Australian Government

Medical Services Advisory Committee

# Public Summary Document

## Application No. 1590 – Review of immunoglobulin use for Multifocal Motor Neuropathy (MMN)

**Applicant:**                      **National Blood Authority (NBA)**

**Date of MSAC consideration:**      **MSAC 79th Meeting, 28-29 July 2020**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

## 1.      Purpose of application

This Post-market Review requested MSAC advice on the Government funded supply of human gamma immunoglobulin (IgG) therapy under the National Blood Arrangements for the treatment of multifocal motor neuropathy (MMN). The application (referral) was received from the National Blood Authority (NBA) by the Department of Health.

The Post-market Review was conducted to assess the clinical safety and clinical effectiveness and cost-effectiveness of Ig therapy for the treatment of multifocal motor neuropathy.

## 2.      MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC advised that funding of immunoglobulin (Ig) therapy should continue for multifocal motor neuropathy, and noted the high clinical need in this population for which there are no alternative treatments. MSAC considered there to be sufficient evidence to suggest that Ig is an effective therapy in this population; however the cost-effectiveness remains uncertain. It is unclear whether current thresholds to access Ig therapy under the *Criteria for the clinical use of immunoglobulin in Australia* (version 3) (the Criteria) for this indication are sufficient to ensure that treatment is constrained to the population with a diagnosis of MMN only. The number of patients currently being treated with Ig therapy for MMN in Australia exceeds that predicted from the range of prevalence estimates referenced in the review.

MSAC noted the estimated net costs to government over five years to 2024 of almost $171 million for this indication, of which $131.5 million is attributable to the cost of Ig alone. MSAC considered this cost to be significant despite the small population of patients, and advised that managing patient numbers to ensure that Ig therapy is directed appropriately to patients with MMN who are most likely to derive benefit could minimise the potential financial risk. MSAC advised that no immediate changes were required to the Criteria (version 3), but recommended that reviewing the utilisation data collected by the NBA

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(BloodSTAR) in 12 months would provide a more definitive answer as to whether further changes are required.

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**Consumer summary**

The National Blood Authority (NBA) sought advice from MSAC on the government-funded supply of human antibodies (immunoglobulin, or Ig) used to treat multifocal motor neuropathy (MMN). The NBA is the statutory agency within the Australian Government Health portfolio that manages and coordinates arrangements for the supply of blood and blood products and services on behalf of the Australian Government and state and territory governments. This referral to review the use of Ig in MMN is included as part of the Ig Reviews, which aim to ensure that government-funded Ig use within Australia is based on evidence of clinical safety, effectiveness and cost-effectiveness.

MMN is a rare condition affecting the nerves, causing weakness of the limbs, often starting in the arms. The condition can appear similar to other conditions such as motor neurone disease. MMN is more common in males than in females and the age at which MMN can start to appear varies from 15-74 years.

Ig therapy has been shown to improve muscle weakness and reduce disability, and has been the standard of care (generally recommended therapy) to treat people with MMN since the 1990s.

MSAC considered that Ig therapy appears to be safe and effective, and should continue to be available to treat people with MMN. MMN can be difficult to diagnose, and currently, the number of people being treated with Ig is higher than the number of people we would expect to be living with MMN in Australia.

MSAC noted Ig is a very expensive therapy – the review predicted that over the next five years to 2024, it would cost the government approximately $171 million to treat this group of patients and most of the cost comes from the Ig product itself ($131.5 million). This is a high cost for a small population; therefore the government needs to ensure Ig therapy is only prescribed to people who obtain ongoing benefit. One way to do this is to analyse data collected from BloodSTAR (https://www.blood.gov.au/bloodstar), the online system used across Australia to manage access to the supply of government funded immunoglobulin products. The system manages the authorisation request and review process for the treatment of conditions identified in the *Criteria for the clinical use of intravenous immunoglobulin in Australia (*https://www.criteria.blood.gov.au/). The requirements or Criteria (version 3) to access Ig therapy were revised in October 2018, and aim to limit the use of Ig to people with MMN whose symptoms improve on Ig therapy. MSAC has advised that this should be reviewed again in 12 months when there is more information available, as part of the process to make sure the people who receive Ig therapy experience clinical benefit.

**MSAC's advice to the National Blood Authority**

MSAC advised that Ig therapy is standard of care for people living with MMN; and the evidence suggests Ig is likely to provide some clinical benefit. Therefore, MSAC supports continued funding of Ig for the treatment of people living with MMN. However, MSAC considered that the cost-effectiveness of Ig for MMN was high and uncertain. BloodSTAR data should be analysed in twelve months' time to check if the initiation and continuation criteria thresholds in the Criteria (version 3), implemented in October 2018, adequately ensure that only those people who have MMN and demonstrate a clinical benefit from Ig, receive ongoing therapy.

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## 3.    Summary of consideration and rationale for MSAC's advice

In Australia, Ig for the treatment of MMN is funded for intravenous administration only and is considered the standard of care for patients with MMN. MSAC noted the subcutaneous form of Ig (SCIg) is not currently funded by the NBA and the department contracted assessment report (DCAR) stated evidence from a randomised controlled trial (RCT) suggests that SCIg was as safe and effective as intravenous Ig (IVIg).

MSAC noted that patients with MMN may be eligible for Ig treatment under the *Criteria for the clinical use of immunoglobulin in Australia* (version 3) (the Criteria) under either:
- First-line and maintenance therapy for MMN
- Relapse of MMN patients within six months of commencement of trial off immunoglobulin therapy.

The diagnosis of MMN must be made by a neurologist and eligible patients may receive IVIg initially for a maximum of four months. MSAC noted that the clinical diagnosis of MMN is based on core, supportive and exclusion criteria, and can then be categorised as either 'definite' or 'probable' depending on the magnitude of the conduction deficit. MSAC noted that one of the supportive criteria for a diagnosis of MMN is the 'response in terms of disability or muscle strength to immunomodulatory therapy'. Thus the diagnosis, based on the assessment using supportive criteria in addition to the core criteria can only be categorically determined after a period of Ig therapy.

After the initial four months of IVIg therapy, patients must be reviewed by a neurologist and evidence of clinical efficacy (improvement in focal weakness and improvement in disability as measured by the Adjusted Overall Neuropathy Limitations Scale (ONLS)) is required for authorisation of continued IVIg therapy for a further 12 months.

Clinical reviews are required annually thereafter, and a trial of weaning/cessation of Ig therapy is considered at each annual review for patients who are clinically stable to identify those in remission. MSAC noted the Criteria states that a valid reason should be provided as to why a trial off Ig is not being planned or is contraindicated at each annual review and suggested the clinical information provided in these reports could be of value in future evaluations of the continuation criteria. Clinicians may need more encouragement to trial patients off Ig, noting that if a patient relapses, they may receive IVIg again under the "Relapse" (within 6 months) or "First-line and maintenance therapy" (relapsed after 6 months off Ig) indications.

MSAC considered there is a high clinical need in this population. IVIg therapy has been the standard of care in patients with MMN since the 1990s and there are no alternative treatments. MSAC agreed the comparator to Ig was no Ig with best supportive care (BSC) and considered each component of the PICO Confirmation to be reasonable.

MSAC noted that the reported frequency of adverse events (AEs) in the RCTs ranged from 1-40% but events usually occurred in less than 20% of participants. With regards to comparative safety of Ig versus placebo, MSAC agreed that the safety profile of intravenous Ig was inferior to placebo. However, MSAC noted that most AEs associated with IVIg were mild, self-limiting and typical of infusion reactions such as headache, fever and chills. One RCT (Hahn et al 2013) reported one patient (n=44) who suffered a pulmonary embolism (PE) which was categorized as a serious AE attributed to the use of IVIg by the investigators; this was later used to estimate the rate of PE in the economic model. MSAC considered feedback from one stakeholder that prescriber information (PI) for IVIg products (Privigen and Intragam) state that PE is a very rare complication; the stakeholder noted that a "very rare

event" is one that occurs at a rate of < 1/10,000 (CIOMS 2001). MSAC agreed that the 4.5% rate of PE applied in the economic model based on this one study is not justified and a rate of 0.01% may be more plausible.

With regards to the clinical effectiveness of Ig, MSAC noted that all five RCTs reported some benefit associated with IVIg and agreed with the clinical claim that Ig is superior to placebo. MSAC noted that meta-analysis using Hahn 2013 and Leger 2001 produced a weighted risk ratio of 1.81 (95% CI 0.74, 4.45) for improvement in disability with Ig. While the point estimate indicates patients could be 80% more likely to improve when treated with Ig, the result was not statistically significant. The meta-analysis of the RCTs reporting the results for improvement in muscle strength/grip found that patients are 3.5 times more likely to improve on Ig therapy than placebo and this result was statistically significant (RR = 3.51 (95% CI 1.12, 11.05: p value = 0.03)). MSAC noted the paucity of evidence with respect to quality of life (QoL) in patients with MMN.

Overall, MSAC considered that the evidence included in the DCAR was sufficient to support the claims that Ig has inferior safety and superior clinical effectiveness in the treatment of MMN. Cognisant of Ig being the accepted standard of care and the limitations of the data (low patient numbers and short follow-up) in the available studies, MSAC also noted that future RCTs of IVIg versus placebo are unlikely in this population.

MSAC noted the cost-utility analysis (CUA) base case produces an incremental cost-effectiveness ratio (ICER) of $317,552 per quality-adjusted life-year (QALY) with a time horizon of 15 years. The base case applied a constant utility in both the 'BSC' and 'responder' health states over time due to uncertainties associated with a reliable source to capture this decline in QoL over time in patients with MMN. MSAC agreed with ESC advice and comments from one stakeholder that deterioration in QoL over time of MMN patients is plausible, and that there would be divergence in QoL between those in the 'BSC' and 'Ig responder' groups. Application of a linear decline in QoL over time due to disease progression was tested in a scenario analysis based on the study by Taylor (2000) and had a significant impact on the ICER, reducing it to $98,559/QALY. This linear decrement was considered a potential overestimate and highly uncertain by the HTA assessors; however, MSAC noted that even a 50% reduction in this annual decline reduced the ICER considerably, to $150,429/QALY. In addition to the utility values used, MSAC noted that the ICER was also highly sensitive to the cost per gram of Ig ($60.41 in the base case) and moderately sensitive to transition probabilities used in the model. MSAC also noted sensitivity analyses performed post-ESC showed the impact on the ICER of varying administration costs to those used in the three preceding Ig Reviews (MSAC 1564, 1565 and 1566). Using the lowest administration cost of $253 from the 1565 DCAR, reduced the base case ICER by approximately 17%. However, MSAC considered that the use of different administration costs in each of the conditions under review is justified in principle, as the treatment patterns and administration may differ across indications. Overall, MSAC considered the cost-effectiveness of Ig to be high and uncertain in patient with MMN.

