

***Review of immunoglobulin use for  
multifocal motor neuropathy (MMN)***

**15 March 2020**

**MSAC application no. 1590**

**Final report**

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

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

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## EXECUTIVE SUMMARY

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### ***Main issues for MSAC consideration***

- The clinical effectiveness of immunoglobulin (Ig) for treating patients with multifocal motor neuropathy (MMN) was derived from a number of randomised controlled trials (RCTs). Three main issues were identified: (1) the small number of patients recruited in each study; (2) different assessment tools were used to measure the effectiveness of Ig, limiting the poolability of the studies; and (3) the cross-over study designs which may bias the estimated treatment effect.
- Given the lack of available data to construct an economic model, several assumptions to the economic model were made:
  - 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 financial estimates may overestimate the future use of intravenous Ig, because the retrospective utilisation data did not fully capture any changes to the patient population resulting from the implementation of The Criteria Version 3.

### **Immunoglobulin for multifocal motor neuropathy (MMN)**

This contracted assessment examines the evidence to support the funding of immunoglobulin (Ig) for the treatment of patients with multifocal motor neuropathy (MMN) under the national blood arrangements. This indication is one of several conditions eligible for funded Ig treatment under the National Blood Authority's Criteria for Immunoglobulin Use in Australia, Version 3 (The Criteria V3).

## **ALIGNMENT WITH AGREED PICO CONFIRMATION**

This contracted assessment of intravenous Ig for treatment of MMN addresses all the PICO elements that were pre-specified in the PICO Confirmation, ratified by the Ig Review Reference Group which performed the function of the PICO Advisory Sub-Committee (PASC). This application followed a fit-for-purpose pathway, in which the PICO Confirmation was presented to and approved by the Ig Review Reference Group, which was convened for the purpose of progressing HTA reviews of the use of Ig in Australia.

## **PROPOSED MEDICAL SERVICE**

In the Australian setting, 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 funded by the NBA for the treatment of MMN, although evidence from a randomised controlled trial (RCT) suggests that SCIg was as safe and effective as intravenous Ig. The specific conditions relating to Ig use, the qualifying criteria, and recommended dosages for MMN were developed by the NBA and established in The Criteria V3. In Australia, intravenous Ig can be delivered in an inpatient setting (private hospital, public hospital (as private or public patient) and outpatient setting (outpatient clinic, patient's home, private same day infusion facility unattached to a hospital).

## **PROPOSAL FOR PUBLIC FUNDING**

The use of intravenous Ig for MMN has been classified as an established therapeutic role and is currently funded by the NBA under The Criteria V3.

## **POPULATION**

The population for this assessment is patients with MMN eligible for Ig treatment under The Criteria V3. MMN is a rare inflammatory neuropathy with a reported prevalence that ranges from 0.3 to 2 cases per 100,000. There are currently no epidemiological data available for MMN in Australia. A proxy to the expected number of patients diagnosed with MMN in Australia can be obtained from the latest utilisation data provided by the NBA for the period 2018-19 which considered both, The Criteria version 2 (V2) and V3 (Table ES.1). These numbers are higher than what could be estimated using international published prevalence estimates (i.e. Cats et al 2010 reported a prevalence of 0.6 per 100,000 population). Given the rarity of the disease and a lack of complete understanding of the underlying pathophysiological mechanism of MMN, there is a risk of misdiagnosis and/or under diagnosis and hence estimates of the prevalence of the condition should be interpreted with caution.

**Table ES.1: Usage of intravenous Ig therapy over recent years for the treatment of MMN based on of The Criteria V2 and V3.**

|                                 | 2013-14          | 2014-15 | 2015-16 | 2016-17 | 2017-18 | 2018-19 <sup>a</sup> |
|---------------------------------|------------------|---------|---------|---------|---------|----------------------|
| New patients                    | 127              | 105     | 137     | 126     | 125     | 123                  |
| Total patients                  | 438              | 444     | 496     | 527     | 560     | 596                  |
| Total grams issued/administered | 239,791          | 256,041 | 293,458 | 331,147 | 354,434 | 372,434              |
| Average grams per patient       | 547 <sup>b</sup> | 577     | 592     | 628     | 633     | 626                  |

Abbreviations: Ig = immunoglobulin; MMN = multifocal motor neuropathy

Note: <sup>a</sup>Data for the 2018-2019 (01 July 2018 – 30 June 2019) period incorporated version 2 and version 3 of The Criteria. <sup>b</sup>This was reported as 546 in the Referral but verified as 547 during the write-up of this assessment report. Data for the period from 2013-2018 reflects usage only under version 2 of The Criteria, which is prior to the introduction of key changes which aimed to address leakage.

Source: Table 7, p.25 of the draft Referral form 1590 MMN. HTA Conditions Report 1, 2 and 3 provided by the NBA on 06 January 2020.

On average, the age at MMN onset varies, ranging from 15-74 years, however MMN is mostly diagnosed in adults (mean age of onset being 41 years). In addition, MMN is a disease more commonly observed in males, with a reported ratio of 2.5-2.7: 1. The Criteria V3 that must be met for access to Ig therapy for MMN in Australia are consistent with the clinical diagnostic criteria established by the European Federation of Neurological Societies and the Peripheral Nerve Society (EFNS/PNS). Diagnosis of MMN is based on a combination of clinical (assessment by a neurologist), electrophysical criteria, and laboratory investigations (genetic testing) as well as treatment response (progressive motor weakness and a disability of  $\geq 2$  as measured by the overall neuropathy limitation scale (ONLS)). In addition, the electrophysiological criteria include definite or probable motor conduction block (CB) and normal sensory nerve conduction.

#### **COMPARATOR DETAILS**

The comparator is defined in the ratified PICO Confirmation as ‘No Ig with active disease surveillance’ hereafter referred to as ‘No Ig with best supportive care (BSC)’. There are no other NBA or Pharmaceutical Benefit Scheme (PBS) treatments subsidised for MMN. The current practice for the treatment of MMN is intravenous Ig accessed and funded through the NBA.

#### **CLINICAL MANAGEMENT ALGORITHM(S)**

The clinical management algorithms for the current use of intravenous Ig from the PICO Confirmation are shown in Figure 1 and Figure 2 (current) and Figure 3 and Figure 4 (proposed treatment algorithms).

#### **KEY DIFFERENCES IN THE DELIVERY OF THE PROPOSED MEDICAL SERVICE AND THE MAIN COMPARATOR**

Currently, patients with MMN not receiving intravenous Ig treatment are those who are; either not eligible or no longer eligible to receive Ig treatment under The Criteria V3, or patients for whom intravenous Ig is contraindicated. These patients are assumed to maintain BSC which includes reviews with a neurologist and other health care professionals such as a physiotherapist and may also involve rehabilitation services.

The main difference in the delivery of the intervention is the actual administration of intravenous Ig, which for MMN patients, is administered mainly in hospital or at outpatient clinics. This requires specialised nurses and the use of hospital facilities and devices for appropriate and safe delivery of the intervention. Some patients may require hospitalisation if they need longer monitoring due to the presence of comorbidities, longer infusion times, or the risk of adverse events.

### CLINICAL CLAIM

On the basis of the available clinical evidence, intravenous Ig was claimed to have superior effectiveness and inferior safety compared to no Ig and BSC in the PICO confirmation for MSAC Referral 1590. This claim is based on limited RCT evidence but large experience of use since intravenous Ig has been the standard of care treatment for MMN since the early 1990s.

### APPROACH TAKEN TO THE EVIDENCE ASSESSMENT

A systematic review of published literature was undertaken in October 2019 on the treatment of MMN during the period 1946 (inception of databases) to 11 October 2019. Studies were selected independently by two reviewers if they met criteria summarised in Table ES.2. The following databases were searched: Embase, Ovid, Medline, Pubmed and the Cochrane library and clinical trials online platforms. Randomised and single arm studies were searched that reported treatment effect measured as improvement in muscle strength, disability or a composite of both (responders). The risk of bias was assessed in both randomised and single arm studies using the Cochrane Risk of Bias (RoB) 2 tool or the Institute of Health Economics (IHE) checklist respectively.

**Table ES.2. Summary of PICO**

| Component    | Description   |
|--------------|---|
| Population   | Patients diagnosed with MMN who are currently eligible for the use of intravenous Ig treatment in Australia according to 'The Criteria V3 for the clinical use of immunoglobulin in Australia'.   |
| Intervention | Intravenous Ig.   |
| Comparator   | The comparator is No Ig with BSC.   |
| Outcomes     | <p>The outcomes listed below are those identified as relevant in the development of the PICO Confirmation. The outcomes identified are:</p> <p><b>Safety outcomes:</b></p> <ul style="list-style-type: none"> <li>• AEs including hypersensitivity reactions, fall in blood pressure with anaphylactic reaction; thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism, deep vein thromboses; acute renal failure; anaphylaxis, veno-occlusive events.</li> </ul> <p><b>Clinical effectiveness outcomes:</b></p> <ul style="list-style-type: none"> <li>• Disease remission;</li> <li>• Change in motor muscle weakness;</li> <li>• Change in disability<sup>a</sup>;</li> <li>• Change in quality of life (QoL);</li> <li>• Quality adjusted life year.</li> </ul> <p><b>Healthcare system resources utilisation as identified in the Referral</b></p> <ul style="list-style-type: none"> <li>• Changes in health system resource utilisation associated with the intervention compared to the comparator for the following: <ul style="list-style-type: none"> <li>○ Intravenous Ig products;</li> <li>○ Other therapies used in patients with progressive MMN;</li> </ul> </li> </ul> |

| Component | Description  |
|-----------|--|
|           | <ul style="list-style-type: none"> <li>○ Infusion equipment;</li> <li>○ Administrative and clinician time (e.g. resources associated with requesting, and authorising, access to Ig);</li> <li>○ Nursing time (for treatment initiation and monitoring of intravenous Ig);</li> <li>○ Hospitalisation (including use of hospital resources);</li> <li>○ Additional treatments used for the occurrence of adverse events (e.g. analgesia or antihistamines);</li> <li>○ Product dispensing and disposal of any unused product;</li> <li>○ Follow-up and/or monitoring visits, including regular neurology visits;</li> <li>○ Disability support services;</li> <li>○ Home nursing and support needs.</li> </ul> |

Abbreviations: AE= adverse events; BSC = best supportive care; Ig= immunoglobulin; MMN = multifocal motor neuropathy; ONLS= Overall Neuropathy Limitations Scale; QoL= quality of life.

Note: <sup>a</sup>Different disability tools were used in the randomised trials to assess the efficacy of intravenous Ig in MMN.

### CHARACTERISTICS OF THE EVIDENCE BASE

A total of 29 studies were included in the final review, 5 RCTs and 24 single arm studies. All five RCTs had a limited number of recruited patients in each study (range 5 – 44 patients), a limited follow-up period (28 days – 11 months) and a cross-over study design. In terms of risk of bias, all except one study (some concerns) were catalogued as low risk. The main issue with these studies was the cross-over study design which may lead to a biased treatment effect given that patients recruited to the placebo arm still received the intervention during the study. The latter would bias the results against the intervention.

The literature search showed that there are a number of single arm studies, some retrospective and some prospective, that provide longer-term evidence on the treatment effect in both induction and maintenance phase. Out of the 24 studies assessed, 20 were found to be at moderate risk of bias and 4 were found to be at a low risk of bias.

### RESULTS

#### Safety

Evidence from RCTs showed that most adverse events (AEs) were mild and mainly infusion reactions like headache, fever and chills. These events are generally characterised as being self-limiting and often resolved by reducing the rate or volume of infusion, or by implementing prophylactic use of antihistamines. Only one RCT, Hahn et al. 2013, reported one patient, who suffered a pulmonary embolism, which was categorized as a serious adverse event attributed to the use of intravenous Ig by the investigators. The safety profile did not show significant differences between the randomised and single arm studies.

Intravenous Ig products have been used in patients with MMN since the early 1990s, thus the safety profile is well understood, even with regard to rare events. The safety profile as presented in the

Product Information (PI) provides a comprehensive overview and understanding on the occurrence of AEs, special warnings and precautions for use.

### Effectiveness

Three out of the five studies reported improvement in disability as an outcome measure, but of these only the study by Hahn et al. 2013 found statistically significant differences (RR = 1.34; 95% CI 1.08, 1.67). The pooled treatment effect reported in Hahn et al 2013 and Leger et al 2001 was RR 1.81 (95% CI 0.74, 4.45), which means that intravenous Ig is superior to placebo (p=0.19) however, no statistical differences were found. These results were produced under the assumption that the improvement was independent of the assessment tools used to measure the outcome. Similarly, all five RCTs showed that intravenous Ig compared to placebo, resulted in an improvement in muscle strength but this difference was only statistically significant in the study conducted by 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) reflects intravenous Ig being superior to placebo for improvement in muscle strength (p = 0.03) as shown in Table ES.3.

**Table ES.3. Balance of clinical benefits and harms of intravenous Ig, relative to No Ig with BSC, and as measured by the critical patient-relevant outcomes in the key studies**

| Outcome                                    | Participants (studies) | Risk of bias | Risk ratio (95% CI)                               | Comment   |
|--|------------------------|--------------|---|---|
| <b>Improvement in disability</b>           | K= 2 studies:<br>N= 60 | Low          | <i>RR = 1.81 (0.74, 4.45)</i><br><i>p = 0.002</i> | The risk of bias of the two studies pooled was considered Low. The meta-analysis showed the pooled treatment effect for improvement in disability was superior in intravenous Ig compared with placebo. It was assumed that the improvement in disability was independent of the tools used to measure the outcome. |
| <b>Improvement in muscle strength/grip</b> | K=4 studies<br>N=82    | Low          | <i>RR = 3.51 (1.12, 11.05)</i><br><i>p = 0.03</i> | The risk of bias of the four studies pooled was considered Low. Independently, all studies showed that intravenous Ig compared with placebo resulted in an improvement in muscle strength.  |

Abbreviations: CI = confidence interval; K= number of studies; N=number of participants in a study; RR= risk ratio

Notes: The risk ratio was calculated during the evaluation (italics); bold text indicates statistically significant differences.

