, van den Berg, LH, de Haan, R, et al 2005, 'Intravenous immunoglobulin for multifocal motor neuropathy', (Cochrane Review) in *The Cochrane Library*, Issue 2, John Wiley & Sons, Ltd, Chichester.

[19] Australian Bureau of Statistics, 3101.0 – Australian Demographic Statistics, released 20 June 2019, accessed on 7 August 2019.

[20] Clinical expert advice, Ig Review Reference Group 2019

Specific Condition	<=0.4 g/kg/ episode n (%)	0.4 – 0.99 g/kg/ episode n (%)	1 – 2 g/kg/ episode n (%)	>2 g/kg/ episode n (%)	No weight Data n(%)	Ig Average g/kg/ episode
Multifocal motor neuropathy	1,935 (24%)	5,115 (64%)	777 (10%)	33 (0%)	151 (2%)	0.58

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

MMN mainly has a chronic or stepwise progressive course[21].

As IVIg is thought to induce and maintain improvement in the majority of people with MMN, but does not eradicate the disease, patients have to be treated with periodic infusions for long periods of time[22]. Clinical expert advice suggests that patients with MMN will have progressive disease and will use Ig indefinitely, albeit with trials of weaning to establish if an end of dose effect is present[23].

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 without a confirmed diagnosis of MMN or without benefit.

To manage this risk, the Criteria V3 has limited the initial authorisation period to four months. To obtain ongoing therapy, response as shown by improvement in (or for those at continuing review after 12 months, stabilisation or improvement in) focal motor weakness and level of disability must be documented. However, a placebo effect may be seen in some patients with MND resulting in continued treatment with Ig and the differential diagnosis of MND not be recognized for some period of time. The requirement in the Criteria to respond to Ig treatment to allow continuation of therapy may therefore not prevent all leakage in this population.

The Criteria also encourages cessation of Ig therapy to be considered at least after each 12 months of treatment for those patients treated under the indication 'First-line and maintenance therapy for MMN', unless contraindicated. For those patients treated under the indication 'Relapse of MMN patients within six months of commencement of trial off immunoglobulin therapy', a subsequent trial of weaning leading to cessation is recommended to be considered after a further two years of Ig therapy.

Another risk of leakage for consideration is in dosing. Some patients may be on higher doses of Ig than required. Dosing should be titrated to the individual's response. 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 2017-18 on grams issued/1,000 population in the relevant state or territory and nationally are provided below. These data indicate substantial variation in practice between jurisdictions.

Table 9: Ig issued per 1,000 population by state and territory for MMN (Report on the Issues and Use of Ig 2017-18)(publication forthcoming, date to be confirmed)

Specific Condition	NSW	VIC	QLD	SA	WA	TAS	NT	ACT	AUS	Fold Variation*

[21] Leger JM 2014, 'Immunoglobulin (Ig) in multifocal motor neuropathy (MMN): update on evidence for Ig treatment in MMN', *Clinical and Experimental Immunology*, vol. 178, pp. 42–44.

[22] Van den Berg-Vos, RM, Franssen, H, Wokke, JH, et al 2002, 'Multifocal motor neuropathy: long-term clinical and electrophysiological assessment of intravenous immunoglobulin maintenance treatment', *Brain*, vol. 125, no. 8, pp. 1875–86.

[23] Clinical expert advice, Ig Review Reference Group 2019

Specific Condition	NSW	VIC	QLD	SA	WA	TAS	NT	ACT	AUS	Fold Variation*
Multifocal motor neuropathy	14	10	15	23	17	15	22	22	14	2.3

*The Fold Variation is a measure describing difference in the Ig grams per 1,000 population between the state being issued the least to the state being issued the most, using only data from the five largest states

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 MMN subsidised via the NBA for domestic Ig products was $ 24,856,555.

Table 10: Breakdown of product costs for MMN (NBA internal data)

Product category	Cost (ex GST)
*Domestic IVIg cost	$ 12,839,881
Imported IVIg cost	$ 12,016,674
Total	$ 24,856,555

*Domestic cost includes 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 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 11: Ig product issued 2017-18: Grams sourced from the National Report on the Issue and Use of Immunoglobulin (Ig) (publication forthcoming, date to be confirmed) and prices sourced from NBA website as at 1 July 2019.

	IVIg					
MMN	Flebogamma 5 percent	Flebogamma 10 prcent	Intragam P	Intragam 10	Privigen 10 per cent	Total
Multifocal motor neuropathy	29,712	55,100	504	132,193	159,970	377,479
NBA current price per gram in $	45	45	58.49	58.49	45	
**Total cost by product in $	1,337,040	2,479,500	29,479	7,731,969	7,198,650	18,776,638

*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. Prices are product costs only and do not include plasma collection or fractionation costs.