Regarding financial and budgetary impacts, MSAC noted the estimated net costs to government over five years to 2024 of almost $171 million for this indication, of which $131.5 million is attributable to the cost of Ig alone. MSAC considered the cost to government to be significant despite the small population of patients, and advised that managing patient numbers to ensure that Ig therapy is directed to patients with MMN most likely to derive benefit would be prudent to minimising potential financial risk.

There are currently no epidemiological data available for the incidence and prevalence of MMN in Australia; however, the DCAR states that prevalence rates reported in international studies range from 0.3-2 cases per 100, 000 population. On the advice of the Ig Review Reference Group, the DCAR used the prevalence reported in Cats et al (0.6/100,000 population) as a proxy to predict that 152 patients in Australia were likely to be living with MMN in 2018-19 – much lower than the 596 patients who received IVIg for MMN in the same period, according to NBA data. MSAC noted that using the higher prevalence rate of 2/100,000 population as reported by Nobile-Orazio 2001 produced an estimate of 503 patients with MMN in Australia, which more closely matches proxy data from BloodSTAR. MSAC considered that while there is uncertainty regarding the true prevalence of MMN in Australia, the number of patients being treated with Ig for MMN in Australia exceeds what can be predicted from the range of published prevalence estimates referenced in the DCAR.

MSAC noted that misclassification could be an underlying factor for this higher prevalence and advised that the applicant consider whether the threshold for patients to qualify for initial or continued Ig therapy under the Criteria V3 are sufficiently stringent. MSAC considered that the current requirements for patients to show improvement or stabilisation at review periods may provide little incentive for patients to discontinue therapy with Ig. MSAC noted that while the Criteria V3, introduced in October 2018, aimed to address potential leakage to a non-MMN population, its effect on patient numbers should now have started to become apparent. MSAC recommended that reviewing the data in a further 12 months would provide a more definitive answer as to whether these thresholds require revision. MSAC advised that capturing data around the justification for continued therapy, cessation of treatment, or reasons why a trial for cessation is not being planned would be informative for potential compliance monitoring of clinician practices in the future. MSAC considered that whilst establishing a patient registry could be used to inform prevalence data, treatment patterns (duration on treatment, breaks in treatment) and capture some QoL data, it is preferable to enhance the reporting of data via BloodSTAR, and consider the Criteria for patients to qualify for treatment with Ig.

MSAC noted that subcutaneous Ig (SCIg) is not currently approved for the treatment of patients with MMN. The use of SCIg and its suitability for self-administration by patients with MMN should be further investigated to improve both convenience and costs associated with Ig therapy.

## 4. Background

All Australian Governments, through the Jurisdictional Blood Committee (JBC), have agreed to conduct robust Health Technology Assessments (HTAs) of immunoglobulin use (Ig Reviews) funded under the National Blood Agreement to ensure government-funded immunoglobulin use is based on strong evidence of clinical effectiveness and cost-effectiveness. The National Blood Agreement provides for MSAC to undertake evidence-based evaluation of blood products funded under the national blood supply arrangements at the request of the JBC.

The Ig Reviews are supported by a bespoke Reference Group, which oversees and provides advice on evaluation of all Ig HTA review applications. The PICO Confirmations for the Ig Reviews have been considered by the Reference Group instead of the PICO Advisory Sub-committee (PASC). Otherwise, the MSAC evaluation process remains the same as for applications for funding of items on the Medical Benefits Schedule (MBS).

The first tranche of Ig Reviews included three applications which have already been considered by MSAC:

- Application 1564 – Review of immunoglobulin use for chronic inflammatory demyelinating polyneuropathy
- Application 1565 – Review of immunoglobulin use for acquired hypogammaglobulinaemia secondary to haematological malignancies, or post-haemopoietic stem cell transplantation (HSCT)
- Application 1566 – Review of immunoglobulin use for Myasthenia Gravis

Application 1590 – Review of immunoglobulin use for multifocal motor neuropathy is the fourth report from the Ig Reviews to proceed to MSAC.

## 5. Prerequisites to implementation of any funding advice

All therapeutic products marketed in Australia require listing on the Australian Register of Therapeutic Goods (ARTG). IVIg products registered by the TGA for the potential treatment of MMN in Australia are summarised in Table 1.

**Table 1: Intravenous Ig products registered in the TGA potentially relevant for the treatment of MMN**

| Product/strength | Presentations | TGA indication for MMN (Yes/No) | NBA price per gram @ 10/10/19 |
|---|---|---|---|
| Flebogamma 5% DIF | 0.5 g/10 mL<br>2.5 g/50 mL<br>5 g/100 mL<br>10 g/200 mL<br>20 g/400 mL | No | NBA funded<br>$45 |
| Flebogamma 10% DIF | 5 g/50 mL<br>10 g/100 mL<br>20 g/200 mL | No | NBA funded<br>$45 |
| Intragam P (6%) | 0.6 g/10 mL<br>60 g/L | No | Not NBA funded |
| Intragam 10 (10%) (plasma derived – domestic) | 2.5 /25 mL<br>10 g/100 mL<br>20 g/200 mL | Yes | NBA funded<br>$58.23[1] |
| Privigen 10% | 5 g/50 mL<br>10 g/100 mL<br>20 g/200 mL<br>40 g/400 mL | Yes | NBA funded<br>$45 |
| Octagam 5% | 1 g/20 mL<br>2.5 g/50 mL<br>5 g/100 mL<br>10 g/200 mL | No | Not NBA funded |
| Octagam 10% | 20 g/200 mL<br>10 g/100 mL<br>2 g/20 mL<br>5 g/50 mL | No | Not NBA funded |
| Gammanorm 16.5% | 3300 mg/20 mL<br>1650 mg/10 mL | No | Not NBA funded |
| Kiovig (10%) | 30 g/300 mL<br>20 g/200 mL<br>10 g/100 mL<br>5 g/50 mL<br>2.5 g/25 mL<br>1 g/10 mL | Yes | Not NBA funded |
| Panzyga 10% | 1 g/10 mL<br>5 g/50 mL<br>20 g/200 mL<br>2.5 g/25 mL<br>30 g/300 mL | No | Not NBA funded |

| Product/strength | Presentations | TGA indication for MMN (Yes/No) | NBA price per gram @ 10/10/19 |
|---|---|---|---|
| Intratect 10% | 20 g/200 mL<br>10 g/100 mL<br>5 g/50 mL<br>1 g/10 mL | No | Not NBA funded |
| Intratect 5% | 5 g/100 mL<br>1 g/20 mL<br>10 g/200 mL<br>2.5 g/50 mL | No | Not NBA funded |
| TBSF human immunoglobulin | NA | No | Not NBA funded |
| Gamunex 10% | 20 g/200 mL<br>10 g/100 mL<br>5 g/50 mL | No | NBA funded; price is confidential. |

**Source**: 1590 DCAR, Table 2 (NBA website; https://www.blood.gov.au/national-product-list, accessed 26 February 2020.)
Abbreviations: Intravenous Ig = intravenous immunoglobulin; MMN = multifocal motor neuropathy; NA= not available; NBA = National Blood Authority; TBA = to be announced; TGA = Therapeutic Goods Association.
Note: [1]The price does not include the starting plasma provided to CSL by the Australian Red Cross Blood Service.

## 6. Proposal for public funding

Ig therapy for MMN is currently funded by the NBA under the national blood supply arrangements. Ig therapy is classified as an established therapeutic role in this population, but the cost-effectiveness of this use has not been evaluated in Australia. NBA procurement of Ig is via competitive tendering and negotiation with suppliers.

Clinical criteria for eligible patients to access subsidised Ig for are specified in Version 3 of the Criteria. Applications for Ig are made through the BloodSTAR online portal and assessed against the Criteria. MMN patients must be approved by meeting the qualifying criteria for either first line/maintenance treatment of MMN, or relapsed MMN in order to access the products.

The Criteria, including eligibility criteria are periodically updated and may be refined according to recommendations of the relevant NBA working group and subsequent approval by the JBC. Access to Ig in this population requires an Australian Health Practitioner Regulation Agency (AHPRA) registered neurologist to both make the initial diagnosis of MMN, and to carry out the patient reviews at four months following initial treatment and annually following continuation thereafter.

## 7. Summary of public consultation feedback/consumer Issues

Public consultation was undertaken on the Referral and DCAR, and sponsor companies had an additional opportunity to comment on the PICO and provide input to the DCAR.

No consumer responses were received for this application. Responses received from clinicians, clinical groups and sponsors were supportive of the use of Ig for patients with MMN. Clinicians noted that Ig is the standard of care for patients with MMN, and is considered to stabilise and improve the overall quality of life in these patients over the long term. Delaying treatment with Ig would result in irreversible nerve damage and reduced QoL for patients presenting with MMN. Noted disadvantages associated with Ig use were potential adverse events, however stakeholders generally considered any disadvantages were minimal compared with the alternative of no active treatment.

Clinicians also noted the actual number of patients treated with Ig for MMN (according to NBA data) appeared high given the rarity of this condition.

One sponsor company raised concerns regarding the modelled economic assumptions, including the use of a constant utility over time in the BSC arm and a high adverse event rate for pulmonary embolism associated with IVIg.

## 8.    Proposed intervention's place in clinical management

**Description of Proposed Intervention**

This referral is for immunoglobulin (Ig) used as immunomodulation therapy.

Ig is a plasma-derived product manufactured to treat a range of medical conditions. Access to government-funded Ig is through the national blood arrangements and is determined by the NBA's *Criteria for Clinical Use of Immunoglobulin in Australia* (the Criteria)[1]. Ig acts as an immune modulator in the treatment of patients with MMN, although the exact mechanism of action is not yet fully understood. In Australia, Ig for the treatment of MMN is administered intravenously only and is considered the standard of care. The subcutaneous form of Ig (SCIg) is not currently funded by the NBA for the treatment of MMN.

**Description of Medical Condition(s)**
This referral includes patients with MMN who are currently eligible for Ig treatment in Australia according to Version 3 of the Criteria. Patients must be eligible under either of the two following indications:
- 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.