### TRANSLATION ISSUES

The economic model presented in Section D is a cost utility analysis. The immunomodulatory effect of intravenous Ig is expected to translate into improved muscle strength, reduced disability and overall improved quality of life. The clinical benefit derived from these outcomes is reflected in the increased time a patient remains stable/maintained improvement, however it does not lead to a cure of MMN. All patients will eventually discontinue treatment and their disease will enter into a slowly progressive



disease phase which ultimately will deteriorate their QoL. Table ES.4 summarises the translational issues identified from the clinical evidence, to the economic model and Australian setting.

**Table ES.4. Summary of results of pre-modelling studies and their uses in the economic evaluation**

| Section       | Pre-modelling study                                   | Results used in Section D   | Overall impact in the results  |
|---------------|---|---|--|
| Applicability | Inclusion and exclusion criteria                      | <p>Some differences were found between the trial population and the Australian population in all five RCTs, mainly:</p> <ul style="list-style-type: none"> <li>All five RCTs considered the presence of CB within the inclusion criteria which differs to The Criteria V3. Because there is some evidence suggesting that patients with and without CB show a similar response to Ig, it is unlikely that this difference will result in a variation of the Tx effect.</li> <li>RCTs did not take into account the baseline disability as required in The Criteria V3 where patients are required to present with a level of significant disability (ONLS<math>\geq</math>2).</li> <li>Azulay et al 1994 recruited patients who may not be considered MMN under the current diagnostic criteria.</li> </ul> | Overall, the differences were considered minor hence unlikely to impact the treatment effect.  |
|               | Intravenous Ig dosing and frequency of administration | <ul style="list-style-type: none"> <li>Induction and maintenance recommended doses were undifferentiated in the RCTs, which may lead to higher doses used in the clinical trial setting compared to Australia.</li> <li>Hahn et al 2013 suggests a dose range consistent to that recommended in The Criteria for both the induction and maintenance phase of Tx (0.4–2 g/kg). However, the average monthly dose was higher (1.17 g/kg) compared to that as informed by the NBA (0.64 g/kg/month).</li> <li>The biggest difference in frequency was compared to Azulay et al 1994 (8 weeks).</li> </ul>  | Overall, the differences were unlikely to impact the treatment effect. Potential treatment effect differences could arise from undifferentiated doses in RCTs compared to Australia. |
|               | Patients demographics and settings                    | Although the patient characteristics is not available in a consistent way to facilitate a proper comparison, it is unlikely that any difference in these regards will lead to differences in the outcomes of interest.  | Unlikely to impact the treatment effect.   |
|               | Outcome measurement tools                             | <p>The tools used to measure the two main clinical outcomes in MMN, muscle strength and disability, differ between the RCTs and compared to the Australian setting.</p> <ul style="list-style-type: none"> <li>4/5 RCTs reported the effect of intravenous Ig for each outcome measure independently only and not as composite outcome as it would in Australia to assess for continuance of Tx.</li> <li>Similar to the ONLS (include climbing stairs and running), Hahn et al. 2013 used the ODSS. The ODSS, compared to the modified Rankin scale, the NDS and the GNDS, is a more specific tool and would likely identify slighter changes in disability compared to the other tools.</li> </ul>  | Differences could alter the interpretation of the treatment effect. The pooled effect was not used in the base case economic model.  |

|                |   |  |  |
|----------------|---|--|--|
|                | Treatment duration  | <p>Tx duration in the clinical setting differs to that expected in the current Australian population, mainly:</p> <ul style="list-style-type: none"> <li>• RCTs showed that Tx duration varied from 28 days to approximately 12 months. This time period was pre-specified and not conditional on an assessment of response.</li> <li>• 3/5 of the RCTs had a trial duration shorter than the current initial Tx phase (induction plus three maintenance cycles) recommended in The Criteria V3 to assess for responsiveness.</li> <li>• The median Tx duration in Hahn et al. 2013 was close to a year, however it may still not capture the expected Tx duration in current practice.</li> <li>• None of the reviewed RCTs considered a weaning off trial phase as recommended in The Criteria.</li> </ul> | Differences could alter the interpretation of the treatment effect and cost of Tx. Assumption on weaning was tested in a SA. |
| Extrapolation  | Treatment effect duration   | The Tx duration reported from the RCTs is unlikely to reflect the actual treatment duration in the Australian setting, hence an extrapolation is required. The treatment effect was kept constant throughout the whole time horizon in order to account for patients that remain as responders (hence stable in their disease).  | Likely to impact the overall results. Different time horizons were tested in a SA.   |
| Transformation | Transformation of clinical outcome to a patient relevant outcome  | <ul style="list-style-type: none"> <li>• Only one study considered responders as a composite outcome (improvement of muscle strength and reduced disability) as it would in Australia (Leger et al. 2001). This study was used in the base case analysis in the economic evaluation to model the treatment effect after treatment initiation.</li> <li>• None of the RCTs reported as secondary outcomes the impact of intravenous Ig on the QoL of patients.</li> </ul>   | Unlikely to impact the treatment effect.   |
|                | Sources that provide utility values to derive QoL for patients with MMN and its applicability to the Australian context | <p>MMN is a disease that does not affect mortality but has an important QoL component, hence QALYs were considered the appropriate outcome.</p> <p>Information on QoL in MMN patients is scarce and only available from single arm studies. This information had to be complemented with the incremental utility from CIDP to derive a baseline utility from patients who are not receiving intravenous Ig.</p>  | Likely to impact the overall results. Utility values were tested in a SA.  |

Abbreviations: CB = conduction block; CIDP = Chronic Inflammatory Demyelinating Polyneuropathy; GNDS = Guy's Neurological Disability Score; Ig = immunoglobulin; MMN = multifocal motor neuropathy; ODSS = overall disability sum score; ONLS = Overall Neuropathy Limitations Scale; QALY = quality adjusted life years; QoL = quality of life; RCT = randomised controlled study; SA = sensitivity analysis; Tx = treatment.

## ECONOMIC EVALUATION

A cost-utility analysis was undertaken to assess the incremental costs and effects associated with the use for intravenous Ig for the treatment of MMN compared to No Ig with BSC. A summary of key characteristics of the economic evaluation is provided in Table ES.5.

**Table ES.5. 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              |

|   |  |
|---|--|
| <b>Model characteristics</b>            | <b>Inputs used in the base case model</b>  |
| <b>Sources of evidence</b>              | Systematic review, expert opinion (Ig Review Reference group), NBA.                        |
| <b>Time horizon</b>                     | 15 years   |
| <b>Outcomes</b>                         | Cost per QALY gained   |
| <b>Methods used to generate results</b> | Markov model   |
| <b>Health states</b>                    | Initial treatment<br>Responder<br>Responder off treatment<br>Best supportive care<br>Death |
| <b>Cycle length</b>                     | 6 months   |
| <b>Discount rate</b>                    | 5%   |
| <b>Software packages used</b>           | TreeAge Pro®   |

Abbreviations: BSC = best supportive care; Ig = immunoglobulin; QALYs = quality adjusted life years; NBA = National Blood Authority. SA=sensitivity analysis.

The base case was generated using a modelled three-stepped evaluation detailed in Table ES.6 (base case corresponds to Step 2).

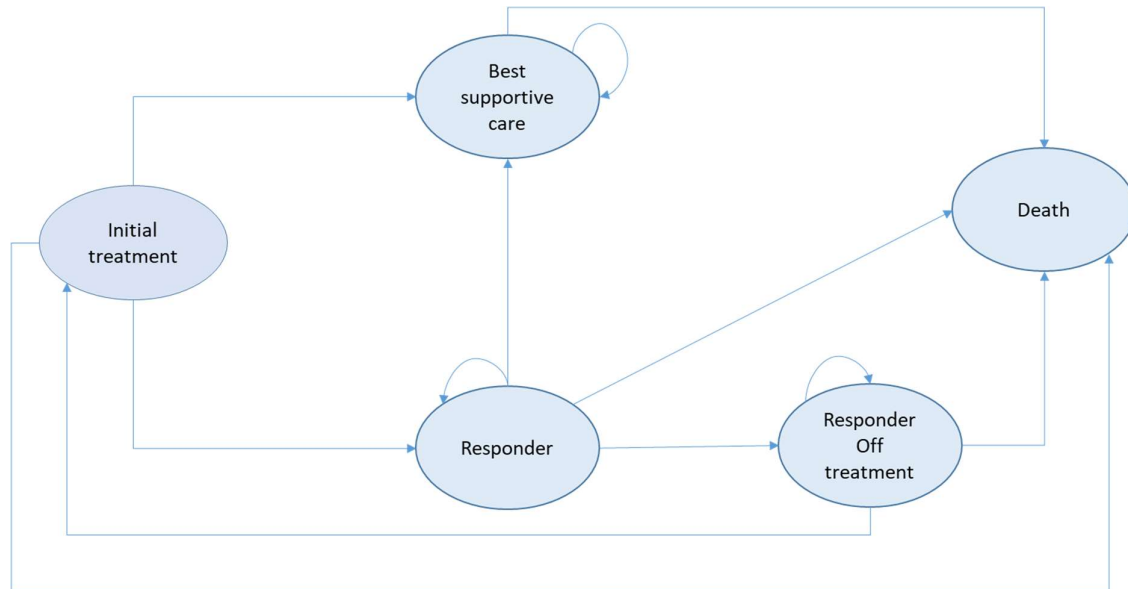
**Table ES.6: Stepped economic evaluation**

| <b>Steps</b>       | <b>Description</b>   |
|--------------------|--|
| Step 1             | Presents a trial-based economic evaluation which spanned the randomised trial time horizon of 4 months (Leger et al. 2001); 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.   |

Abbreviations: QALY = quality adjusted life years.

In the absence of any relevant economic evaluation applicable to MMN that could inform the current model, a Markov model was developed *de novo*. The model consisted of five health states: Initial treatment; Responder; Responder off-treatment; BSC and Death (the absorbing health state) (Figure ES.1).

Figure ES.1. Decision analytic structure of the economic evaluation.



Notes: arrows represent the direction of each transition probability.

Key structural assumptions of the model are:

- The model does not capture the fact that patients may slowly deteriorate overtime because there is no adequate data to model the rate of deterioration in terms of utility values and as per the natural history of the disease described in Section A. For this reason, MMN patients that transit to the ‘BSC’ health state (not receiving active treatment with intravenous Ig) are assumed to have a constant utility. This assumption was tested in a sensitivity analysis by assuming an annual utility decrement to demonstrate deterioration in QoL over time (further details provided in Section D.4).
- MMN patients who do not receive active treatment with intravenous Ig (only BSC), but who’s health does not deteriorate (i.e. remain ‘stable’) move to the ‘Respond’ health state, and are assumed to remain stable with no deterioration for a maximum of six months (1 cycle) after the initial treatment phase. After this period, all patients (100%) transit to the ‘BSC’ health state.
- Because the literature search did not identify any trials that implemented a weaning off trial phase, it was assumed that 5% (kept constant throughout the whole time horizon) of patients would transit to the ‘Responder off-treatment’ health state each cycle. This was based on expert opinion from the Ig Review Reference Group that suggested that it was more common in Australia to assess Ig treated patients for an end of dose effect (i.e. patient demonstrates an improvement in symptoms on the current dose) rather than weaning.

- The proportion of patients in the ‘Responder off-treatment’ health state likely to relapse and reinitiate treatment was assumed as 50% as per advice from the clinical expert on the Ig Review Reference Group.
- Patients who re-initiate (pre-treated patients) treatment were assumed to have the same chance of not responding to treatment as would treatment naïve patients. This assumption was tested in a sensitivity analysis where pre-treated patients were assumed to have a higher probability of responding to treatment compared to treatment naïve patients.
- The model included the costs and associated disutility of the serious adverse events (pulmonary embolism) that were reported in the RCTs. It was assumed that the proportion of MMN patients on intravenous Ig treatment who will experience this event is the same as that observed in one of the RCTs (Hahn et al. 2013), and that the event will be experienced once per patient in the model.

The results of the stepped analysis of the base case economic evaluation are presented in Table ES.7. The incremental cost effectiveness ratio (ICER) for the trial-based evaluation (Step 1) is \$740,635 per QALY gained. The base case ICER per 15 years’ time horizon (Step 2) is \$317,552 per QALY gained. Finally, the ICER (Step 3) over a lifetime time horizon is \$315,258 per QALY gained. An individual with MMN gains more QALY over a lifetime time horizon compared to 15 years’ time horizon (1.00 versus 0.79 QALYs). However, this benefit is offset by the incremental costs over the lifetime time horizon, resulting in a similar ICER. Extending the time horizon to a life time introduces more uncertainty, hence Step 2 was considered the base case analysis.

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

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

Abbreviations: ICER= incremental cost effectiveness ratio; Ig = immunoglobulin; QALY= quality adjusted life years

Note: <sup>a</sup> Trial duration was 7 months but outcome was reported at 4 months after treatment.

The modelled results were most sensitive to the price of intravenous Ig, the utility values associated with the ‘BSC’ and ‘Responder’ health states as well as an annual decline in utility weights demonstrating a deterioration in QoL over time due to disease progression (Table ES.8). There is uncertainty around the incremental benefit associated with intravenous Ig treatment applied in the

model, as this value was based on a CIDP patient population. In addition, assuming an annual deterioration in the QoL of MMN patients due to disease progression resulted in a large impact on the ICER (69%↓). However, this result should be interpreted with caution due to the limitations identified in the source used to inform the estimates to capture the decline in QoL overtime. This assumption was not considered for the base case scenario as there is no evidence in the literature reporting utility weights for disease progression and how this may change over time.

**Table ES.8. Key drivers of the economic model**

| Variable Description  | SA      |          | ICER (\$/QALY) |           | Impact |
|---|---------|----------|----------------|-----------|--------|
|   | Low     | High     | Low            | High      |        |
| <b>Base case</b>  | 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 |

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%.

### ESTIMATED EXTENT OF USE AND FINANCIAL IMPLICATIONS

A market-based approach based on NBA utilisation data was used to estimate intravenous Ig use in patients with MMN. Most of the available data reflect The Criteria V2 except for the period 2018-2019, where the data captures both V2 and V3 of The Criteria. The impact of fully implementing Version 3 may not be reflected in the available data as this version was implemented in October 2018.