MMN is a rare motor neuropathy characterised by motor deficits that present as slowly progressive, predominantly distal, asymmetrical limb weakness without associated sensory loss. Weakness often begins in the arms and the combination of weakness, wasting, cramps and fasciculation may mimic motor neuron disease. If left untreated, the quality of life of patients with MMN continues to deteriorate as more nerves lose functionality over time. The DCAR states that the age of disease onset is variable, ranging from 15-74 years, with a mean age of onset of 41 years. The diagnosis of MMN has been standardised per the guideline of the European Federation of Neurological Societies/Peripheral Nerve Society.[2]

There are currently no epidemiological data available for MMN in Australia. The DCAR used the population-based prevalence rate estimates for MMN reported by Cats et al. 2010 as a proxy to project the number of Australians likely to be living with MMN. This prevalence estimate was recommended by the Ig Review Reference Group because the study was conducted in a systematic way and their findings are widely used, and the clinical criteria used in the study were consistent with the qualifying criteria (The Criteria V3) for intravenous Ig therapy for MMN used in Australia. The estimated prevalence rate (0.6 cases per 100,000 population) from Cats et al. 2010 was applied to an estimate of the Australian population as at June 2019 of 25,364,307. This would equate to 152 patients in Australia with a definite MMN diagnosis and is much fewer than the number of patients receiving Ig for MMN according to data provided by the NBA (596 patients in the period 2018-19). The DCAR notes that this difference could be partly explained due to patients being treated according to The Criteria V2 having been categorised in all the diagnostic categories of

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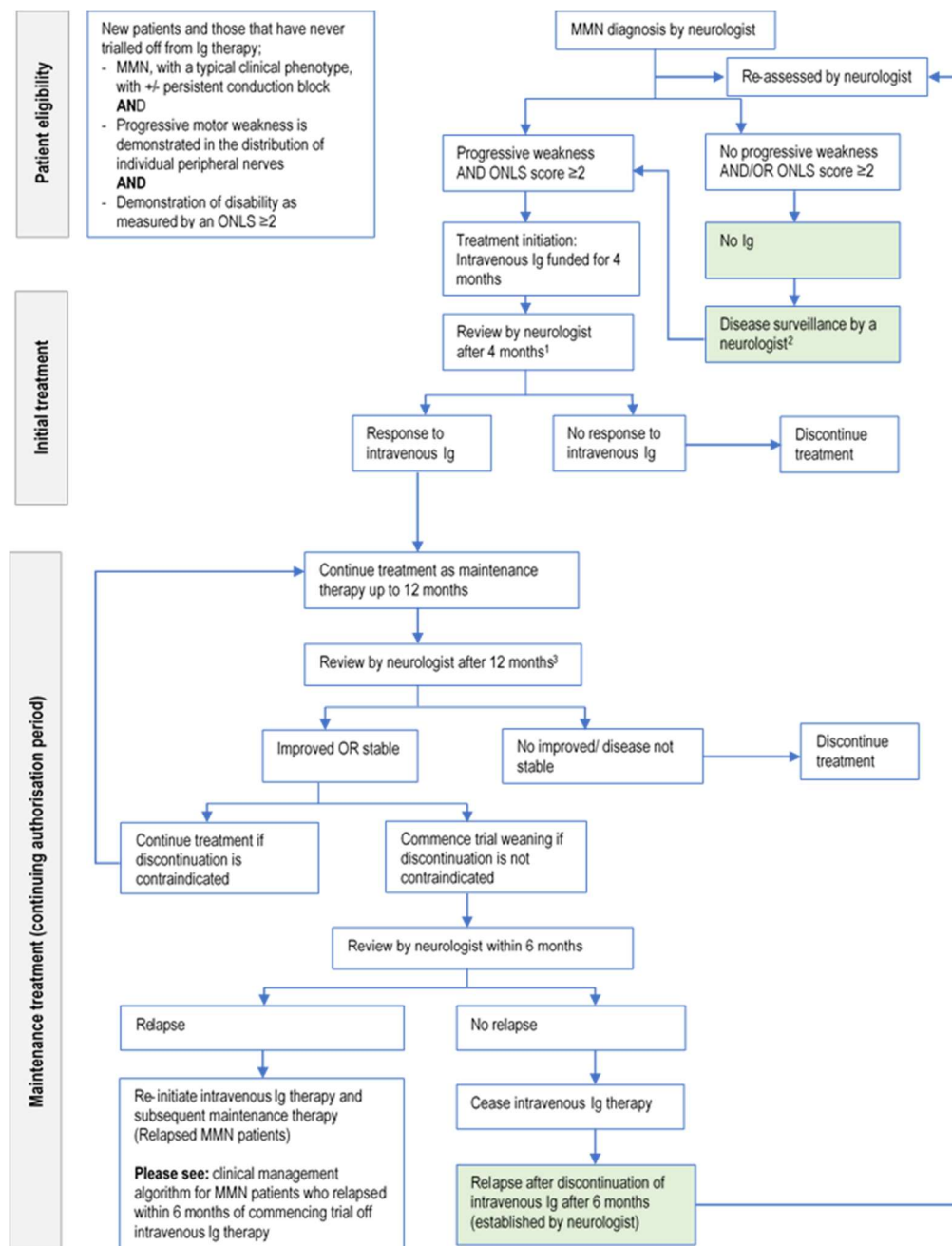[1] National Blood Authority, 2018, *Criteria for the clinical use of immunoglobulin in Australia* (version 3).
[2] European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of multifocal motor neuropathy. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society – first revision. J Peripher Nerv Syst. 2010;15(4):295–301.

MMN: definite, probable and possible. It could also be a result of misdiagnosis (e.g. motor neurone disease as MMN) or misclassification potentially representing Ig use in a non-MMN population being encompassed under the use for MMN.

The DCAR notes that due to the risk of misdiagnosis and/or under diagnosis, prevalence estimates should be interpreted with caution.

The clinical management algorithm for the initial and maintenance use of intravenous Ig developed during the PICO Confirmation for each indication are presented at Figure 1 and Figure 2.

**Figure 1: Proposed clinical management algorithm: initial and maintenance treatment (continuing authorisation) to Ig under NBA for first indication.**
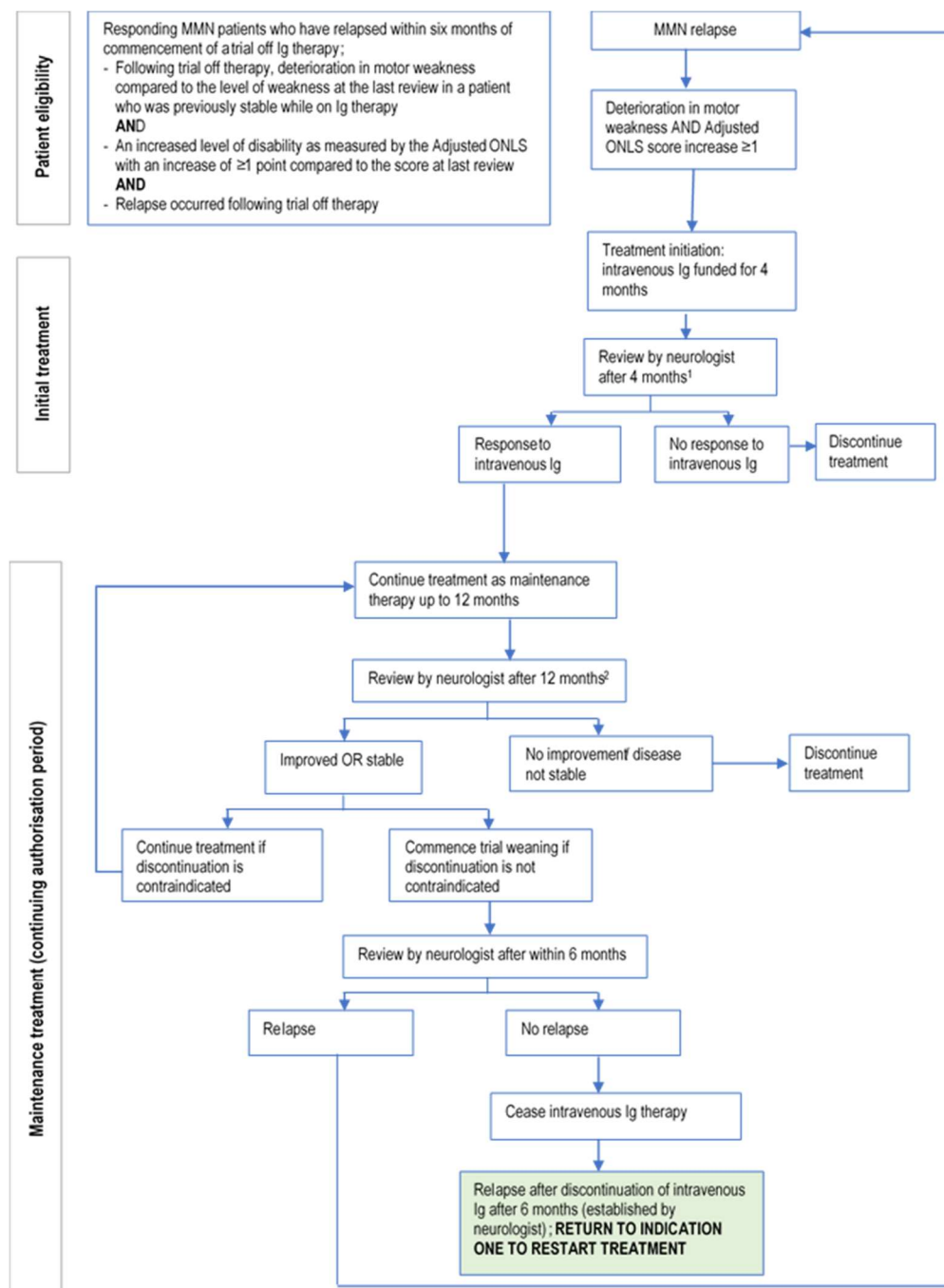


Abbreviations: Intravenous Ig= intravenous immunoglobulin; MMN= multifocal motor neuropathy; NBA= National Blood Authority; ONLS = Overall Neuropathy Limitations Scale.

Note: [1] Clinical effectiveness (response) of Ig therapy can be assessed by: Improvement in focal motor weakness in previously weak (but not end stage) muscles **AND** Improvement in the level of disability as measured by the Adjusted ONLS of at least one point less than the qualifying score; [2]Refers to no changes in the patient's disease status; blocks highlighted in green were added during the PICO Confirmation.

[3] Clinical effectiveness (response) of Ig therapy can be assessed by: Improvement in, or stabilisation of, weakness after previous evidence of deterioration in motor strength. It is acknowledged that very slow deterioration may occur over several years in stable patients **AND** Improvement in or stabilisation of disability as measured by the Adjusted ONLS score compared to the previous review score. (Note: Gradual deterioration of one point over several years may occur) **AND** A trial of Ig weaning/cessation of Ig therapy is planned for patients who are clinically stable to identify those in remission or a reason provided as to why a trial is not planned
Blocks coloured in green were added during the PICO confirmation.

**Sources**: 1590 DCAR, Figure 3 (Prepared during PICO Confirmation based on Figure 1 and Figure 2 of the MMN Referral and the reviewed content.)

**Figure 2: Proposed clinical management algorithm: initial and maintenance treatment (continuing authorisation) to intravenous Ig under NBA for second indication (patients who relapse within six months of weaning.**



Abbreviations: Ig= immunoglobulin; MMN= multifocal motor neuropathy; NBA= National Blood Authority; ONLS = Overall Neuropathy Limitations Scale.
Note: [1] Clinical effectiveness (response) of Ig therapy can be assessed by: Improvement in focal motor weakness in response to four months of Ig therapy compared to muscle strength at the qualifying assessment following relapse **AND** Improvement in disability as measured by the Adjusted ONLS compared to the qualifying assessment at relapse;[2] Clinical effectiveness (response) of Ig therapy can be assessed by: Improvement in, or stabilisation of, focal motor weakness as compared to the focal muscle strength at the previous review assessment **AND** Improvement in or stabilisation of disability as measured by the Adjusted ONLS compared to the previous review score (gradual deterioration of one point over several years is acceptable) **AND** A trial of weaning/cessation of Ig therapy are considered annually for patients who are clinically stable to identify those in remission or a valid reason provided as to why a trial is not being planned or is contraindicated at this time.
Blocks coloured in green were added during the PICO confirmation
**Sources**: 1590 DCAR, Figure 4 (Prepared during PICO Confirmation based on Figure 1 and Figure 2 of the MMN Referral and the reviewed content.)

## 9.    Comparator

The comparator is defined in the PICO Confirmation as 'No Ig with active disease surveillance'. The DCAR refers to this as 'No Ig with best supportive care (BSC)'.

## 10.    Comparative safety

Evidence from four RCTs and 14 single arm studies were used to assess the safety of Ig. A summary of adverse events (AEs) reported in the RCTs is provided at Table 2. Overall, the safety profile of intravenous Ig was inferior to placebo.

In the RCTs, AEs were mild and typical of infusion reactions such as headache, fever and chills. These events were generally characterised as self-limiting and often resolved by reducing the rate or volume of infusion, or by preventive measures such as prophylactic use of antihistamines. One RCT, Hahn et al 2013, reported one patient who suffered a pulmonary embolism which was categorised as a serious adverse event that could be attributed to the use of intravenous Ig by the investigators.

The single arm studies were used to assess potential long-term AEs from Ig treatment and showed similar results to the RCTs. Safety data reported in these studies included reports of systemic AEs directly related to the infusion over a longer follow-up period than what was available in the RCTs. Infusion related AEs were frequent but generally mild and manageable with adjustments to infusion rate. Overall, few patients discontinued treatment due to AEs.

**Table 2: Summary of adverse events reported in randomised controlled trials.**

| Study | Intravenous Ig treatment n/N (%) | Placebo treatment n/N (%) | Relative Risk (95%CI) | Risk difference (95%CI) |
|---|---|---|---|---|
| **Azulay et al. 1994(24)** | | | | |
| Cutaneous rash | 2/5 (40.0) | 0/5 (0) | NE | 0.40 (-0.03, 0.83) |
| Transient fever | 2/5 (40.0) | 0/5 (0) | NE | 0.40 (-0.03, 0.83) |
| **Van den Berg et al. 1995(25)** | | | | |
| | NR | NR | NR | NR |
| **Federico et al. 2000(26)** | | | | |
| Total events | 13/16 (81.2) | 1/16 (6.3) | **13 (1.92, 87.99)** | **0.75 (0.52, 0.98)** |
| Headache | 5/16 (31.3) | 1/16 (6.3) | 5 (0.66, 38.15) | 0.25 (-0.01, 0.51) |
| Headache and rash | 3/16 (18.8) | 0/16 (0) | NE | 0.19 (-00, 0.38) |
| Rash only | 2/16 (12.5) | 0/16 (0) | NE | 0.13 (-0.04, 0.29) |
| Headache and malaise | 1/16 (6.3) | 0/16 (0) | NE | 0.06 (-0.06, 0.18) |
| Anorexia, chills and fever | 1/16 (6.3) | 1/16 (6.3) | 1 (0.07, 14,64) | 0.00 (-0.17, 0.17) |
| Transient hypertension | 1/16 (6.3) | 0/16 (0) | NE | 0.06 (-0.06, 0.18) |
| **Leger et al. 2001(27)** | | | | |
| Headache | 3/9 (33.3) | 0/9 (0) | NE | **0.33 (0.03, 0.64)** |
| Flushing | 1/9 (11.1) | 0/9 (0) | NE | 0.11 (-0.09, 0.32) |
| Shivering | 2/9 (22.2) | 0/9 (0) | NE | 0.22 (-0.05, 0.49) |
| Fever | 1/9 (11.1) | 0/9 (0) | NE | 0.11 (-0.09, 0.32) |
| Cold feet | 0/9 (0) | 1/9 (11.1) | NE | -0.11 (-0.32, 0.09) |
| Visual blur | 2/9 (22.2) | 0/9 (0) | NE | 0.22 (-0.05, 0.49) |
| Eczema | 1/9 (11.1) | 0/9 (0) | NE | 0.11 (-0.09, 0.32) |
| **Hahn et al. 2013(28)** | | | | |
| One or more moderate or severe adverse events[b] | | | | |
| Pulmonary embolism | 1/22 (9.1) | 0/22 | NE | 0.045 (-0.042, 0.13) |
| Intravenous Ig then placebo sequence | 1/22 (9.1) | 6/22 (27.3) | 0.17 (0.02,1.27) | -0.23 (-0.43, -0.02) |
| Placebo then intravenous Ig sequence | 4/21 (19) | 1/21 (9.1) | 4 (0.49,33.00) | 0.14 (-0.05, 0.32) |

**Source:** 1590 DCAR, Table 14

Abbreviations: CI = confidence interval; Ig = immunoglobulins; NE = not estimable; NR = not reported.

Note: Bold text refers to statistically significant; [a]study reported that two patients have cutaneous rash and transient fever, but did not specify if patients were MMN or LMNS; [b]one or more moderate or severe adverse events that began during infusion or within 72hrs of completion of infusion regardless of causality. Severe adverse events were pulmonary embolism (serious and severe) and headaches and nausea (severe but non-serious).

## 11. Comparative effectiveness

Clinical effectiveness is defined in the PICO by the following outcome measures:
- Disease remission;
- Change in motor muscle weakness;
- Change in disability (e.g. measured by the ONLS);
- Change in quality of life (QoL);
- Quality adjusted life year.

Five RCTs assessed clinical effectiveness of Ig versus No Ig mainly in terms of change in disability and muscle strength. All five RCTs reported some benefit associated with Ig, but noted limitations include the low number of patients recruited, limited follow up and cross-over study design. Some difficulties were found in comparing results because different tools were used to measure the outcomes. Only one study (Leger et al. 2001) reported overall response to Ig treatment as an effectiveness measure. None of the RCTs reported improvement in quality of life as an outcome for patients with MMN.

Change in disability

Three of the five studies reported improvement in disability as an outcome measure (see Table 3), but of these, only the study by Hahn et al. 2013 found statistically significant differences (RR = 1.37; 95% CI 1.07, 1.76). The pooled treatment effect reported in Hahn et al 2013 and Leger et al 2001 was of RR 1.81 (95% CI 0.74, 4.45), indicating that intravenous Ig is superior to placebo, however no statistical differences were found (p=0.19).

**Table 3: Results of disability across randomised controlled trials**

| Study ID | | Intravenous Ig treatment Mean/median (SD/SEM) | Placebo treatment Mean/median (SD/SEM) | 95% CI) | Relative difference (95% CI) |
|---|---|---|---|---|---|
| **Improvement in disability** | | | | | |
| Azulay et al. 1994 (24) | Some concern | 0/5 | 0/5 | NE | NE |
| Van den Berg et al. 1995 (25) | Low | NR | NR | NR | NR |
| Federico et al. 2000 (26) | Low | NR | NR | NR | NR |
| Leger et al. 2001 (27) | | | | | |
| Total patients | | 7/9 (77.8)[a] | 2/9(22.2)[a] | 3.5 (0.98, 12.48) | 0.56 (0.17, 0.94) |
| Treatment naïve patients | Low | 2/4 (50)[b] | 2/5(40)[b] | 1.25 (0.29, 5.34) | 0.10 (-0.55, 0.75) |
| Pre-treated patients | | 5/5 (100)[c] | 0/4 (0)[c] | NE | 1 (1, 1) |
| Hahn et al. 2013 (28) | Low | 37/42 (88.1)[e] | 27/42 (64.3)[e] | **1.37 (1.07, 1.76)** | 0.24 (0.06, 0.41) |
| | | 39/42 (92.9)[f] | 29/42 (69)[f] | **1.34 (1.08, 1.67)** | 0.24 (0.08, 0.40) |
| Pooled result | *RR = 1.81 (95% CI 0.74, 4.45; p value = 0.19)* | | | | |
| **Mean change in disability** | | | | | |
| Azulay et al. 1994 (24) | Some concern | 0/5 | 0/5 | NE | NE |
| Van den Berg et al. 1995 (25) | Low | NR | NR | NR | NR |
| Federico et al. 2000 (26) | Low | - 6.7 (3.3) | 2.1 (3) | NE | NE |
| Leger et al. 2001 (27) | Low | -7[g] | 0[g] | NE | NE |
| Hahn et al. 2013 (28) | Low | 4.09 (0.95)[h] | 5.56 (0.84)[h] | NE | NE |
| | | 73.33 (94.60)[i] | 289.93 (96.99)[i] | NE | NE |
| Pooled result | *RR = -5.04 (95% CI -12.22, 2.14; p value = 0.17)* | | | | |

**Source**: 1590 DCAR, Table 16

Abbreviations: CI = confidence interval; NE = not estimable; NR = not reported; RR = risk ratio; SD = standard deviation; SEM = standard error of mean.