As described in Section A, intravenous Ig is already available for the treatment of MMN in Australia. Therefore, the hypothetical scenario is presented where intravenous Ig is replaced with BSC (No Ig with BSC). In that instance, all health services directly related to the use intravenous Ig were excluded but those required for active disease surveillance and other palliative treatments were maintained.

The financial implications associated with funding Ig for patients with MMN are summarised in Table ES.9.

**Table ES.9. 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 |
|-----------------|--------------|--------------|--------------|--------------|--------------|--------------------|
| IVIg total cost | \$23,699,504 | \$24,934,847 | \$26,234,583 | \$27,602,068 | \$29,040,833 | \$131,511,835      |

|  |   | Year 1               | Year 2               | Year 3               | Year 4               | Year 5               | Total over 5-<br>years |
|--|---|----------------------|----------------------|----------------------|----------------------|----------------------|------------------------|
|  | IVlg cost to the Commonwealth <sup>a</sup>          | \$14,930,687         | \$15,708,954         | \$16,527,787         | \$17,389,303         | \$18,295,725         | \$82,852,456           |
|  | IVlg cost to the states <sup>a</sup>                | \$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            |
|  | <b>Total</b>  | <b>\$32,712,467</b>  | <b>\$34,427,875</b>  | <b>\$36,207,677</b>  | <b>\$38,055,227</b>  | <b>\$39,974,058</b>  | <b>\$181,377,304</b>   |
| 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           |
|  | <b>Total</b>  | <b>\$1,892,537</b>   | <b>\$1,993,341</b>   | <b>\$2,094,145</b>   | <b>\$2,194,949</b>   | <b>\$2,295,753</b>   | <b>\$10,470,726</b>    |
| <b>Net costs (Intravenous Ig versus No Ig)</b> |   |                      |                      |                      |                      |                      |                        |
|  | 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          |
|  | <b>Total net costs</b>                              | <b>-\$30,819,929</b> | <b>-\$32,434,534</b> | <b>-\$34,113,532</b> | <b>-\$35,860,278</b> | <b>-\$37,678,305</b> | <b>-\$170,906,578</b>  |

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: <sup>a</sup> The National Blood Agreement states that 63% of products are funded by the Commonwealth and 37% by the states and territories. Source: Projections from observed data from the HTA Conditions Report 1, 2 and 3 provided by the NBA on 06 January 2020 ('Phase 2 HTA conditions data.xlsx' workbook).

## CONSUMER IMPACT SUMMARY

Targeted feedback was sought in August 2019 from stakeholders including consumer groups, clinicians and sponsor companies to assist in developing the PICO Confirmation. Responses were received from one clinician and two sponsor companies. Sponsor companies considered intravenous Ig to be a safe and effective treatment for patients with MMN, and therefore would not encourage further limitation to access of intravenous Ig based on the current level of evidence. Clinician feedback indicated that the treatment algorithm was reasonable for commencement, but that data on the rates of continuation would be valuable to the review considering that continuation rates as expected from RCTs seldom match actual rates of continuation.

Sponsors of intravenous Ig were given the opportunity to provide input to the Contracted Assessment following finalisation of the PICO Confirmation. Two sponsors provided feedback for consideration in the development of this Contracted Assessment. A summary of the main issues are presented in Table ES.10.

**Table ES.10. Feedback provided by Sponsors on the PICO Confirmation**

| <b>Issue</b>   | <b>Sponsor's feedback</b>  |
|--|--|
| Reliability of the prevalence source by Cats et al 2010.                         | Reported estimate of 0.6 cases per 100,000 persons represents an underestimate   |
| Funding of SCIg for the treatment of MMN   | Noted there was available evidence from a randomised controlled trial that supports its use in MMN patient population.   |
| The impact of implementation of The Criteria V3 on average duration of treatment | Acknowledged the potential impact. Noted the potential impact has to be evaluated after a longer time after the implementation than what was currently available (6 months). |
| Intravenous Ig dosing and potential for leakage                                  | Disagreed, given the changes implemented to The Criteria V3 and the nationwide availability of BloodSTAR.  |
| Intravenous Ig pricing   | Suggested using weighted average price for all available Intravenous Ig products in the economic evaluation and financial impact analyses.                                   |

Abbreviations: Ig = immunoglobulin; MMN = multifocal motor neuropathy; SCi = subcutaneous immunoglobulin; V3 = version 3



## ACRONYMS AND ABBREVIATIONS

| <b>Acronym/abbreviation</b> | <b>Meaning</b>   |
|-----------------------------|--|
| ABS                         | Australian Bureau of Statistics  |
| AIHW                        | Australian Institute of Health and Welfare                             |
| ADL                         | activities of daily living   |
| ADR                         | adverse drug reactions   |
| AE                          | adverse events   |
| AR-DRG                      | The Australian Refined Diagnosis Related Groups                        |
| BSC                         | best supportive care   |
| CB                          | conduction block   |
| CBC                         | complete blood count   |
| CI                          | confidence interval  |
| CIDP                        | chronic inflammatory demyelinating polyneuropathy                      |
| CEA                         | cost-effectiveness analysis  |
| CFS                         | cerebrospinal fluid  |
| CHERE                       | Centre for Health Economics Research and Evaluation                    |
| CMAP                        | compound muscle action potential                                       |
| CUA                         | cost-utility analysis  |
| DB                          | double blinded   |
| EFNS/PNS                    | European Federation of Neurological Societies/Peripheral Nerve Society |
| EQ-5D                       | Euroqol five dimensions  |
| GNDS                        | The Guy's Neurological Disability Scale                                |
| HRQoL                       | health-related quality of life   |
| HTA                         | health technology assessment   |
| ICER                        | incremental cost-effectiveness ratio                                   |
| Ig                          | immunoglobulin   |
| IHE                         | Institute of Health Economics  |
| IVIg                        | intravenous immunoglobulin   |
| JBC                         | Jurisdictional Blood Committee   |
| LB                          | lower bound  |
| LQI                         | life quality Index   |
| LY                          | life years   |
| MBS                         | Medicare Benefits Schedule   |
| MC                          | multi centre   |
| MND                         | motor neuron disease   |
| MMN                         | multifocal motor neuropathy  |
| MRC                         | Medical Research Council   |
| MRCSS                       | Medical Research Council Sum Score                                     |
| MSAC                        | Medical Services Advisory Committee                                    |
| MRI                         | magnetic resonance imaging   |
| MVIC                        | maximal voluntary isometric contraction                                |
| NBA                         | National Blood Authority   |
| NDS                         | neurological disability score  |
| NE                          | not estimable  |
| NR                          | not reported   |
| ODD                         | overall disability sum score   |
| ONLS                        | overall neuropathy limitations scale                                   |
| OL                          | open label   |
| OTC                         | over the counter   |
| PASC                        | PICO Advisory Sub-committee  |
| PBS                         | Pharmaceutical Benefit Scheme  |
| PCS                         | physical component summary   |
| PE                          | pulmonary embolism   |

| <b>Acronym/abbreviation</b> | <b>Meaning</b>                                   |
|-----------------------------|--|
| PI                          | product information                              |
| PICO                        | Population, Intervention, Comparator and Outcome |
| PDN                         | proximal diabetic neuropathy                     |
| RCT                         | randomised controlled trial                      |
| SD                          | standard deviation                               |
| SF-36                       | 36-Item Short Form Survey                        |
| SEM                         | standard error of mean                           |
| QALY                        | quality adjusted life year                       |
| QoL                         | quality of life                                  |
| RR                          | relative risk                                    |
| SA                          | sensitivity analysis                             |
| SAE                         | serious adverse event                            |
| SClg                        | subcutaneous immunoglobulin                      |
| TGA                         | Therapeutic Goods Administration                 |
| TRALI                       | transfusion-related acute lung injury            |
| Tx                          | treatment  |
| UB                          | upper bound                                      |
| UTS                         | University of Technology Sydney                  |

This contracted assessment of immunoglobulin (Ig) for the treatment of patients diagnosed with multifocal motor neuropathy (MMN) is intended for the Medical Services Advisory Committee (MSAC). MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Schedule (MBS) in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise. Ig in this indication is currently funded under the national blood supply arrangements mainly based on clinical effectiveness arguments, however the cost-effectiveness has not previously been established.

The National Blood Agreement provides for MSAC to undertake evidence-based evaluation of blood products funded under the national blood supply arrangements at the request of the Jurisdictional Blood Committee (JBC). The Department of Health has convened an Ig Review Reference Group to provide advice for evaluation of Ig funded by the National Blood Authority (NBA). The Population, Intervention, Comparator and Outcome (PICO) confirmations for these products are considered by the Ig Review Reference Group instead of the PICO Advisory Sub-committee (PASC). Otherwise, the MSAC evaluation process remains the same as for applications for funding of items on the Medical Benefits Schedule (MBS).

The Centre for Health Economics Research and Evaluation (CHERE) at the University of Technology Sydney (UTS), has been commissioned by the Australian Government Department of Health to conduct a systematic literature review and economic evaluation for MSAC application 1590. This assessment has been undertaken in order to inform MSAC's decision-making and advice to the JBC regarding the clinical safety, effectiveness and cost-effectiveness of intravenous Ig for patients with MMN as a basis to inform the provision of government funded Ig in Australia.

The criteria for evaluation of Ig as it is currently funded for this indication in Australian clinical practice were outlined in a PICO Confirmation that was discussed at the Ig Review Reference Group (meeting of 9 October 2019) and ratified on 22 November 2019.

Appendix A provides a list of the people involved in the development of this assessment report.

## **A.1. ITEMS IN THE AGREED PICO CONFIRMATION**

This contracted assessment of Ig addresses all of the PICO elements that were pre-specified in the PICO Confirmation that was ratified by the Ig Review Reference Group (see summary in Table 7, section A.9).

## **A.2. MEDICAL SERVICE REVIEWED**

MMN is a rare motor neuropathy characterised by motor deficits that present as slowly progressive, predominantly distal, asymmetrical limb weakness without associated sensory loss (1-4). The prognosis for maintaining usual functioning with MMN is usually good given that around 70-80% of patients respond to treatment with Ig. For patients who do not respond, disease progression generally occurs slowly and the majority of patients are able to maintain usual activities, including employment (5). As progression continues to develop, the quality of life of patients continues to deteriorate mainly because, physiologically, more nerves begin and continue to lose functionality over time. There is some evidence suggesting that significant deterioration leading to more severe stages of the disease will depend on the patient's age and disease duration. Overall, this may become a significant issue in patients that have remained untreated for 20 years or more (5). At more severe stages of the disease patients are at a higher risk of falls and dependency and a number of patients will require supporting services like wheelchair, walkers and even residential care. The implications of this do not only negatively impact the QoL of patients from increased disability, but ultimately, also impacts the overall costs to the health care system and the patient. The signs, symptoms and results from diagnostic tests of MMN patients vary across individuals; some will present with conduction block (CB) while others will not, and some patients will have high titres of anti-ganglioside GM1 (anti-GM1) while others will not show any alteration. Because the pathophysiology of the disease is not fully understood, challenges remain in regards to accurate and timely diagnosis of MMN.

The intervention under review is intravenous Ig for the treatment of MMN with or without persistent CB. Since the early 90s, there is evidence suggesting that treatment with Ig positively impacts a patient in terms of reduced disability, increased muscle strength and overall quality of life. The role of Ig is to act as an immunomodulator, although the exact mechanism of action leading to treatment response is not yet fully understood (1, 2, 5, 6).

In Australia, Ig products are available through the NBA that manages and coordinates arrangements for the supply of blood and blood products. The NBA, through The Criteria for the clinical use of Ig in Australia (hereafter - The Criteria), defines the circumstances for which the use of Ig is clinically appropriate and for which patients can access publicly funded Ig, under the National Blood Agreement. The Criteria for the use of Ig for the treatment of MMN were updated in 2018 with the aim of limiting inappropriate use and avoiding leakage. The latest version of The Criteria is Version 3 (V3) which differs from Version 2 (V2) in the following points (3):

- Restricts the initial use of Ig to patients who have a progressive motor weakness and have minimum level of disability as per the overall neuropathy limitations scale (ONLS) score of two points;
- Introduces a restriction for treatment re-initiation in patients who relapse;
- Expands on the exclusion criteria for diagnosing MMN; and
- Recommends a lower dose range for the induction phase of treatment in patients who relapse (1-2 g/kg versus 2g/kg).

The current contracted assessment incorporated the changes reflected in The Criteria V3.

In the Australian setting, 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 funded by the NBA for the treatment of MMN, although evidence from a randomised controlled trial (RCT) (7) suggests that SCIg was as safe and effective as intravenous Ig. The potential impact of introducing the SCIg form to the NBA will be tested in a sensitivity analysis in Section D of this report assuming equi-effective doses.

#### DOSAGE AND FREQUENCY

The permissible dose of intravenous Ig for each indication according to The Criteria V3 (3) is presented in Table 1.

**Table 1: Current effective dose of intravenous Ig for MMN in Australia as established in The Criteria V3.**

| Indication  | Dose  |
|---|---|
| 'First-line and maintenance therapy for MMN'  | <p><u>Induction dose</u><br/>2 g/kg divided in 2 to 5 doses.</p> <p><u>Maintenance dose</u><br/>0.4–1 g/kg, 2–6 weekly. The amount per dose should be titrated to the individual's response, up to a maximum dose of 2 g/kg in any 4 week period. This might be administered in divided doses. The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.</p>                       |
| 'Relapse of MMN patients within six months of commencement of a trial off Ig therapy' | <p><u>Induction Dose</u><br/>1-2 g/kg divided in 2 to 5 doses.</p> <p><u>Maintenance Dose</u><br/>0.4–1 g/kg, 2–6 weekly. The amount per dose should be titrated to the individual's response, up to a maximum dose of 2 g/kg in any 4 week period. This might be by smaller doses more frequently than fortnightly. The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.</p> |

Abbreviations: g = gram; Ig = immunoglobulin; kg = kilogram; MMN = multifocal motor neuropathy.

Note: For both indications the aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient. Refer to the current product information sheet for further information on dose, administration and contraindications.

Source: BloodSTAR (2018). The Criteria for clinical use of immunoglobulin in Australia (the Criteria); multifocal motor neuropathy, Version 3 (<https://www.criteria.blood.gov.au/MedicalCondition/View/2558> accessed September 2019).