Notes: Relative risk, risk difference and pooled risk ratios were calculated during the evaluation (italics); bold text indicates statistically significant differences.

a = all patients in the trial. One patient in the Intravenous Ig treatment at was lost to follow-up before the evaluation period. This patient was treatment naïve; b = treatment naïve patients; c = pre-treatment patients; d = represent the number of patients who remained stable or improved; e = using GNDS disability scale; f = using ODSS disability scale;

g = self-evaluation score reported for five motor activities of daily living. This was assumed to be synonymous to/represent a disability score. The estimate reported is a change (in median) in score between baseline and 4 months;

h = Mean estimate for patient global impression of change scores that represent perceived deterioration since the last efficacy assessment; i = score on visual analogue scale: higher scores represent more severe disability.

Change in muscle strength

All five RCTs reported that intravenous Ig treatment compared to placebo, resulted in an improvement in muscle strength (see Table 4) but was only found to be statistically significant in Hahn et al. 2013 (RR = 1.67; 95% CI 1.27, 2.18). The pooled treatment effect of RR 3.51 (95% CI 1.12, 11.05) indicates that intravenous Ig is superior to placebo for improvement in muscle strength (p=0.03).

**Table 4: Results of improvement and change in muscle strength across RCTs**

| Study ID | Risk of bias | Intravenous Ig treatment Mean/median (SD/SEM) | Placebo treatment Mean/median (SD/SEM) | Relative risk (95% CI) | Risk difference (95% CI) |
|---|---|---|---|---|---|
| **Improvement in muscle strength/grip** | | | | | |
| Azulay et al. 1994 (24) | Some concern | 5/5 (100) | 0/5 (0) | *NE* | *1 (1, 1)* |
| Van den Berg et al. 1995 (25) | Low | 5/6 (83) | 1/6 (16.7) | *5 (0.81, 31.00)* | *0.67 (0.25, 1.09)* |
| Federico et al. 2000 (26) | Low | 11/16 (68.8)[a] | 0/16 (0)[a] | *NE* | *0.67 (0.46, 0.92)* |
| Leger et al. 2001 (27) | | | | | |
| All patients | | 7/9 (77.8)[b] | 2/9(22.2)[b] | *3.5 (0.98, 12.48)* | *0.56 (0.17, 0.94)* |
| Treatment-naïve patients) | Low | 2/4 (50)[c] | 2/5(40)[c] | *1.25 (0.29, 5.34)* | *0.10 (-0.55, 0.75)* |
| Pre-treated patients) | | 5/5 (100)[d] | 0/4 (0)[d] | *NE* | *1 (1, 1)* |
| Hahn et al. 2013 (28) | Low | 40/42 (95.2)[e] | 24/42 (57.1)[e] | ***1.67 (1.27, 2.18)*** | *0.38 (0.22, 0.54)* |
| Pooled result | ***RR = 3.51 (95% CI 1.12, 11.05: p value = 0.03)*** | | | | |
| **Mean change in muscle strength or grip** | | | | | |
| Azulay et al. 1994 (24) | Some concern | 103.2[f] | -1.6[f] | NE | NE |
| Van den Berg et al. 1995 (25) | Low | NR | NR | NE | NE |
| Federico et al. 2000 (26) | Low | 6.4 (1.9) | -1 (0.8) | NE | NE |
| Leger et al. 2001 (27) | Low | 3[g] | 3[h] | NE | NE |
| Hahn et al. 2013 (28) | Low | 3.75 (9.09) | -31.38 (9.32) | NE | NE |

**Source**: 1590 DCAR, Table 17

Abbreviations: CI = confidence interval; NE = not estimable; NR = not reported; RR = risk ratio; SD = standard deviation; SEM = standard error of mean.

Notes: Relative risk, risk difference and pooled risk ratios were calculated during the evaluation (italics); bold text indicates statistically significant differences.

[a]Subjective rating of patients; [b]all patients in the trial. One patient in the intravenous Ig treatment was lost to follow-up before the evaluation period. This patient was treatment naïve; [c]treatment naïve patients; [d]pre-treatment patients

[e]this represent the number of patients who remained stable or improved

[f]Estimate (mean change in muscle strength) reported was calculated during the evaluation for day 28 after treatment. Mean change in muscle strength on day 56 was 60.7 N for intravenous Ig treatment and -7.2 for placebo treatment.

[g]reported a median change between baseline score and score at month 4.

[h]reported a median change between baseline score and score at month 4. This estimate was reported as 1 in the previously published meta-analysis.

<u>Quality of life</u>
QoL was not reported in the RCTs and the studies failed to capture how outcomes of change in muscle strength and disability translate into an improvement in the QoL for patients with MMN. Of the single arm studies that did report QoL, the baseline pre-treatment and after treatment QoL was not reported. In order to assess the potential impact in QoL, the primary literature search was extended in order to also take into account studies that compared SCIg versus intravenous Ig and had assessed patient's QoL. These studies aimed to find potential differences between the two forms of administration rather than capturing any potential difference between patients without treatment and patients receiving intravenous Ig. However, the additional information was used to better understand the tools that have been used in the past to assess the QoL of patients with MMN, capture the absolute outcome measure for patients receiving intravenous Ig and ultimately assess all potential sources for QoL in MMN patients at different stages of their disease.

Overall, on the basis of the clinical evidence, intravenous Ig was superior to No Ig with BSC in terms of improvements in muscle strength and disability.

## 12.    Economic evaluation

Based on the claim that intravenous Ig has superior effectiveness and inferior safety compared to 'No Ig with BSC' in patients with MMN, the DCAR presents a cost-utility analysis (CUA).

The CUA uses data from Leger et al. 2001 as the main source of treatment effect as it was the only study that considered responders as a composite outcome of both improvement in muscle strength and reduced disability as it would in Australia. Although this study used a different tool to measure disability, it was considered the evidence that best captured that clinical response to treatment should consider both disability and muscle strength.

Where data was not available and/or not reported by Leger et al. 2001, the model relied on data from Hahn et al. 2013 and other non-randomised single arm studies. The base case (Step 2) was generated using a modelled stepped evaluation detailed below.

**Table 5: Stepped economic evaluation**

| Steps | Description |
|---|---|
| Step 1 | Presents a trial-based economic evaluation which spanned the randomised trial time horizon of 4 months (Leger et al. 2001(27)): outcome reported as the incremental cost per QALY. |
| Step 2 (base case) | Presents a modelled economic evaluation over a 15 years' time horizon (extrapolated to 15 years) and estimates the incremental cost per QALY gained. |
| Step 3 | Presents a modelled economic evaluation over a lifetime time horizon and estimates the incremental cost per QALY gained. |

**Source**: 1590 DCAR, Table 28
Abbreviations: QALY = quality adjusted life years.
Note: The stepped evaluation does not include steps that evaluated incremental cost per life years because the results are not informative as both treatment arms experience the same rate of death (i.e. death due to all causes using the Australian life tables).

A summary of the key characteristics of the economic evaluation is given in Table 6.
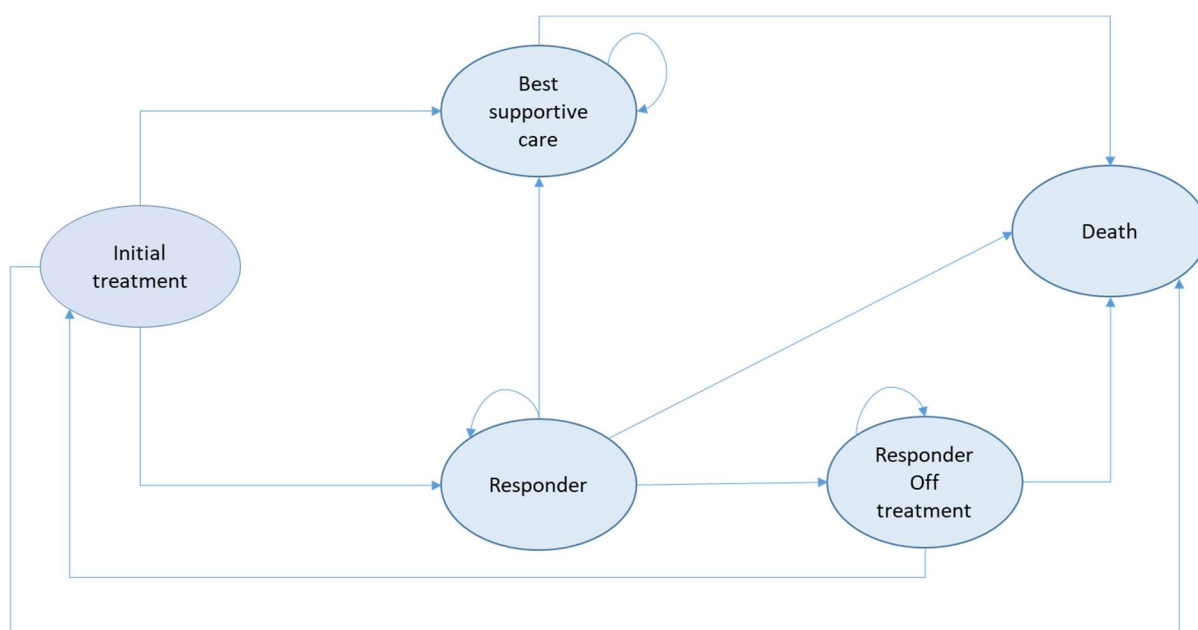
**Table 6: Summary of the economic evaluation**

| Model characteristics | Inputs used in the base case model |
|---|---|
| Perspective | Australian health care system |
| Comparator | No Ig with BSC |
| Type of economic evaluation | Cost utility analysis |
| Sources of evidence | Systematic review, expert opinion (Ig review reference group), NBA. |
| Time horizon | 15 years |
| Outcomes | Cost per QALY gained |
| Methods used to generate results | Markov model |
| Health states | Initial treatment<br>Responder<br>Responder off treatment<br>Best supportive care<br>Death |
| Cycle length | 6 months |
| Discount rate | 5% |
| Software packages used | TreeAge Pro® |

Source: 1590 DCAR, Table 29
Abbreviations: BSC = best supportive care; Ig = immunoglobulin; QALYs = quality adjusted life years; NBA = National Blood Authority.
SA=sensitivity analysis.

The information provided in The Criteria V3 was used to inform the structure of the Markov model, presented below.

**Figure 3: Decision analytic structure of the economic evaluation.**



Source: 1590 DCAR, Figure 11
Notes: arrows represent the direction of each transition probability.

The base case model uses a cost of Ig of $60.41 per gram, based on the domestic unit cost of IVIg excluding plasma collection and fractionation costs, and is the cost agreed by the Ig Review Reference Group to be used as the base case for consistency across all of the Immunoglobulin Reviews. This cost was provided by the Applicant to inform the economic and financial analyses and had been estimated retrospectively based on the reported total domestic product cost in 2017/18 ($195 million) minus domestic SCIg product costs ($4

million) in that same year, divided by the number of IVIg domestic grams issued (3,161,673) as published in the National Report on the Issues and Use of Ig in 2017/18 (NBA 2019b). The Applicant provided a range of Ig costs derived from the 2017/18 National Report on the issue and use of Ig in Australia. The DCAR presents these additional estimates assuming:

- The highest cost of Ig (i.e. domestic IVIg, including the cost of plasma fractionation), $140.18
- The lowest cost of Ig (i.e. imported IVIg), $44.94
- The weighted average cost of Ig across all indications, $94.51.

The annual dose per patient was estimated to be 626 grams per patient, and patients are assumed to enter the model at age 59, based on NBA data for the average age of patients receiving Ig for MMN. The cycle length for the model was established as 6 months to reflect the time point at which Australian MMN patients would have their usual follow-up visits.

Given the lack of available data, several assumptions to the economic model were made, including:

- Limited follow-up data available from the RCTs meant that data from single arm studies had to be used to populate the model and the effectiveness of Ig had to be extrapolated to reflect the long-term duration of treatment, from 4 months to a life-time horizon.
- No utility values were available for patients with MMN, therefore the utility values used in the model were derived from a published study of patients with chronic inflammatory demyelinating polyneuropathy (CIDP), a similar condition.
- The utility data could not be adjusted for age. Therefore, it was assumed that MMN patients that transit to the 'best supportive care' health state had a constant utility value.

The model does not capture the fact that patients with MMN slowly deteriorate over time, and patients who re-initiate (pre-treated patients) were assumed to have the same chance of not responding to treatment as would treatment naïve patients. Some transitional probabilities (e.g. probability of weaning, and probability of relapse/re-initiation of treatment) are based on advice from the Ig Review Reference Group. Assumptions to the model are discussed further in Section D.3 of the DCAR.

The results of the stepped economic evaluation are shown in Table 7. Step 2 represents the base case with an incremental cost-effectiveness ratio (ICER) of $317,552/QALY gained for Ig versus No Ig. When a lifetime horizon (Step 3) is modelled, the resulting ICER is similar, at $315,258 /QALY gained. As a result, the ICER is somewhat independent of the time horizon.

**Table 7: Results of stepped economic evaluation**

|  | Total costs | Incremental cost | Total Effectiveness | Incremental effectiveness | ICER ($/QALY) |
|---|---|---|---|---|---|
| **Step 1**: trial-based evaluation, 7 months' time horizon | | | | | |
| Intravenous Ig | $15,560.31 | $14,278 | 0.32 | 0.02 | 740,635 |
| No Ig with BSC | $1,282.71 | - | 0.30 | - | |
| **Step 2**: modelled evaluation, 15 years' time horizon (Base case). | | | | | |
| Intravenous Ig | $275,853 | $249,662 | 6.83 | 0.79 | 317,552 |
| No Intravenous Ig | $26,191 | - | 6.04 | - | - |
| **Step 3**: modelled evaluation, lifetime time horizon. | | | | | |
| Intravenous Ig | $350,387 | $314,506 | 9.28 | 1.00 | 315,258 |
| No Intravenous Ig | $35,881 | - | 8.28 | | - |

**Source**: 1590 DCAR, Table 32
Abbreviations: ICER= incremental cost effectiveness ratio; Ig = immunoglobulin; QALY= quality adjusted life years

The ICER is most sensitive to the utility weights and to the price of intravenous Ig. Assuming a deterioration in QoL of MMN patients over time had a significant impact on the ICER; however, this result should be considered with caution due to uncertainty around the source used to capture this decline in QoL over time. A summary of key drivers of the economic model are presented below.

**Table 8: Key drivers of the economic model**

| Variable Description | SA | | ICER ($/QALY) | | Impact |
|---|---|---|---|---|---|
| | Low | High | Low | High | |
| **Base case** | **NA** | | **317,552** | | **NA** |
| Utility: assuming deterioration in QoL over time | NA | | 98,559 | | High |
| Utility of BSC | 0.27 | 0.33 | 209,740 | 653,441 | High |
| Utility of 'Responder' | 0.33 | 0.39 | 211,388 | $637,945 | High |
| Cost of Ig per gram | $44.94 | $140.18 | 257,765 | 625,839 | High |
| Transition probability from 'Responder' to 'Responder off-treatment (i.e. probability of weaning) intravenous Ig arm. | 0.00 | 0.25 | 290,746 | 327,375 | Medium |
| Transition probability of 'Responder off-treatment to 'Initial treatment' (probability of relapsing). | 0.3 | 0.7 | 306,535 | 323,091 | Medium |

**Source**: 1590 DCAR, Table 34
Abbreviations: AE = adverse event; BSC = best supportive care; ICER = incremental cost-effectiveness ratio; Ig= immunoglobulin.
Notes: High impact was considered if the ICER varied more than 10% and medium impact if the ICER varied between 1% and 9.9%.

## 13.    Financial/budgetary impacts

The financial implications and predicted use of intravenous Ig in patients with MMN were estimated for a 5-year period from 2019 to 2024. A market-based approach based on current utilisation of data of intravenous Ig use in patients with MMN was used to estimate the financial implications of its current use. Most of the available data reflect The Criteria V2 except for the period 2018-19, which captures both V2 and V3 (from October 2018). Therefore, there is some uncertainty regarding how trends observed in previous years would represent the expected use of intravenous Ig for the treatment of MMN patients in Australia.

A summary of the variables with their corresponding source and assumption is presented below.

**Table 9: Variables and data sources used in the analysis**

| Variable | Data source | Assumption |
|---|---|---|
| MMN prevalent cases | HTA Conditions Report 2018-2019, NBA | 5-year linear projection using data from 2013-2019. |
| Average grams per patients | HTA Conditions Report 2018-2019, NBA | Assumed constant as per data from the period 2018-2019. Projecting usage was considered inappropriate because changes from The Criteria V3 will likely reduce the dose/frequency of administration. |
| Cost per intravenous Ig gram | Provided by the DoH. | Base case price corresponds to domestic price not including plasma fractioning. SA will be conducted assuming imported price and domestic price including plasma fractioning. |
| Number of episodes per year | HTA Conditions Report 2018-2019, NBA | Average number of episodes as per the periods 2017-2018 and 2018-2019 was used and (kept constant. |
| Intravenous Ig administration costs | MBS (Section D) | Intravenous Ig administered in hospital (private and public) with a set of pathology tests before each episode. |
| Prophylactic medications[a] (antihistamine for infusion reactions) | Assumption, PBS (Section D) | Prophylactic medication administered before each episode to all patients assuming in-hospital use of promethazine 50 mg/2 mL injection. |
| Follow-up costs | The criteria V3, EFNS/PNS guideline, MBS (Section D) | 2 follow-up visits per year with pathology tests and associated imaging. |
| Adverse events (incidence, costing source) | Hahn et al. 2013(28) & AR-DRG (Section D) | The occurrence of PE was the only SAE considered. |

**Source**: 1590 DCAR, Table 35

Abbreviations: DoH = Department of Health; EFNS/PNS = European federation of neurological societies/Peripheral nerve society; Ig = immunoglobulin; MBS = Medicare Benefits Schedule; NBA = National Blood Authority; PBS = Pharmaceutical Benefit Schedule; PE = pulmonary embolism; SAE = serious adverse event.

Note: [a]It was assumed that all patients received a prophylactic dose of antihistamines (promethazine) before receiving their corresponding intravenous Ig infusion.

The net financial implications for the government budget associated with the funding of intravenous Ig for the treatment of MMN are presented below. Overall, the net reduction in government costs of ceasing supply of intravenous Ig for the treatment of MMN would be $170,906,578 over 5 years to 2024.

**Table 10: Net financial implications to government associated with the use of intravenous Ig for the treatment of MMN**

| | | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Total over 5-years |
|---|---|---|---|---|---|---|---|
| Intravenous Ig | IVIg total cost | $23,699,504 | $24,934,847 | $26,234,583 | $27,602,068 | $29,040,833 | $131,511,835 |
| | IVIg cost to the Commonwealth[a] | $14,930,687 | $15,708,954 | $16,527,787 | $17,389,303 | $18,295,725 | $82,852,456 |
| | IVIg cost to the states[a] | $8,768,816 | $9,225,893 | $9,706,796 | $10,212,765 | $10,745,108 | $48,659,379 |
| | MBS costs (administration, follow-up, BSC and AEs). | $8,688,226 | $9,150,994 | $9,613,763 | $10,076,532 | $10,539,300 | $48,068,815 |
| | PBS costs | $324,737 | $342,034 | $359,331 | $376,628 | $393,924 | $1,796,654 |
| | **Total** | **$32,712,467** | **$34,427,875** | **$36,207,677** | **$38,055,227** | **$39,974,058** | **$181,377,304** |
| No Ig with BSC | MBS costs (follow-up and BSC) | $1,892,537 | $1,993,341 | $2,094,145 | $2,194,949 | $2,295,753 | $10,470,726 |
| | **Total** | **$1,892,537** | **$1,993,341** | **$2,094,145** | **$2,194,949** | **$2,295,753** | **$10,470,726** |
| **Net costs (Intravenous Ig versus No Ig)** | | | | | | | |
| Net costs Commonwealth | | -$14,930,687 | -$15,708,954 | -$16,527,787 | -$17,389,303 | -$18,295,725 | -$82,852,456 |
| Net costs to the states and territories | | -$15,889,242 | -$16,725,581 | -$17,585,744 | -$18,470,975 | -$19,382,580 | -$88,054,122 |
| Total net costs | | -$30,819,929 | -$32,434,534 | -$34,113,532 | -$35,860,278 | -$37,678,305 | -$170,906,578 |

**Source**: 1590 DCAR, Table 46
Abbreviations: AE = adverse events; BSC = best supportive care; Ig = immunoglobulin; MBS = Medicare Benefit Scheme; MMN = multifocal motor neuropathy; NBA = National Blood Authority; PBS = Pharmaceutical Benefit Scheme.
Notes: [a] The National Blood Agreement states that 63% of products are funded by the Commonwealth and 37% by the states and territories.