## MARKETING STATUS OF INTRAVENOUS I<sub>G</sub>

The available alternative presentations of intravenous Ig registered by the TGA for the potential treatment of MMN in Australia are summarised in Table 2. The NBA price per gram is also provided for currently NBA funded alternatives.

**Table 2: 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 <sup>1</sup> |
| 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                     |
| 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                     |

| Product/strength | Presentations                           | TGA indication for MMN (Yes/No) | NBA price per gram @ 10/10/19      |
|------------------|---|---------------------------------|------------------------------------|
| Gamunex 10%      | 20 g/200 mL<br>10 g/100 mL<br>5 g/50 mL | No                              | NBA funded; price is confidential. |

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: <sup>1</sup>The price does not include the starting plasma provided to CSL by the Australian Red Cross Blood Service.

Source: NBA website; <https://www.blood.gov.au/national-product-list>, accessed 26 February 2020.

## SERVICE DELIVERY

Intravenous Ig can be delivered in different settings depending on various factors. In Australia, it can be delivered in one of the following settings:

- Inpatient private hospital
- Inpatient public hospital (as private or public patient)
- Outpatient clinic
- Patient's home
- Private same day infusion facility unattached to a hospital.

The timeframe taken to administer intravenous Ig varies between patients and depends on:

- Dose required;
- Weight of the patient;
- Specifications of product information and administering centre protocol on infusion rate;
- Patient's response during infusion.

Patients requiring smaller doses are likely to attend the hospital/clinic for a day procedure. Patients requiring larger doses may require a number of infusions and patients may (or may not) be required to attend a 'day procedure' on a number of days (usually consecutive) each month. However, some patients may require admission to hospital due to comorbidities, advanced age, doses required over multiple days and patient preference.

The required dose of intravenous Ig must be established by the treating doctor (neurologist) while its administration can be also undertaken by a doctor or by nursing staff. During the course of the infusion, the patient's vital signs have to be monitored (temperature, pulse and blood pressure). Some intravenous Ig products, such as Flebogamma 5% DIF<sup>®</sup> and Flebogamma 10% DIF<sup>®</sup>, require that the patient is hydrated before infusion and that urine output and serum creatinine levels be monitored. Concomitant medications such as antihistamines may be required to manage infusion reactions (e.g. rash and flushes).

It should be noted that in December 2018, the Ig guidance in England was updated (8) which recommends a dosage different to that recommended in Australia. The main difference is the higher dose for treatment initiation reaching 4 g/kg which should be divided into two courses of 1-2 g/kg each and given over a 4-8 week period. In Australia, summary level data from Bloodstar provided by NBA for the period 2018-2019 shows that, on average, a patient receiving Ig for MMN is administered 0.64 g/kg per month (equivalent to 0.41 g/kg per treatment episode as per NBA data) (9).

## CURRENT USAGE OF INTRAVENOUS I<sub>g</sub> THERAPY FOR MMN IN AUSTRALIA

The use of intravenous Ig therapy for MMN based on NBA internal data, is provided in Table 3 (9). Compared to the 2017-2018 period, the average quantity (in grams) used per patient has remained constant over the past three years (628, 633 and 626 grams respectively). As discussed previously, The Criteria V3 restricts the qualifying criteria for the initial use of intravenous Ig as well as for patients who relapse. Furthermore, it is more specific and expands on the exclusion criteria and recommends a lower induction dose for patients who relapse. These changes have not yet translated into lower use of intravenous Ig per patient or a reduction in the number of patients receiving treatment. In terms of the expected dose per patient, there is evidence in Australia for the period 2015-2016 that shows that most patients with MMN (61%) received the lowest recommended dose (0.4 g/kg) while 38% received a dose between 0.4-0.99 g/kg. The latter is consistent with data from the period 2018-19 that shows that, on average, a patient is administered 0.64 g/kg per month. This suggests that neurologists in Australia may have a conservative treatment approach for the management of MMN (10). However, it should be noted that the annual data as per the NBA database includes patients who discontinue treatment and who were assigned 0 grams for an unknown number of months. The latter means that, from this database, the average monthly dose could be higher than 0.64 g/kg.

**Table 3: Usage of intravenous Ig therapy over recent years for the treatment of MMN based on of The Criteria V2 and V3.**

|                                 | 2013-14          | 2014-15 | 2015-16 | 2016-17 | 2017-18 | 2018-19 <sup>a</sup> |
|---------------------------------|------------------|---------|---------|---------|---------|----------------------|
| New patients                    | 127              | 105     | 137     | 126     | 125     | 123                  |
| Total patients                  | 438              | 444     | 496     | 527     | 560     | 596                  |
| Total grams issued/administered | 239,791          | 256,041 | 293,458 | 331,147 | 354,434 | 372,434              |
| Average grams per patient       | 547 <sup>b</sup> | 577     | 592     | 628     | 633     | 626                  |

Abbreviations: Ig = immunoglobulin; MMN = multifocal motor neuropathy

Note: <sup>a</sup>Data for the 2018-2019 (01 July 2018 – 30 June 2019) period incorporated version 2 and version 3 of The Criteria. <sup>b</sup>This was reported as 546 in the Referral but verified as 547 during the write-up of this assessment report. Data for the period from 2013-2018 reflects usage only under version 2 of The Criteria, which is prior to the introduction of key changes which aimed to address leakage.

Source: Table 7, p.25 of the draft Referral form 1590 MMN. HTA Conditions Report 1, 2 and 3 provided by the NBA on 06 January 2020.

## CONDITIONS FOR THE FUNDING OF I<sub>g</sub>

The review criteria outlines steps for assessing the effectiveness of intravenous Ig in the management of MMN. For each indication, clinical effectiveness of intravenous Ig therapy should be assessed as follows:

- An initial review (by a neurologist) within four months after treatment commences (referred to as 'on review of the initial authorisation period' by The Criteria V3).
- Ongoing reviews (by neurologist) to justify the continuous use of intravenous Ig (referred to as 'on review of the continuing authorisation period' by The Criteria V3).

Details of the review criteria for the use of intravenous Ig for the treatment of MMN are provided in Table 4. The Criteria establish the use of intravenous Ig as initial and subsequent maintenance and



continuing in two different patient populations, previously untreated patients (first indication) and relapsed patients<sup>1</sup> (second indication). Funding for both subgroups would include an initial treatment phase where patients are trialled for four months before they are assessed by a neurologist as a responder or non-responder. Only responders are eligible to access continuing treatment for up to 12 months. A patient is said to benefit from Ig if the disease remains stable or there is an improvement in muscle weakness and the level of disability as measured by the adjusted ONLS (Table 4). The Criteria encourages a trial of weaning phase leading to cessation of intravenous Ig therapy to be considered at least 12 months after treatment for all patients who have initiated continuing therapy (either as first line or relapsed) unless otherwise contraindicated. A trial of weaning of Ig therapy is considered to test whether remission has been achieved (11). Stable patients may achieve long-term remission which will only be evident if trialled off Ig therapy. Gradual dose reductions may occur over a period of up to a year prior to a trial cessation. Based on clinical expert opinion (Ig Review Reference Group), weaning was not considered common practice in Australia, instead it was more likely that patients were assessed for an end of dose effect (i.e. patient demonstrates an improvement in symptoms on the current dose). Those patients with no clear end of dose effect may be considered for weaning for which the actual dose may be reduced and/or the dose interval increased. Only a proportion of these patients will eventually cease treatment.

**Table 4: Review criteria for assessing the effectiveness of intravenous Ig therapy use in MMN as established in Version 3 of the ‘Criteria for Clinical Use of Immunoglobulin in Australia’**

| Indication  | Review criteria  |
|---|--|
| ‘First-line and subsequent maintenance therapy for MMN’ | <p><u>Initial treatment</u></p> <p>Upon establishing diagnosis, intravenous Ig should be used for a maximum of four months (induction plus three maintenance cycles) before determining whether the patient has responded. If there is no benefit after this treatment, intravenous Ig therapy should be discontinued.</p> <p>Review by a neurologist is required within four months of treatment and annually thereafter. Documentation of clinical efficacy is necessary for continuation of Ig therapy.</p> <p><u>On review of an initial authorisation period</u></p> <p>Clinical effectiveness of Ig therapy will be demonstrated by:</p> <ul style="list-style-type: none"> <li>• Improvement in focal weakness in previously weak (but not end-stage) muscles;</li> <li>AND</li> <li>• Improvement in the level of disability as measured by the adjusted ONLS of at least one point less than the qualifying score.</li> </ul> |

<sup>1</sup> Relapsed patients are MMN patients who relapse within six months of commencement of a trial off Ig therapy. These patients access intravenous Ig therapy under the second indication. It should also be noted that MMN patients who relapse after six months of commencement of a trial off Ig therapy are also able to access intravenous Ig therapy after reassessment by a neurologist but under the first indication (Ig Review Reference Group).

| Indication   | Review criteria   |
|--|---|
|  | <p><u>On review of a continuing authorisation period</u></p> <p>After a period of intravenous Ig treatment of no more than 12 months, all patients need to be assessed for clinical effectiveness and may be eligible for continuing if they demonstrated clinical improvement measured as:</p> <ul style="list-style-type: none"> <li>• 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;<br/>AND</li> <li>• Improvement in or stabilisation of disability as measured by the adjusted ONLS score compared to the previous review score (gradual deterioration of one point over several years is acceptable);<br/>AND</li> <li>• A trial of weaning/cessation of intravenous 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 being planned.</li> </ul> <p>For patients in remission on continuing therapy, a trial of weaning potentially leading to cessation should be considered. If the patient relapses within six months, they may be eligible for further Ig therapy under the indication 'Further and subsequent maintenance therapy for MMN patients who relapse within six months of commencement of a trial off Ig therapy'. A subsequent trial of weaning leading to cessation might be considered after a further two years of Ig therapy.</p> <p><i>If a patient relapses after six months of a trial of weaning leading to cessation, they may be eligible for further Ig therapy under the indication 'First-line and subsequent maintenance therapy for MMN'.</i></p>                               |
| <p>'Further and subsequent maintenance therapy for MMN patients who relapse within six months of commencement of a trial off Ig therapy'</p> | <p><u>Initial treatment</u></p> <p>Intravenous Ig should be used for a maximum of four months (induction plus three maintenance cycles) before determining whether the patient has responded. If there is no benefit after this treatment, intravenous Ig therapy should be abandoned.</p> <p>Review by a neurologist is required within four months of treatment and annually thereafter. Documentation of clinical efficacy is necessary for continuation of intravenous Ig therapy.</p> <p>Patient qualifies for continuing treatment with intravenous Ig once its clinical benefit/effectiveness has been confirmed within four months of treatment initiation by a neurologist.</p> <p><u>On review of the initial authorization period</u> (e.g. initial treatment)</p> <p>Clinical effectiveness of intravenous Ig therapy will be demonstrated by:</p> <ul style="list-style-type: none"> <li>• Improvement in focal motor weakness in response to four months of Ig therapy compared to muscle strength at the qualifying assessment following relapse<br/>AND</li> <li>• Improvement in disability as measured by the adjusted ONLS compared to the qualifying assessment at relapse.</li> </ul> <p><u>On review of a continuing authorisation period</u></p> <p>Clinical effectiveness of intravenous Ig therapy will be demonstrated by:</p> <ul style="list-style-type: none"> <li>• Improvement in or stabilisation of focal motor weakness as compared to the focal muscle strength at the previous review assessment;<br/>AND</li> <li>• 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);<br/>AND</li> </ul> |

| Indication | Review criteria  |
|------------|--|
|            | <ul style="list-style-type: none"> <li data-bbox="552 220 1369 304">• A trial of weaning/cessation of intravenous Ig therapy is 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.</li> </ul> <p data-bbox="503 304 1369 462">For patients in remission on continuing therapy, a trial of weaning leading to cessation should be considered. If the patient relapses, again within six months of commencement of a trial off Ig therapy, they may be eligible for further intravenous Ig therapy under this indication. A subsequent trial of weaning leading to cessation might be considered after a further two years of intravenous Ig therapy.</p> <p data-bbox="503 462 1369 556"><i>If a patient relapses after six months of a trial of weaning leading to cessation, they may be eligible for further Ig therapy under the indication 'First-line and subsequent maintenance therapy for MMN'.</i></p> |

Abbreviations: Ig = immunoglobulin; MMN = multifocal motor neuropathy; ONSL = overall neuropathy limitations scale.

Note: Italicised sentences are contributions/advice from the Ig reference group during the PICO confirmation and compilation of this report. Source: BloodSTAR (2018). The Criteria for clinical use of immunoglobulin in Australia (the Criteria); multifocal motor neuropathy, Version 3 (<https://www.criteria.blood.gov.au/MedicalCondition/View/2558> accessed September 2019).

There is the potential that continuing therapy may be provided to patients who do not have a confirmed diagnosis of MMN or who have not shown a treatment response, which may result in leakage. In the context of this assessment, leakage refers to the use of intravenous Ig outside the specified criteria which may have implications in terms of product availability and likely to have financial implications to the NBA. Much of the review assessment described above was implemented to control leakage and ensure the appropriate use of intravenous Ig in MMN. Despite The Criteria's approach to control leakage, dosing may become another factor with a potential risk of leakage for consideration. However, the introduction of The Criteria V3 coupled with the now Nation-wide implementation of the BloodSTAR system to manage the authorisation and review process, will further improve the national process for the delivery of Ig and may adequately address possible concerns around leakage.

## CURRENT FUNDING

Intravenous Ig is currently being used in Australia for several different indications, for some as replacement therapy and for others as immunomodulatory therapy. The role of Ig for each indication can be classified as an established therapeutic role, emerging therapeutic role or use under exceptional circumstances only. The use of intravenous Ig for MMN has been classified as an established therapeutic role and is currently funded by the NBA under The Criteria V3. The purpose of this contracted assessment is to consider the new available clinical evidence and cost-effectiveness of this intervention as currently funded through the NBA.

### A.3. PUBLIC FUNDING

Intravenous Ig therapy for MMN is already funded by the NBA and represents the standard of care in Australia.