Sensitivity analyses (see Table 11) were performed to explore the uncertainty in the assumptions used to determine the financial implications. The results were most sensitive to the cost of Ig, and linearly projecting the total number of grams used per patient (which was kept constant in the base case).

**Table 11: Sensitivity analyses around the financial implication estimates.**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Total over 5 years |
|---|---|---|---|---|---|---|
| Base case | -$30,819,929 | -$32,434,534 | -$34,113,531 | -$35,860,278 | -$37,678,305 | -$170,906,578 |
| Ig low cost ($44.94) | -$24,750,879 | -$26,049,133 | -$27,395,290 | -$28,791,846 | -$30,241,429 | -$137,228,576 |
| Ig high cost ($140.18) | -$62,114,573 | -$65,360,420 | -$68,755,688 | -$72,308,166 | -$76,026,050 | -$344,564,897 |
| Intravenous Ig based on agreed weighted domestic and international price ($94.51) | -$44,197,732 | -$36,534,614 | -$38,427,329 | -$40,398,934 | -$42,453,539 | -$202,012,149 |
| Linear projection of utilised Ig grams | -$32,124,806 | -$35,255,912 | -$38,689,870 | -$42,460,012 | -$46,603,335 | -$195,133,934 |
| Ig administration 100% via public hospitals | -$30,700,757 | -$32,309,014 | -$33,981,664 | -$35,722,063 | -$37,533,742 | -$170,247,241 |
| Incidence of AE doubled | -$31,037,120 | -$32,663,293 | -$34,353,859 | -$36,112,173 | -$37,941,769 | -$172,108,213 |
| Linear projection of number of episodes per patient | -$30,848,318 | -$32,484,369 | -$34,186,828 | -$35,959,053 | -$37,804,575 | -$171,283,143 |
| Prevalence from Cats et al 2010 (0.6/100,000) | -$29,418,559 | -$29,854,964 | -$30,296,401 | -$30,742,946 | -$31,194,674 | -$151,507,545 |

**Source**: 1590 DCAR, Table 47
Abbreviations: AE = adverse event; Ig = immunoglobulin.

## 14.    Key issues from ESC for MSAC

| ESC key issue | ESC advice to MSAC |
|---|---|
| The number of patients receiving Ig for MMN in Australia is higher than the estimated prevalence based on published international epidemiological studies.<br><br>According to NBA data, 596 patients received IVIg for the treatment of MMN in 2018-19.  Cats et al 2010 reported a prevalence of 0.6 per 100,000 population, which would equate to 152 cases of MMN when applied to the Australian population for the same period.<br><br>The average age of patients receiving Ig for MMN, per BloodSTAR data is 59 years, compared to the published mean age of onset of 41 years. | ESC noted that prevalence rates should be considered with caution as NBA data includes patients continuing to receive IVIg therapy who qualified under the Criteria V2 and may include patients with MND.<br><br>ESC considered the introduction of Criteria V3 in October 2018 would minimise potential leakage into other conditions such as MND. Therefore, the predicted cost of Ig for MMN over the forward estimates may be an over-estimate, as there has been insufficient time post the implementation of Criteria V3 to capture any reduction in the treated population. |
| The available clinical evidence on the effectiveness of Ig for MMN is limited due to: small trial populations; the use of different assessment tools and outcomes in these trials; and the use of cross over study designs. | ESC noted that the small evidence base is due to the rarity of MMN, and that there is limited published evidence to base conclusions on the clinical effectiveness and cost-effectiveness of IVIg.<br><br>ESC considered the evidence presented in the DCAR appropriate to support the economic model but noted the long-term effects of IVIg treatment could not be determined from the RCTs which all reported follow up periods of less than one year. ESC noted that the economic model included the treatment effect from the study by Leger et al. 2001, and considered whether data from Hahn et al. 2013 was more appropriate as it had the highest patient enrolment (n=44), longest follow up period (11 months) and reported statistically significant outcomes. ESC requested that further analyses be performed to explore the effect of this evidence on the ICER. Refer to Addendum 2 to the DCAR. |
| What are the main drivers of cost-effectiveness and what is the certainty around these inputs?<br>Due to the lack of available evidence to construct an economic model, some assumptions were made, including:<br>• The use of single arm studies were extrapolated to inform long term effectiveness of Ig;<br>• No utility values for MMN meant that the utilities derived from a study of people with CIDP were modelled;<br>• Utilities were not adjusted for age and the base case assumes a constant utility value in the BSC health state.<br><br>Stakeholder feedback noted the variation in the cost of IVIg administration used in the economic model across Ig reviews. | ESC considered the economic model to be well structured and reflective of the Criteria V3.<br>The main drivers in the economic model are the cost of Ig ($60.41 in the base case) and the utility values.<br>There was no evidence in the literature reporting utility values for MMN patients and how this may change over time. The base case included constant utilities over time that were tested in a sensitivity analysis. The SA that assumed a linear decline in QoL of MMN patients, with a greater decline in the BSC health state (No Ig) compared to patients receiving Ig treatment, had a significant impact on the ICER, reducing it to $98,559/QALY (from $317,552/QALY in the base case).<br><br>ESC requested that additional sensitivity analyses be explored using the higher treatment effect from Hahn et al. 2013, and a decline in QoL. Refer to Addendum 2 to the DCAR. Addendum 2 also includes additional multi-way sensitivity analyses on the variation of Ig administration costs and their effect on the ICER, based on administration costs used in previous Ig Reviews (MSAC Applications 1564, 1565 and 1566). |
| What research could be conducted to better inform the cost-effectiveness of Ig for this condition, e.g. studies to better inform optimal dosing or dose based on ideal body weight? | ESC considered that IVIg has been the standard of care in this population since the 1990s and future RCTs are unlikely in this population. The lack of evidence on change in quality of life over time was also a concern. ESC considered whether there could be ways to collect QoL  data in BloodSTAR or a patient |

| ESC key issue | ESC advice to MSAC |
|---|---|
| | registry to better inform HTAs in the future, noting that QoL data collected in BloodSTAR in its current form would only capture information relevant to patients with MMN receiving IVIg and not for untreated patients.

ESC considered that further clinical information on interventions and health resource usage may be obtained by linking NBA data to MBS/PBS/hospital data and / or a patient registry e.g. the proportion of patients receiving Ig infusions in day clinics versus outpatient clinics.
The criteria enabling (i) continuation of the initial period of therapy, (ii) continuation of therapy period without a trial off Ig therapy, (iii) review of continuation after re-initiation, include the undefined item "Improvement in or stabilisation of weakness after previous evidence of deterioration in motor strength". It should be explored whether this criterion can be categorically defined in order to identify which patients should continue to receive Ig therapy.

In BloodSTAR, prescribers are required to state reasons why patients do not undergo weaning or cessation – these reasons should be explored in order to inform why the prevalent population appears larger than anticipated.

ESC noted the clinical criteria describing conduction block in MMN include a 'definite' diagnosis and two categories of 'probable' diagnosis. Given the BloodSTAR criteria require a 'clinical phenotype' of MMN, it should be explored whether data for those patients with a 'definite' diagnosis can be compared with those with 'probable' diagnosis. Similarly, whether only patients with a 'definite' diagnosis of MMN should be permitted to receive IVIg. |

***ESC post-meeting comments to Addendum 2 (additional sensitivity analyses)***
*Tables 1 and 2 of the 'Addendum 2 to the DCAR' present the impact of applying a deterioration in QoL over time, using the treatment effect from the Leger and Hahn studies, respectively. ESC noted that using the treatment effect from the Hahn study instead of Leger (used in the base case) had little effect on the resulting ICER.*

*ESC noted the true rate at which patients with MMN would deteriorate is uncertain given the lack of real data, over time, but considered that the real ICER may fall between $98,559 and $150,429/QALY.*

*ESC noted that varying the administration costs associated with Ig treatment had an impact on the ICER and more certainty around what would best reflect clinical practice in Australia would be informing to the cost-effectiveness of Ig.*

**ESC discussion**

Application 1590 requests MSAC advice on the supply of immunoglobulin (Ig) therapy under the national blood arrangements for the treatment of multifocal motor neuropathy (MMN). In line with the PICO confirmation, the DCAR reviews the evidence on safety and effectiveness of intravenous Ig (IVIg) for MMN to ensure Ig use under the national blood arrangements is based on best evidence of clinical safety, effectiveness and cost-effectiveness.

MMN is a rare, distal neuropathy, characterised by slowly progressive limb weakness without sensory impairment. ESC noted that MMN is a degenerative disease which has an important impact on the quality of life of patients but does not affect life expectancy. The reported prevalence of MMN ranges from 0.3 to 2 cases per 100,000 population, with a mean age of onset of 41 years and occurs more commonly in males than females, with a reported ratio of 2.5-2.7:1. ESC noted that the clinical diagnosis of MMN can be either 'definite' or 'probable' depending on both the extent of disease and magnitude of conduction deficit.

The clinical criteria for subsidised access to IVIg for MMN is set out under version 3 of the *Criteria for the clinical use of immunoglobulin in Australia*[3] (the Criteria). The current indications under which patients with MMN may be eligible for IVIg therapy according to Version 3 of the Criteria are:

- First-line and maintenance therapy for MMN
- Relapse of MMN patients within six months of commencement of trial off immunoglobulin therapy.

ESC noted the clinical algorithm which requires the initial diagnosis to be made by a neurologist, and eligible patients may receive IVIg for a maximum of four months (induction plus three maintenance cycles) before determining whether the patient has responded. After four months, patients must be reviewed by a neurologist and evidence of clinical efficacy is required for authorisation of continued IVIg therapy for a further 12 months. Clinical efficacy is determined by both an improvement in focal motor weakness (this does not currently have a defined method of assessment or threshold to quantify 'improvement') and improvement in disability as measured by the Adjusted Overall Neuropathy Limitations Scale (ONLS). Clinical reviews of the continuation period are required annually thereafter, and trial of weaning/cessation of Ig therapy are considered at each annual review for patients who are clinically stable to identify those in remission or a valid reason provided as to why a trial is not being planned or is contraindicated at this time. If a patient relapses after a trial off therapy, they may receive IVIg again under the "Relapse" (within 6 months) or "First-line and maintenance therapy" (relapsed after 6 months off Ig) indications.

ESC noted that the exclusion criteria described in the Criteria V3, which preclude Ig use, are consistent with the exclusion criteria in the European Federation of Neurological Societies/Peripheral Nerve Society guideline for the initial diagnosis of multifocal motor neuropathy.

For patients who have been initially treated with Ig, the criteria for continuation are:
*Improvement in focal motor weakness in previously weak (but not end-stage) muscles*
*AND*
*Improvement in the level of disability as measured by the Adjusted Overall Neuropathy Limitations Scale (ONLS) of at least one point less than the qualifying score*

The method of assessment and magnitude of 'improvement in focal weakness' is not stated, and so may permit patients to continue Ig in the face of non-significant improvement.

For patients who have been treated beyond the initial 4 month period, the criteria for continuation are:
*Improvement in or stabilisation of weakness after previous evidence of deterioration in motor strength. It is acknowledged that very slow deterioration may occur over several years in stable patients*
*AND*

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[3] National Blood Authority, 2018, *Criteria for the clinical use of immunoglobulin in Australia (*version 3).

*Improvement in or stabilisation of disability as measured by the Adjusted Overall Neuropathy Limitations Scale (ONLS) score compared to the previous review score. (Note: Gradual deterioration of one point over several years may occur)*
*AND*
*A trial of Ig weaning/cessation of Ig therapy is planned for patients who are clinically stable to identify those in remission or a reason provided as to why a trial is not planned.*

As with the initial review criteria, the method and magnitude of motor improvement are not stated, and Ig may continue erroneously.

Five randomised controlled trials (RCTs) and 24 single arm studies were included in the evidence base for this review. The RCTs had limited number of patients recruited (5 – 44 patients) and limited follow-up periods (28 days – 11 months). ESC noted that the low evidence base is due to the rarity of MMN, resulting in limited published evidence to base conclusions on the clinical effectiveness and cost-effectiveness of IVIg for these patients. In addition, IVIg has been the standard of care in for the treatment of MMN since the 1990s. There are no alternative treatments for this condition and therefore the comparator of no Ig is appropriate. ESC considered that the evidence included in the review was sufficient, noting that future RCTs are unlikely in this population.

ESC noted that in terms of comparative safety of Ig treatment versus placebo, the frequency of adverse events (AEs) in the RCTs ranged from 1-40% but was usually less than 20%. Most AEs were mild and typical of infusion reactions such as headache, fever and chills. AEs were generally self-limiting and often resolved by reducing the rate or volume of infusion, or implementing premedication with analgesics or antihistamines. Only one RCT, Hahn et al. 2013, reported one patient out of 44 patients (2.27%) who suffered a PE which was categorised as a serious AE attributed to the use of IVIg by investigators. On this basis, ESC considered that the 4.5% rate applied to the probability of patients receiving IVIg experiencing PE in their first cycle of treatment with IVIg used in the economic model may not be justified. ESC also noted that the safety outcomes associated with IVIg therapy described in the PICO included thromboembolic reactions including myocardial infarction, deep vein thrombosis (DVT) and pulmonary embolism (PE). ESC considered that patients with inflammatory conditions such as MMN may have a higher baseline risk for these vascular events, and it is possible that treatment with IVIg may decrease this risk, although the mechanism of action is not established. Thus, there is conflicting evidence on whether IVIg in this population would increase or decrease the likelihood of such events. Overall, ESC agreed that the safety of Ig is inferior to no Ig.

With regard to comparative effectiveness, all five RCTs reported some benefit associated with IVIg. Effectiveness was assessed in terms of improvement in disability and muscle strength, which favoured IVIg. None of the RCTs reported improvement in quality of life as an outcome for patients with MMN. ESC noted that a number of single arm studies, although of low-level evidence, provided data on treatment effect that indirectly support the clinical claim of superiority as suggested by the RCTs. Overall, ESC agreed that based on the available evidence, IVIg treatment is superior to placebo in improving muscle strength and disability in patients with MMN.

The DCAR presents a cost-utility analysis (CUA) based on superior effectiveness and inferior safety and estimates an incremental cost-effectiveness ratio (ICER) of $317,552 per quality-adjusted life-year (QALY) gained over a 15-year time horizon (base case). The base case model uses a cost of Ig of $60.41 per gram, which is based on the domestic unit cost of IVIg excluding plasma, and is the cost agreed at the beginning of the Ig Reviews to be used as the

base case across all of the Immunoglobulin Reviews. The annual dose per patient was estimated to be 626 grams per patient, and patients are assumed to enter the model at age 59, based on NBA data for the average age of patients receiving Ig for MMN. The cycle length for the model was 6 months to reflect the time point at which Australian MMN patients would have their usual follow-up visits.

ESC considered the economic model to be well structured and reflective of the Criteria V3, based on the limited clinical evidence. The CUA uses data from Leger et al. 2001 as the main source of treatment effect as it was the only study that considered responders as a composite outcome of both improvement in muscle strength and reduced disability as it would in the Australian setting. Where data was not available and/or not reported by Leger et al. 2001, the model relied on data from Hahn et al. 2013 and other non-randomised single-arm studies. ESC noted that Hahn et al 2013 was the largest RCT (44 patients) identified in the DCAR and the only one with statistically significant effect, yet the treatment effect in the base case was from the Leger et al. 2001 study.

ESC noted comments from one stakeholder that a lifetime horizon may be more appropriate as the base case, but considered that this had minimal effect on the ICER, reducing it to $315,258/QALY. The DCAR explains that extending the time horizon to a lifetime horizon introduces greater uncertainty, and long-term effects of IVIg could not be determined from the RCTs, hence 15 years was considered in the base case analysis. ESC noted the model uses a patient age of 59 years sourced from NBA data which is older than that reported in the RCTs, but considered this to be acceptable noting that this had been tested in sensitivity analyses.

ESC noted that the ICER is most sensitive to the price of intravenous Ig, and to the utility values associated with 'best supportive care' (BSC) and the 'responder' health state, and the lack of annual decline and divergence in utility values between both these states. ESC noted that due to limited evidence, some key assumptions had to be made in the model. Information on QoL in MMN patients was scarce and had to be complemented with data from a study (McCrone et al. 2003) of patients with chronic inflammatory demyelinating polyneuropathy (CIDP) to derive a baseline utility value for MMN patients. The effect of initiating treatment with intravenous Ig resulted in a non-statistically significant gain in QoL of 0.12 (p= 0.072). This source was used in the economic evaluation, and assumes that patients with MMN have a comparable QoL profile to patients with CIDP. Due to the lack of evidence of deterioration in QoL associated with disease progression, the base case applied a constant utility (no deterioration) in both the 'BSC' and 'responder' health states over time. The DCAR justified the use of constant utilities over time as the only evidence was a study of the natural history of MMN conducted by Taylor et al. (2000), which reported a proxy for this decrement in QoL. The results of this study were considered highly uncertain due to the small number of patients who were followed beyond 9 months and inclusion criteria that may have biased the results. However, ESC agreed it was clinically plausible that the QoL of MMN patients would deteriorate over time and that there would be divergence in QoL between those in the 'BSC' and 'responder' groups and noted that this was tested in a scenario analysis based on the study by Taylor (2000). Application of a linear decline in QoL over time due to disease progression had a significant impact on the ICER, reducing it to $98,559/QALY. ESC requested that an additional sensitivity analyses be explored, testing the interaction of using both the higher treatment effect from Hahn et al. 2001, and deterioration in the QoL of patients in the 'BSC' group.

Data from the NBA (2014-2018) collected on patients with MMN were used to estimate the population and predicted use of IVIg for the 5-year period from 2019 to 2024. Overall, the

net cost to Government of providing intravenous Ig for the treatment of MMN was estimated to be $170,906,578 over the 5 years to 2024, of which $131,511,835 is attributed to the cost of Ig (at $60.41/gm) alone. ESC considered these forward estimates were a likely over-estimate as the introduction of Criteria V3 was expected to reduce overall use through exclusion of patients with conditions such as motor neurone disease (MND). ESC also noted that a stakeholder had queried the high infusion costs presented in the DCAR, and that these infusion costs were higher than those applied in other Reviews of Ig. The Department will consult with the HTA evaluators to review the impact of the varying administration costs ahead of MSAC consideration.

Overall, ESC considered the ICER in the base case model to be high and sensitive to both the cost of Ig and the utility values applied. ESC acknowledged that current clinical evidence is limited and that future RCTs are unlikely in this population. The lack of evidence on change in quality of life over time was also a concern. ESC considered whether there could be ways to collect QoL data in BloodSTAR or a patient registry to better inform HTAs in the future.

Additional clinical data could be collected in BloodSTAR. For example, the addition of QoL assessments could be collected through clinicians including EQ-5D or SF-12 surveys at baseline and follow-up reviews. However, ESC noted that this would not capture comparative evidence, i.e. only information relevant to patients with MMN receiving IVIg and not for untreated patients. ESC considered that further clinical information on this patient group may be obtained by linking NBA data to MBS/PBS/hospital data to capture information on health resource use and patterns of treatment e.g. the proportion of patients receiving treatment in day clinics versus outpatient clinics. ESC also considered whether a patient registry could be established to generate hypothesis generating data to inform future trials on optimal dosing and/or identify subgroups who may or may not benefit from IVIg.

## 15.    Other significant factors

Nil

## 16.    Applicant comments on MSAC's Public Summary Document

The National Blood Authority appreciates MSAC's recommendations and agrees that data should continue to be collected on the patterns of use of Ig therapy, including why trial off may be contraindicated. The ability of BloodSTAR, or other sources, to capture long-term health benefits in this group will be considered and prescriber compliance to the V3 Criteria will continue to be monitored through the Ig Governance Program. Unless new diagnostic tests can clearly distinguish between MND and MMN prior to Ig therapy, it will not be possible to ensure only patients with MMN initiate Ig therapy. The NBA will monitor the developments and evidence in this area. This review followed the transition from Version 2 to Version 3 of the Criteria for Clinical Use of Immunoglobulin in Australia. An important addition to Version 3 of the Criteria was to provide greater guidance for prescribers as to when a patient may be ready to trial off Ig therapy. The Criteria will continue to be reviewed on both a reactive and proactive basis, based on available evidence and clinical expert advice, to ensure the supply of Ig continues for those patients who benefit from it the most. Furthermore, the NBA plans to continue to undertake and support research into the effectiveness and utilisation of Ig, of which these recommendations will assist to prioritise. The NBA negotiates prices of Ig through tendering processes and will continue to strive to achieve the best prices for governments within existing limitations.

## 17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website:
[visit the MSAC website](#)