#### A.4. POPULATION

##### EPIDEMIOLOGY OF MMN AND PATIENT CHARACTERISTICS

MMN is a rare inflammatory neuropathy with a reported prevalence that ranges from 0.3 to 2 cases per 100,000 depending on jurisdiction and on how the estimates were derived (12-14) (See Table 5). The age at disease onset is variable ranging from 15-74 years, however MMN is mostly diagnosed in adults, with a mean age of onset of 41 years. MMN is very rare in paediatric populations with very few cases being reported in the literature (15). The available epidemiological studies consistently show that this is a disease more commonly observed in males compared to females, with a reported ratio of 2.5-2.7 : 1 (12-14).

Given the rarity of the disease and lack of complete understanding of the underlying pathophysiological mechanism of MMN, there is a risk of misdiagnosis and/or under diagnosis and hence estimates of the epidemiology of the condition should be interpreted with caution.

**Table 5: Overview of MMN prevalence estimates in the literature**

| Study (author, year)      | Country     | Study design/method  | Estimated prevalence per 100,000 | Male: female ratio | Mean age of onset (range) |
|---------------------------|-------------|--|----------------------------------|--------------------|---------------------------|
| Miyashiro et al. 2014(12) | Japan       | Retrospective analysis using a nationwide survey. Diagnosis of MMN was based on 2006 EFNS/PNS criteria.              | 0.29                             | 2.5 : 1            | 42.5 (16-74)              |
| Nobile-Orazio. 2001(13)   | Italy       | Approximate estimate using proportion of MMN in patients initially diagnosed of MND.                                 | Approximately 1 to 2             | 2.6 : 1            | 41 (15-72)                |
| Cats et al. 2010 (14)     | Netherlands | Nationwide survey. MMN was diagnosed using the diagnostic criteria recommended by Van den Berg-Vos et al. 2000 (16). | 0.6                              | 2.7 : 1            | 40 (22-66)                |

Abbreviations: EFNS/PNS = European federation of neurological societies/Peripheral nerve society; MMN = multifocal motor neuropathy.

There are currently no epidemiological data available for MMN in Australia. This Contracted Assessment used the population-based prevalence rate estimates for MMN reported by Cats et al. 2010 (14) 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 at the Ig review meeting (9 October 2019), because the study was conducted in a systematic way and their findings are widely used. In addition, the clinical criteria used for Ig therapy for MMN in the Cats et al. 2010 study(14) were consistent with the qualifying criteria (The Criteria V3) for intravenous Ig therapy for MMN used in Australia. The estimated prevalence rate from Cats et al. 2010 was applied to an estimate of the Australian population as at June 2019 of 25,364,307 individuals (17). By assuming a prevalence rate of 0.6 per 100,000 population, this would equate to 152 patients with a definite MMN diagnosis (versus

596 MMN Ig treated patients in the period 2018-2019). However, this estimate is lower than the number of patients who received intravenous Ig treatment for MMN in Australia based on the latest utilisation data provided by the NBA for the period 2018-19 which considered both, The Criteria V2 and V3 of (see Table 3). A further discussion on the prevalence sources available is provided in Section E.6.

### **HOW ARE PATIENTS DIAGNOSED?**

MMN is difficult to diagnose because of the incomplete understanding of the pathophysiology of the illness and the similarities of clinical symptoms associated with motor neuron disease (MND) and chronic inflammatory demyelinating polyneuropathy (CIDP). In particular, there is difficulty in distinguishing between MMN and MND clinically because both are characterised by weakness in the arms in combination with cramps, wasting and fasciculation. One potential implication of not being able to establish an accurate diagnose, is that patients with a diagnosis different to MMN (possibly MND) may be receiving intravenous Ig treatment and potentially not deriving the expected clinical benefit. A discussion regarding the differences observed in the estimated prevalence from epidemiological data and number of cases as per NBA data is discussed further in Section E.6. The principal differential diagnosis of MMN to MND is that motor deficits in MMN occur in the distribution of a single nerve whilst in MND they occur in the distribution of spinal segments (6). In addition, in contrast to MMN, MND is characterised by muscle rigidity, inability to move muscles and loss of the ability to control muscles over time.

Due to the difficulty in diagnosing MMN, the Ig Review Reference Group recommended that MMN should be diagnosed by two clinicians (neurologists) but this may have an impact on access and equity. The draft Referral for MMN 1590 noted that referral pathways to a neurologist are varied including general practitioners (GPs) or other specialists such as rheumatologists or orthopaedic surgeons. It was further stated that to rule out the main differential diagnosis, MND, genetic testing may be conducted, however the gene based diagnostic test for MND is not currently funded under the MBS. The recommendation for two neurologists to confirm diagnosis and conduct the genetic testing for MMN may lead to equity issues due to difficulties in gaining access to specialists and potential out of pocket expenses. As indicated in Table 1, the clinical criteria for assessing intravenous Ig for MMN in Australia include progressive motor weakness and a disability of  $\geq 2$  as measured by the ONLS (3).

The European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) guideline (18) suggests that the diagnosis of MMN should be based on clinical and electrophysiological criteria, and supplemented with other supportive criteria. The criteria for these diagnostic tests and recommendations for good practice as included in the 2010 EFNS/PNS guideline are presented in Table 6. The main clinical characteristics of MMN are slowly progressive or stepwise progressive weakness, weakness without objective sensory loss, asymmetric involvement of two or more nerves, and the absence of upper motor neuron signs. The criteria used for Ig therapy for MMN in Australia are consistent with the clinical diagnostic criteria established by the EFNS/PNS. In addition, the

electrophysiological criteria include definite or probable motor CB and normal sensory nerve conduction.

Other tests that could support the diagnosis of MMN are: elevated IgM anti-ganglioside GM1 antibodies, normal or mildly increased cerebrospinal fluid protein (<1 g/l) and increased signal intensity on T2-weighted magnetic resonance imaging (MRI) scans of the brachial plexus associated with a diffuse nerve swelling. In addition, an objective clinical improvement following intravenous Ig treatment could also support the diagnosis of MMN noting that this may have a placebo effect on MND patients for a short term. Therefore, it should be noted that, objective clinical response to Ig therapy and all of these other tests (for supportive criteria) are not required for patients who satisfy the clinical and electro-diagnostic criteria of MMN: that is when a definitive diagnosis of MMN can be made (see Table 6).

**Table 6: Diagnostic criteria and diagnostic tests for MMN as presented in the 2010 EFNS/PNS guideline (18)**

| Clinical criteria  | Electrophysiological criteria  | Supportive criteria  |
|--|--|--|
| <p>Core (required)</p> <ol style="list-style-type: none"> <li>1. Slowly progressive or stepwise progressive, focal, asymmetric limb weakness; that is, motor involvement in the motor nerve distribution of at least two nerves for more than 1 month. If symptoms and signs are present only in the distribution of one nerve, only a possible diagnosis can be made.</li> <li>2. No objective sensory abnormalities except for minor vibration sense abnormalities in the lower limbs.</li> </ol> <p>Supportive</p> <ol style="list-style-type: none"> <li>3. Predominant upper limb involvement.</li> <li>4. Decreased or absent tendon reflexes in the affected limb.</li> <li>5. Absence of cranial nerve involvement.</li> <li>6. Cramps and fasciculations in the affected limb.</li> <li>7. Response in terms of disability or muscle strength to immunomodulatory therapy.</li> </ol> <p>Exclusion criteria</p> <ol style="list-style-type: none"> <li>8. Upper motor neuron signs.</li> <li>9. Marked bulbar involvement.</li> <li>10. Sensory impairment more marked than minor vibration loss in the lower limbs.</li> <li>11. Diffuse symmetric weakness during initial weeks.</li> </ol> | <p>Definite motor CB<sup>a</sup></p> <ol style="list-style-type: none"> <li>1. Negative peak CMAP area reduction on proximal versus distal stimulation of at least 50% regardless of nerve segment length (median, ulnar, and peroneal).</li> <li>2. Negative peak CMAP amplitude on stimulation of the distal nerve segment &gt;20% of the lower limit of normal and &gt;1 mV.</li> <li>3. Increase of proximal to distal negative peak CMAP duration of ≤30%.</li> </ol> <p>Probable motor CB<sup>a</sup></p> <ol style="list-style-type: none"> <li>4. Negative peak CMAP area reduction of at least 30% over a long segment (eg, wrist to elbow or elbow to axilla) of an upper limb nerve with increase of proximal to distal negative peak CMAP duration of ≤30%.</li> <li>OR</li> <li>5. Negative peak CMAP area reduction of at least 50% with an increase of proximal to distal negative peak CMAP duration of &gt;30%.</li> <li>6. Normal sensory nerve conduction in upper limb segments with CB (see exclusion criteria under clinical criteria).</li> </ol> | <ol style="list-style-type: none"> <li>1. Elevated IgM anti-ganglioside GM1 antibodies.</li> <li>2. Increased CSF protein (&lt;1 g/l).</li> <li>3. Magnetic resonance imaging showing increased signal intensity on T2-weighted imaging associated with a diffuse nerve swelling of the brachial plexus.</li> <li>4. Objective clinical improvement following Ig treatment.</li> </ol> |
| <p><u>Diagnostic categories</u></p> <p>Definite MMN:</p> <ul style="list-style-type: none"> <li>• clinical criteria 1,2, AND 8-11 AND electrophysiological criteria 1 and 3 in one nerve.</li> </ul>   |  |  |

| Clinical criteria   | Electrophysiological criteria | Supportive criteria |
|---|-------------------------------|---------------------|
| Probable MMN: <ul style="list-style-type: none"> <li>clinical criteria 1,2, AND 8-11 AND electrophysiological criteria 2 and 3 in two nerves;</li> <li>clinical criteria 1,2, and 8-11 AND electrophysiological criteria 2 and 3 in two nerves AND at least two supportive criteria 1-4.</li> </ul> Possible MMN: <ul style="list-style-type: none"> <li>clinical criteria 1, 2, AND 8-11 AND normal sensory nerve conduction studies AND supportive criteria 4;</li> <li>clinical criteria 1 with clinical signs present in only one nerve, clinical criteria 2 AND 8-11 AND electrophysiological criteria 1 or 2 and 3 in one nerve.</li> </ul> |                               |                     |
| Good practice points for diagnostic criteria <ol style="list-style-type: none"> <li>Clinical: the two core criteria and all exclusion criteria should be met.</li> <li>Electro-diagnostic: definite or probable CB in at least one nerve.</li> <li>Supportive: anti-GM1 antibodies, MRI, CSF, and treatment response</li> <li>Categories: definite and probable MMN</li> </ol>  |                               |                     |
| Good practice points for diagnostic tests <ol style="list-style-type: none"> <li>Clinical examination and electro-diagnostic tests should be done in all patients.</li> <li>Anti-ganglioside GM1 antibody testing, MRI of the brachial plexus, and CSF examination should be considered in selected patients.</li> <li>Investigations to discover concomitant disease or exclude other possible causes should be considered, but the choice of tests will depend on the individual circumstances</li> </ol>   |                               |                     |

Abbreviations: CB = conduction block; CMAP = compound muscle action potential; CSF = cerebrospinal fluid; Ig = immunoglobulin; MMN = multifocal motor neuropathy; MRI = magnetic resonance imaging.

Note: <sup>a</sup>Evidence of CB must be found at sites distinct from common entrapment or compression syndromes.

Source: van Schaik et al, 2010 (Table 1, p.298; Table 2, p.297; Table 3, p.298; Table 4, p.299; and text p298).

## A.5. COMPARATOR DETAILS

There are no other NBA or Pharmaceutical Benefit Scheme (PBS) subsidised treatments for MMN. The current practice for the treatment of MMN is intravenous Ig available through the NBA.

### NO IG WITH BEST SUPPORTIVE CARE

Immunoglobulins have been the gold standard of treatment for MMN since the early 1990s and are the standard treatment recommended in the 2010 EFNS/PNS MMN guideline (18) and The Criteria V3 in Australia. Hence, the comparator represents a hypothetical scenario where Ig is not available and patients would receive what is currently given as BSC. The latter would include health checks with a neurologist, physiotherapy and rehabilitation services.

A systematic literature review that assessed the use of immunosuppressant and immunomodulatory therapies suggested there might be a possible therapeutic role for cyclophosphamide in the treatment of patients who do not respond to intravenous Ig and have progressed in their disease to a level where the benefits outweigh the safety risks associated (1). Cyclophosphamide is sometimes used in patients who have not responded to or have failed intravenous Ig however, it is used later in the disease course and as observed in case series, in a minority of patients (19)<sup>2</sup>. It should be noted that all the available

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<sup>2</sup> CSL Behring (Australia) Pty Ltd in their response to the Department of Health Targeted Consultation Survey on MSAC Ig Referral 1590 MMN noted that cyclophosphamide for the treatment of MMN is currently limited to subsequent lines of therapy or in refractory cases due to its toxicity.

evidence comes from non-randomised studies and that this is not the patient population targeted in this Contracted Assessment.

Cyclophosphamide was the first immunosuppressive agent assessed for the treatment of MMN. The evidence available to support the use of cyclophosphamide comes from several case reports available since 1988, where two patients achieved an improvement in limb strength after receiving intravenous cyclophosphamide 3g/m<sup>2</sup> followed by 100 mg oral cyclophosphamide (20). Several series of case reports have been published thereafter with differences identified in terms of previous line of treatment (e.g. failed to corticosteroid and/or plasma exchange) and adjuvant treatments (e.g. plasma exchange, azathioprine, among others). Overall, high dose intravenous cyclophosphamide has been shown to be effective in up to 50% of patients, with lower doses being ineffective (20-23), with all reports showing a non-favourable safety profile. Patients treated with cyclophosphamide often suffer adverse events, some of which are serious, including death. Of the 56 patients receiving cyclophosphamide from 14 published articles, all reported adverse events (AEs), such as bone marrow suppression, alopecia, haemorrhagic cystitis, delayed bladder cancer, teratogenicity, azoospermia, and infections (2). There were also two deaths reported, one due to listeria meningitis and the other a bone myelogenous leukaemia.

Cyclophosphamide is not specifically approved by the TGA for the treatment of MMN, however the PI states that it can be 'recommended for use in treatment of non-malignancies only when, in the opinion of the physician, the benefits to the patient outweigh the risk of treatment with cyclophosphamide'.

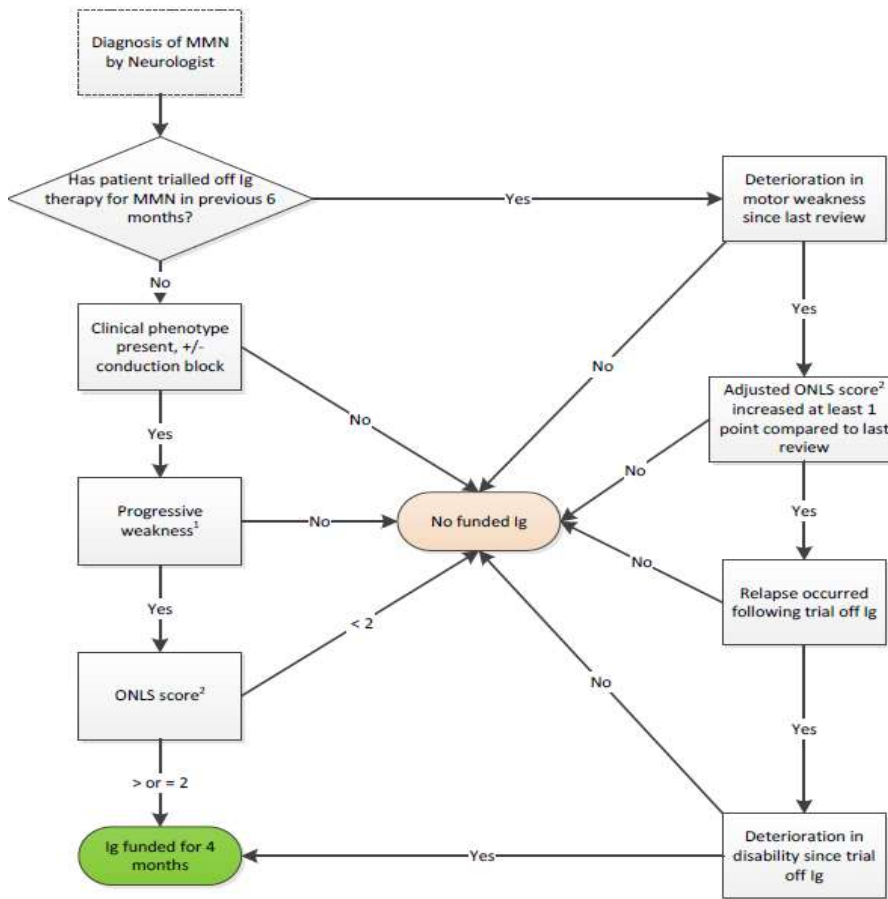
Accordingly, cyclophosphamide was not considered a relevant comparator because of inappropriately high toxicity in a non-life-threatening illness like MMN. Furthermore, the Ig Review Reference group stated that there is no convincing literature that cyclophosphamide actually benefits patients with MMN and that it should not be regarded as an alternative treatment in Australia. For this reason, 'No Ig with BSC' is considered the relevant comparator to intravenous Ig in MMN.

## **A.6. CLINICAL MANAGEMENT ALGORITHM(S)**

The clinical management algorithm for the initial and maintenance use of intravenous Ig from the PICO Confirmation is presented in Figure 1 and Figure 2 (current) and Figure 3 and Figure 4 (proposed treatment algorithms).



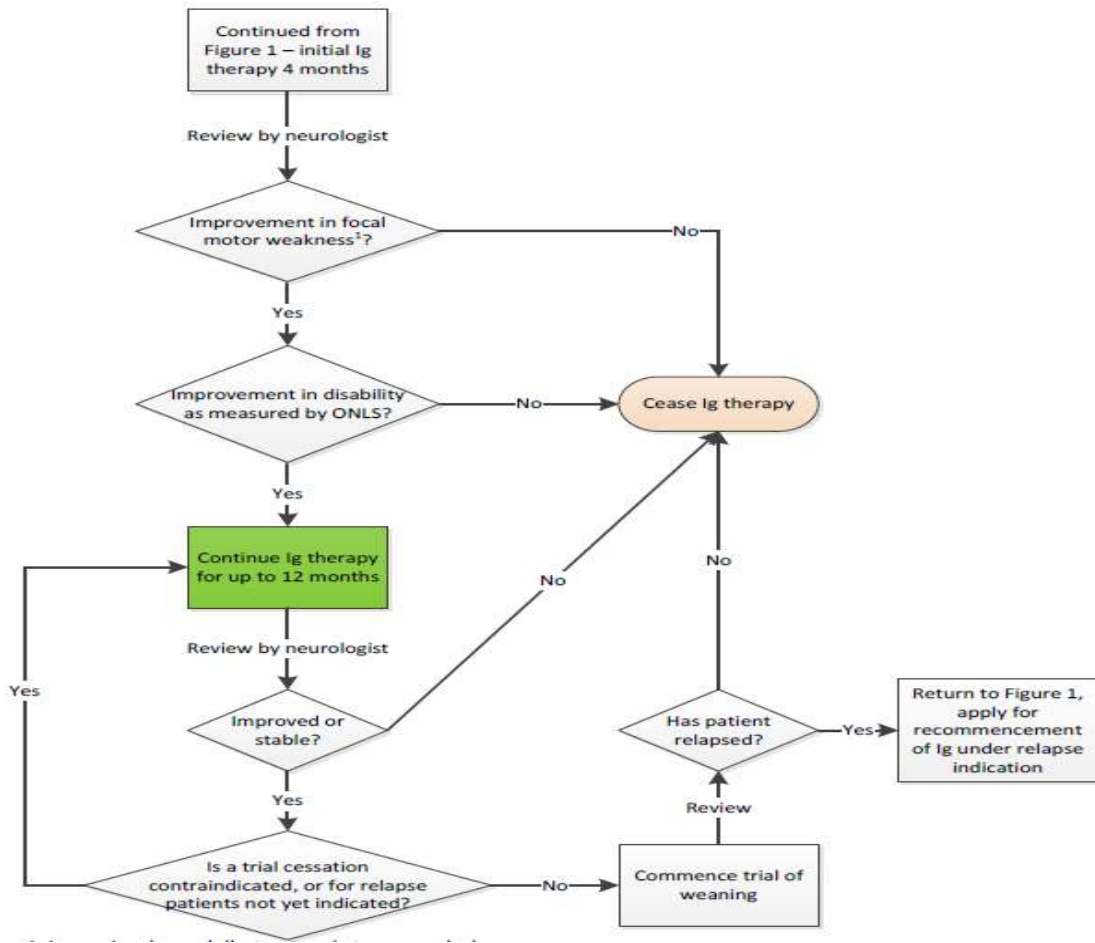
Figure 1. Current Clinical management algorithm initial access to Ig under NBA as per MMN Referral



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

Note: 1Progressive weakness as demonstrated in the distribution of individual peripheral nerves; 2Overall Neuropathy Limitations Scale.  
Source: Figure 2, p. 14 of the 1590 MMN draft Referral Form.

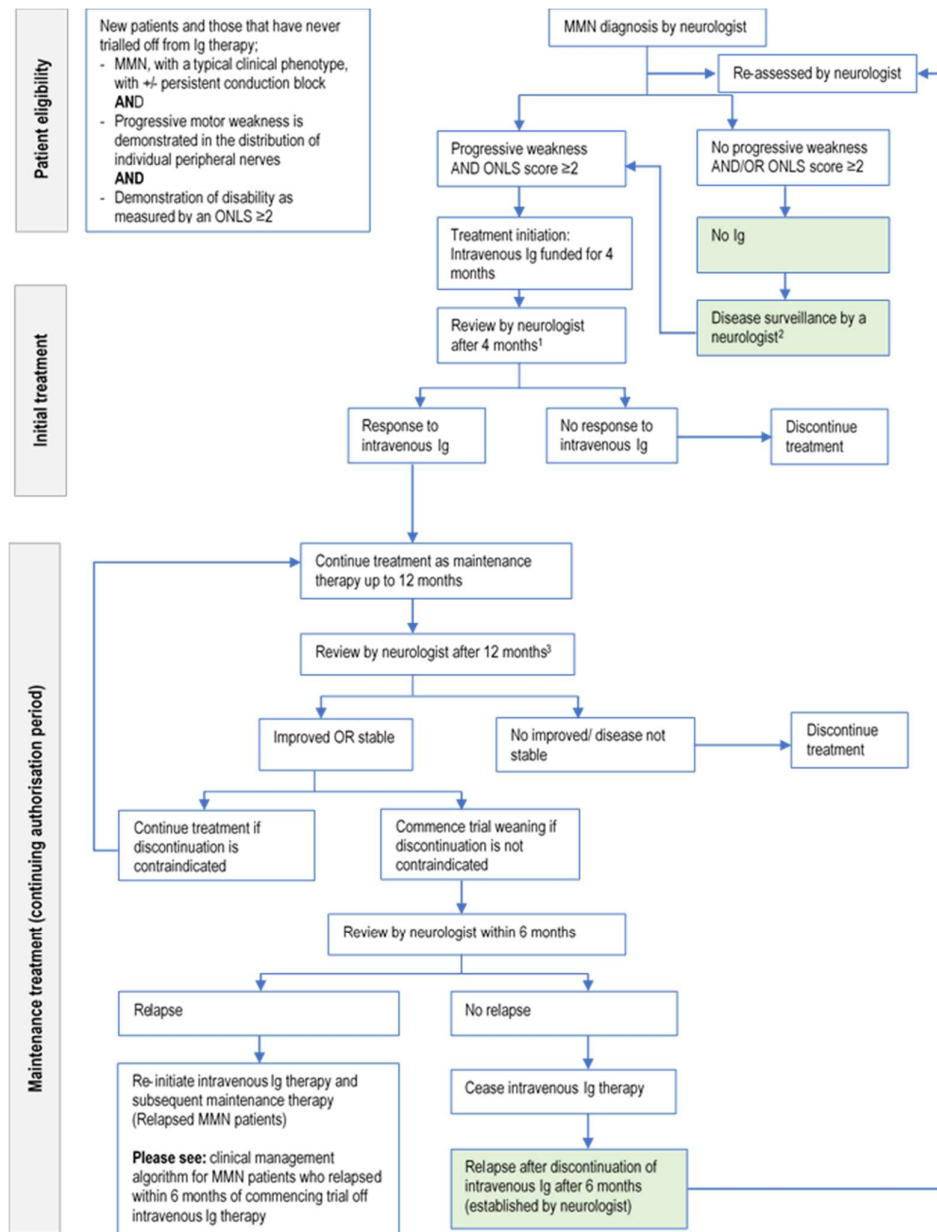
Figure 2. Current Clinical management algorithm continuing access to Ig under NBA as per MMN Referral



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

Sources: Figure 2, p. 19 of the 1590 MMN draft Referral Form.

**Figure 3: 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.

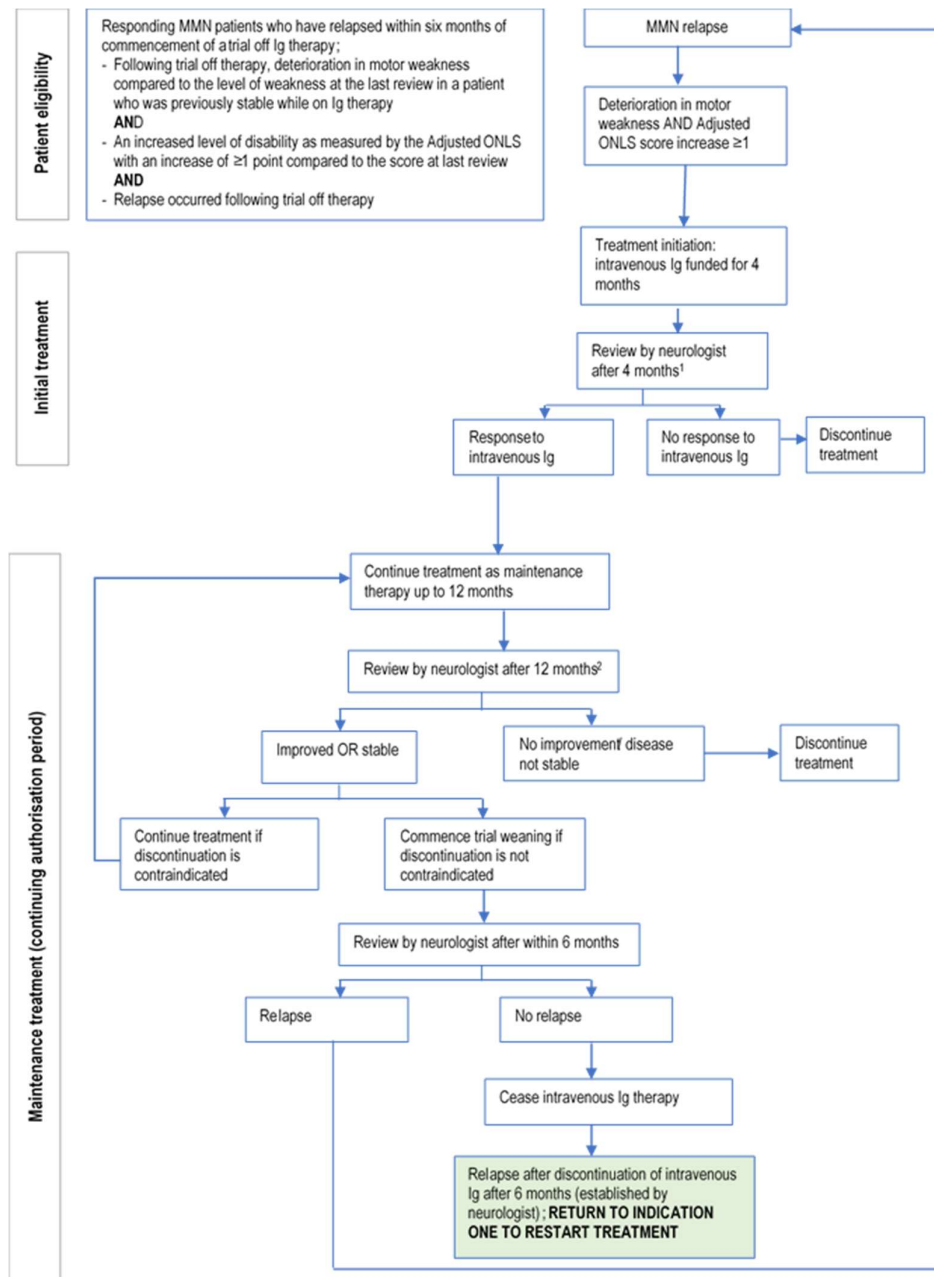
Note: <sup>1</sup> Clinical effectiveness (response) of Ig therapy can be assessed by: Improvement in focal motor weakness in previously weak (but not end stage) muscles **AND** Improvement in the level of disability as measured by the Adjusted ONLS of at least one point less than the qualifying score;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

<sup>3</sup> 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: Prepared during PICO Confirmation based on Figure 1 and Figure 2 of the MMN Referral and the reviewed content.

**Figure 4: 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: <sup>1</sup> 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;<sup>2</sup> 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: Prepared during PICO Confirmation based on Figure 1 and Figure 2 of the MMN Referral and the reviewed content.

## A.7. KEY DIFFERENCES IN THE DELIVERY OF THE PROPOSED MEDICAL SERVICE AND THE MAIN COMPARATOR

The main comparator as defined in the PICO Confirmation was ‘No Ig with active disease surveillance’ (hereafter referred to as best supportive care, or BSC). Currently, patients not receiving intravenous Ig treatment are those who are not eligible or no longer eligible to receive active treatment under The Criteria V3 or patients for whom intravenous Ig is contraindicated. These patients are assumed to maintain BSC with a neurologist and other health care professionals such as physiotherapists where applicable.

The main difference in the delivery of the intervention is the actual administration of intravenous Ig, which for MMN patients, is administered mainly in hospital (outpatient setting). This requires specialised nurses and the use of hospital facilities and devices for a proper and safe delivery of the intervention. Some patients may require hospitalisation because they may require longer monitoring due to the presence of comorbidities, longer infusion times or the risk of adverse events.

## A.8. CLINICAL CLAIM

The clinical claim in the PICO Confirmation was “intravenous Ig is claimed to have superior effectiveness and inferior safety compared to ‘placebo’ in treatment of patients with MMN.”

## A.9. SUMMARY OF THE PICO

The guiding framework of a PICO Confirmation is recommended by MSAC for each assessment. The PICO Confirmation describes current clinical practice and reflects the likely future practice with the proposed medical service.

The summary PICO from the PICO Confirmation is presented in Table 7.

**Table 7: Summary of PICO**

| Component    | Description  |
|--------------|--|
| Population   | Patients diagnosed with MMN who are currently eligible for the use of intravenous Ig treatment in Australia according to ‘ <i>The Criteria V3 for the clinical use of immunoglobulin in Australia</i> ’.   |
| Intervention | Intravenous Ig.  |
| Comparator   | The comparator is No Ig with BSC.  |
| Outcomes     | <p>The outcomes listed below are those identified as relevant in the development of the PICO Confirmation. The outcomes identified are:</p> <p><b>Safety outcomes:</b></p> <ul style="list-style-type: none"> <li>• AEs including hypersensitivity reactions, fall in blood pressure with anaphylactic reaction; thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism, deep vein thromboses; acute renal failure; anaphylaxis, veno-occlusive events.</li> </ul> <p><b>Clinical effectiveness outcomes:</b></p> <ul style="list-style-type: none"> <li>• Disease remission;</li> <li>• Change in motor muscle weakness;</li> </ul> |

| Component | Description   |
|-----------|---|
|           | <ul style="list-style-type: none"> <li>• Change in disability<sup>a</sup>;</li> <li>• Change in quality of life (QoL);</li> <li>• Quality adjusted life year.</li> </ul> <p><b>Healthcare system resources utilisation as identified in the Referral</b></p> <ul style="list-style-type: none"> <li>• Changes in health system resource utilisation associated with the intervention compared to the comparator for the following: <ul style="list-style-type: none"> <li>○ Intravenous Ig products;</li> <li>○ Other therapies used in patients with progressive MMN;</li> <li>○ Infusion equipment;</li> <li>○ Administrative and clinician time (e.g. resources associated with requesting, and authorising, access to Ig);</li> <li>○ Nursing time (for treatment initiation and monitoring of intravenous Ig);</li> <li>○ Hospitalisation (including use of hospital resources);</li> <li>○ Additional treatments used for the occurrence of adverse events (e.g. analgesia or antihistamines);</li> <li>○ Product dispensing and disposal of any unused product;</li> <li>○ Follow-up and/or monitoring visits, including regular neurology visits;</li> <li>○ Disability support services;</li> <li>○ Home nursing and support needs.</li> </ul> </li> </ul> |

Abbreviations: AE= adverse events; BSC = best supportive care; Ig= immunoglobulin; MMN = multifocal motor neuropathy; ONLS= Overall Neuropathy Limitations Scale.

Note: <sup>a</sup>Different disability tools were used in the randomised trials to assess the efficacy of intravenous Ig in MMN: the Norris scale, modified Rankin scale, modified NDS, GNDS, ODSS, VAS and other self-evaluation scales. More recently the Rasch-built Overall Disability Scale has been developed specifically for MMN.

## A.10. CONSUMER IMPACT STATEMENT

Targeted feedback was sought in August 2019 from stakeholders including consumer groups, clinicians and sponsor companies to assist in developing the PICO Confirmation. Responses were received from one clinician and two sponsor companies. Sponsor companies considered intravenous Ig to be a safe and effective treatment for patients with MMN, and therefore would not encourage further limitation to access of intravenous Ig based on the current level of evidence. Clinician feedback indicated that the treatment algorithm was reasonable for commencement, but that data on the rates of continuation would be valuable to the review considering that continuation rates as expected from RCTs seldom match actual rates of continuation.

No feedback from consumer groups was available at the time of the elaboration of this second draft report.

### Sponsor Consultation

Sponsors were asked to provide input to the Contracted Assessment in regard to evidence of safety efficacy and utilisation that may inform the health technology assessment (HTA).

Sponsors of intravenous Ig were contacted by the Department and given the opportunity to provide input. Intravenous Ig feedback to the PICO confirmation report was provided from two sponsors on

27 November 2019 for consideration in the development of this report. The summary of the main issues is presented in Table 8.

**Table 8. Feedback provided by Sponsors on the PICO Confirmation**

| <b>Issue</b>   | <b>Sponsor's feedback</b>  |
|--|--|
| Reliability of the prevalence source by Cats et al 2010(14).                     | Reported estimate of 0.6 cases per 100,000 persons represents an underestimate   |
| Funding of SCIg for the treatment of MMN   | Noted there was available evidence from a randomised controlled trial that supports its use in MMN patient population.   |
| The impact of implementation of The Criteria V3 on average duration of treatment | Acknowledged the potential impact. Noted the potential impact has to be evaluated after a longer time following the implementation than what was currently available (6 months). |
| Intravenous Ig dosing and potential for leakage                                  | Disagreed, given the changes implemented to The Criteria V3 and the nationwide availability of BloodStar.  |
| Intravenous Ig pricing   | Suggested using weighted average price for all available Intravenous Ig products in the economic evaluation and financial impact analyses.                                       |

Abbreviations: Ig = immunoglobulin; MMN = multifocal motor neuropathy; SCi = subcutaneous immunoglobulin; V3 = version 3.

## SECTION B

## CLINICAL EVALUATION

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### B.1. LITERATURE SOURCES AND SEARCH STRATEGIES

The medical literature was searched in October 2019 to identify relevant studies and systematic reviews published during the period 1946 (inception of databases) to 11 October 2019. The complete search strategy is presented in Appendix B while the summarised terms are presented in Table 9.

**Table 9. Search terms used (Embase, Ovid Medline, Pubmed, the Cochrane library and clinical trials.com platform)**

| Element of clinical question | Search terms   |
|------------------------------|--|
| Population                   | Patients diagnosed with multifocal motor neuropathy  |
| Intervention                 | Immunoglobulin/Intravenous immunoglobulin  |
| Comparator                   | No immunoglobulin/ placebo   |
| Outcomes                     | Clinical effectiveness, safety and quality of life.  |
| Limits                       | Human beings<br>Studies published in English<br>1946 to 11 October 2019; 1974 to 11 October 2019 |

### B.2. RESULTS OF LITERATURE SEARCH

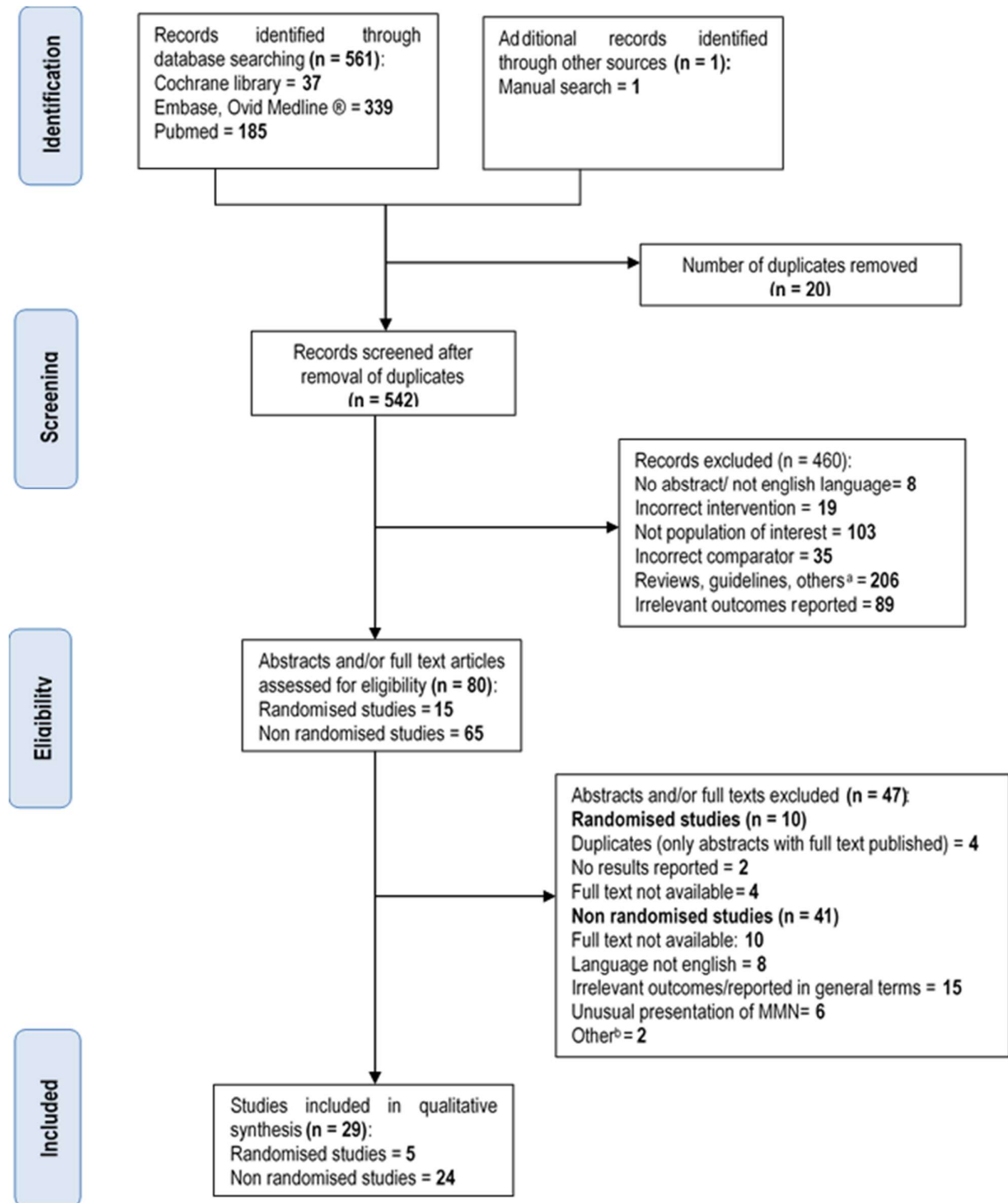
A PRISMA flowchart is provided in Figure 5 and shows the process used in identifying results of the literature search. Studies were selected independently by two reviewers. Disagreements regarding study selection were resolved by discussion between the two reviewers on the merits for including/excluding studies in the final review.

Studies assessed for eligibility were mainly excluded if:

- Duplicate publications of the same trial;
- Full text was not available;
- Irrelevant outcomes were reported (mainly identified in single arm studies that aimed to assess diagnostic features of MMN, focused on molecular parameters of MMN, economic evaluations not relevant to MMN, cost studies and disability tool validation studies);
- Incorrect intervention and/or comparator;
- Case studies targeting a non-typical presentation of MMN (e.g. pregnant women with MMN, cases with rapid onset of the disease).
- Single arm studies that reported outcomes in a general way only (e.g. if it did not provide a definition of the outcome).



Figure 5. Summary of the process used to identify and select studies for the assessment



Note: <sup>a</sup>Letters to the editor, comments, survey; <sup>b</sup>one study was not the most updated version and one assessed the wrong intervention (dexamethasone)

A total of 29 studies were included in the final review, 5 randomised controlled studies (RCTs) and 24 single arm studies.

The overview of relevant RCTs identified in the literature review included in the assessment is presented in Table 10.

**Table 10. General characteristics of studies**

| Study                         | Study title  | Study design   | Patient population   | Number        | Intravenous Ig dose | Comparator  | Follow-up | Primary outcome   | Secondary outcomes  | Time point of outcome assessment           |
|-------------------------------|--|--|--|---------------|---------------------|---|-----------|---|---|--|
| Azulay et al. 1994 (24)       | Intravenous Ig treatment in patients with motor neuron syndromes associated with anti-GM1 antibodies: A double-blind, placebo-controlled study | Double-blind, placebo-controlled, cross-over trial               | MMN with CB and LMNS patients associated with high titre of anti-GM1 antibodies.                                 | 5 MMN; 7 LMNS | 0.4 g/kg/d          | Saline solution. Patients were cross over after 8 weeks | NR        | Disability (change in disability)<br>Muscle strength (improvement in muscle strength)                                 | Motor nerve conduction velocity   | 28 days (1 month) after the last treatment |
| Van den Berg et al. 1995 (25) | Treatment of MMN with high dose intravenous Ig: a double blind, placebo controlled study   | Open trial followed by a single patient double blind placebo RCT | Patients with MMN with CB  | 6             | 0.4 g/kg/d          | Pasteurised plasma solution                             | NR        | Disability (improvement in disability scale)<br>Muscle strength (improvement in muscle strength)                      | Motor nerve conduction block  | Different time points; between 2-6 weeks   |
| Federico et al. 2000 (26)     | MMN improved by intravenous Ig: Randomised, double-blind, placebo controlled study   | Double-blind, placebo controlled, cross-over trial               | Naïve patients with asymmetric lower motor neuron syndrome with no sensory or bulbar signs and partial CB (>30%) | 16            | 0.4 g/kg/d          | 5% dextrose or 0.9% saline                              | NR        | Disability (change in NDS in response to Intravenous Ig treatment)<br>Maximal grip strength (improvement in strength) | Motor nerve conduction block (change in conduction block)   | 28 days (1 month) after the last treatment |
| Leger et al. 2001 (27)        | Intravenous Ig therapy in MMN. A double blind, placebo-controlled study  | Double-blind, placebo controlled cross over trial                | Naïve and previously treated patients.   | 19            | 0.5 g/kg/d          | 1% human albumin, lyophilized once a month for 3 months | 7 months  | Muscle strength (responder or non-responder to Intravenous Ig treatment)  | Self-evaluation scale to assess five motor activities of daily living<br>Change in conduction block | 28 days (1 month) after the last treatment |

| Study                 | Study title                                | Study design   | Patient population                                | Number | Intravenous Ig dose                     | Comparator  | Follow-up            | Primary outcome  | Secondary outcomes   | Time point of outcome assessment   |
|-----------------------|--|--|---|--------|---|---|----------------------|--|--|--|
| Hahn et al. 2013 (28) | A controlled trial of Intravenous Ig n MMN | Phase III randomised withdrawal, double-blind, placebo-controlled, cross-over study. | Probable or definite MMN, all previously treated. | 44     | 0.4 – 2g/kg body weight every 2-4 weeks | 0.25% human albumin with normal saline from BUMINATE 25%, or human albumin 200g/l Baxter solution for infusion. . | 335 days (11 months) | Disability in the upper limb portion (deterioration according to the upper limbs section of GNDS)<br>Maximal grip strength in the more affected hand (increased maximal grip strength) | Anti-GM1 titres<br>Decline of ≥30% in grip strength in the more and less affected arm<br>Maximal grip strength in the less affected arm<br>Overall disability sum score (increased ODSS of at least one grade represent a clinically relevant worsening of disability)<br>Time required for 9-hole board test with the dominant and non-dominant hand<br>Patient global impression of change score<br>Visual analogue scale of disability<br>Safety and tolerability | Day 8 (±1 day) for a 2-week treatment interval and day 15 (±2 days) for a 3 or 4-week treatment interval |

Abbreviations: CB = conduction block; d = day; g = gram; GNDS = Guy's Neurological Disability Score; Ig = immunoglobulin; Kg = kilogram; LMNS = lower motor neuron syndrome; MMN = multifocal motor neuropathy; MRC = medical research council; NDS = neurologic disability scale; RCT = randomised controlled trial.

MMN is a rare disease and consequently the RCTs included in the final review (24-28) tend to recruit small numbers of patients which may lead to potential uncertainties when estimating the treatment effect. In addition, the study follow-up periods are limited which may not reflect the long-term outcomes. The literature search showed that there are a number of single arm studies, some retrospective and some prospective, some of which provide evidence on the treatment effect in both induction and maintenance phases of treatment. Although prone to bias, these single arm studies are an important form of research evidence that may be used to obtain potentially relevant data in the context of HTA, in particular in a disease like MMN. For this reason, this section presents separately both RCTs and single arm open label studies.

A profile of each included study is provided in Table 50 and Table 51, with study characteristics summarised in a shorter format in Section B.4.

### **APPRAISAL OF THE EVIDENCE**

Appraisal of the evidence was conducted in 4 stages:

Stage 1: Appraisal of the risk of bias within individual studies included in the review.

Stage 2: Rating the overall quality of the evidence per outcome, across studies, based on the study limitations (risk of bias), imprecision, inconsistency of results, indirectness of evidence, and the likelihood of publication bias. This was done to provide an indication of the confidence in the estimate of effect in the context of Australian clinical practice (Table 53).

- For RCTs, the Risk of Bias 2 (RoB 2) Cochrane tool was used to assess the quality and reliability of the evidence.
- For single arm studies, some of which were case reports, the Institute of Health Economics (IHE) check list was implemented. This checklist was considered adequate as it evaluates the quality of both non randomised single arm studies as well as case reports.

Stage 3: Extraction of the pre-specified outcomes for this assessment, synthesising (meta-analysing or a narrative synthesis) to determine an estimate of effect per outcome. A meta-analysis was conducted to estimate the pooled effect for the outcomes of disability (improvement and mean change) and improvement in muscle strength.

Stage 4: Integration of this evidence for conclusions about the net clinical benefit of the intervention in the context of Australian clinical practice (Sections B.6).

### B.3. RISK OF BIAS ASSESSMENT

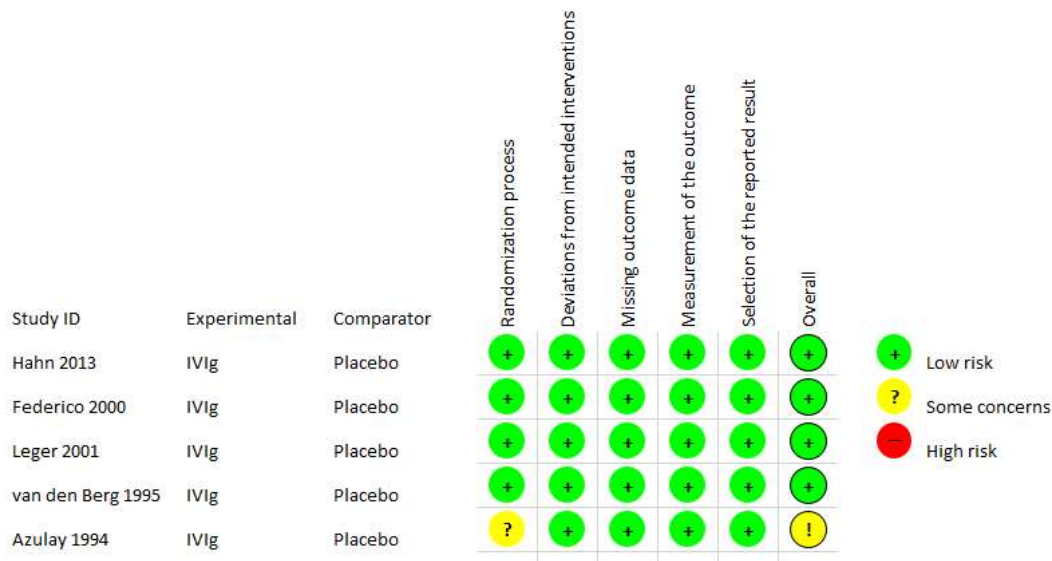
#### RANDOMISED STUDIES

All five RCTs reported some benefit associated with the use of intravenous Ig, however these results should be interpreted with caution because of the limited number of patients in each study, the limited follow-up and the cross-over study design. The latter means that patients randomised to receive the intervention or placebo were later crossed-over to the respective comparator arm at some point in the study. The reported treatment effect could then be affected by the fact that the placebo arm still received the intervention at some point during the study. Detailed risk of bias assessment of these studies is presented in Table 53 of Appendix D. Overall, the studies included in the review had a low risk of bias (Figure 6).

Only Federico et al. 2000 and Hahn et al. 2013 provided an explicit statement on how randomisation of patients was conducted (26, 28). Two other studies (25, 27) stated that randomisation occurred but did not provide any details on the randomisation method. On the other hand, Azulay et al. 1994 did not mention any form of randomisation (24). None of the RCTs provided an adequate description of how allocation concealment prior to assignment was ensured.

With the exception of Azulay et al. 1994 and Leger et al. 2001 (Table 10), studies provided sufficient details to assess the blinding of participants and personnel involved in the study (24, 27). All studies had a low risk of attrition and reporting bias mainly due to the low number of patients lost to follow-up and completeness of data and the way outcomes were reported respectively.

Figure 6: Diagrammatic presentation of risk of bias assessment of the five randomised controlled studies



Abbreviations: IVIg= intravenous immunoglobulin

## SINGLE ARM STUDIES

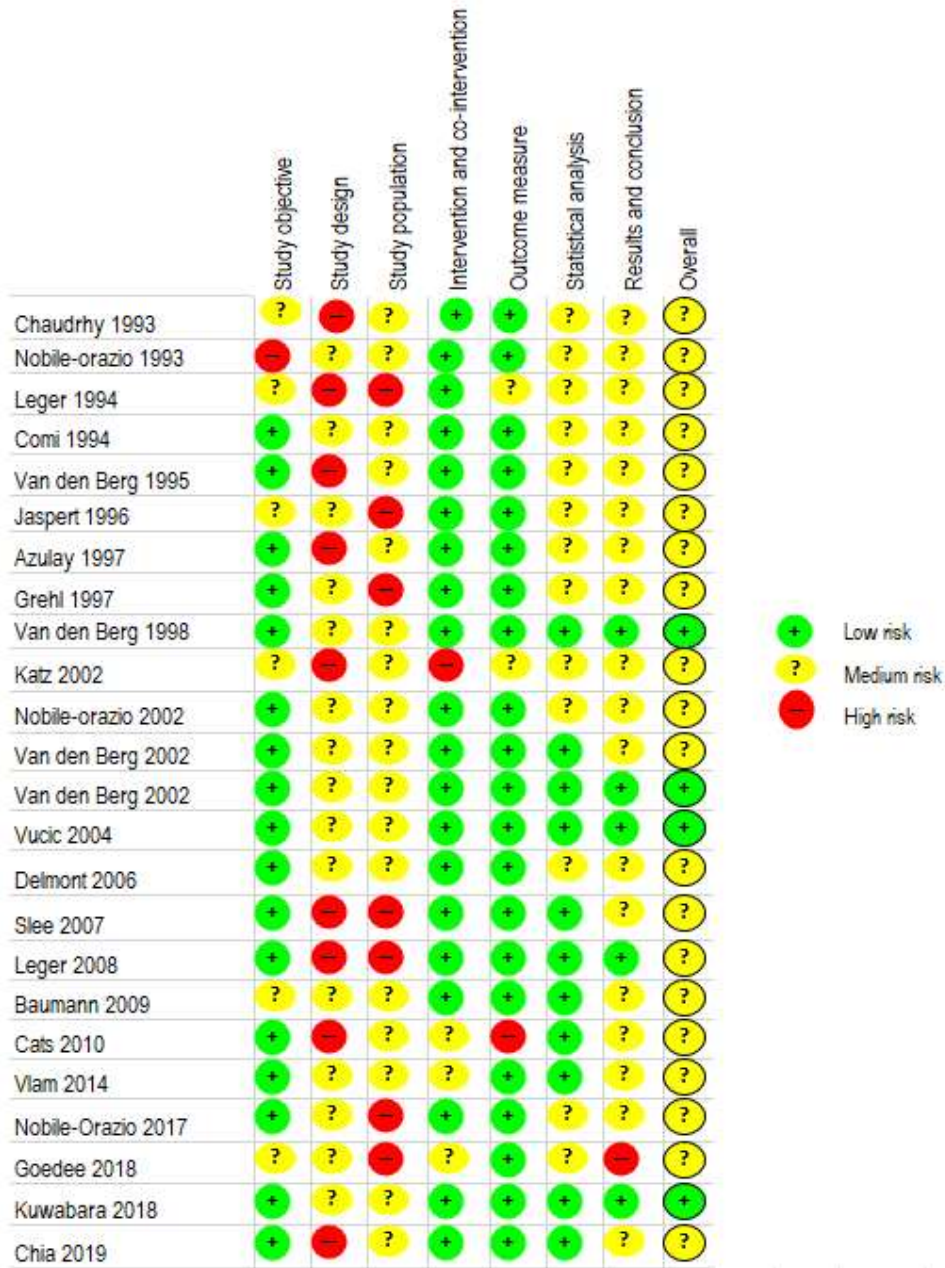
For the implementation of the IHE tool, the following assumptions were taken into consideration:

- Competing interests and sources of support criteria were not considered for consistency with the RoB 2 Cochrane tool.
- Equal weight was assigned for all assessed criteria.
- From a total of 36 points, each study was considered at low risk of bias if the total score was >25, moderate risk of bias if  $\geq 13$  and  $< 25$  and high risk of bias if  $\leq 12$  points. A similar scoring system was used to establish the levels of risk for each section of the studies assessed for bias.

The IHE checklist evaluates the quality of studies under seven categories, each with sub questions: study objectives, study design, study population, intervention and co-intervention, outcome measure, statistical analysis and results and conclusions. Of the 24 studies assessed, 20 were found to be at moderate risk of bias and 4 were found to be at a low risk of bias (29-32) (Figure 7). In general, the biggest source of bias was related to study design and study population. The outcome measures were generally established a priori, estimated using appropriate measures and clearly reported before and after the intervention was implemented.

It is acknowledged that the trial design has several limitations that may limit the interpretation of the results, mainly because not having a comparator arm does not distinguish between the treatment effects, a placebo effect or what could be explained by the natural history of the disease. However, this study design is a good alternative when the pool of patients is low, like in MMN, and thus randomisation poses additional challenges.

Figure 7. Diagrammatic presentation of risk of bias assessment of the 24 single arm studies



#### B.4. CHARACTERISTICS OF THE EVIDENCE BASE

##### RANDOMISED STUDIES

A summary of the features of the included RCTs is presented in Table 11 (see Table 51 Appendix C for details on the individual studies). Four of the five studies were published in the period between the mid-90s and early 2000s and all measured improvement in muscle strength and improvement in disability. All the five studies had placebo as their comparator, however, some differences were identified in the type of formulations used (Table 10). The RCTs did not provide any description of



additional services that could be considered for the management of the disease (BSC) other than active treatment with intravenous Ig. It is uncertain whether the placebo group from the RCTs would be reflective of BSC as available in Australia and accounted for in the economic model in Section D.

The main differences within the studies were the tools used to measure the clinical outcomes which may lead to difficulties in the interpretation of overall results. All studies had a cross-over design, where patients treated with the intervention were then switched to the placebo and vice-versa. In addition, all studies enrolled patients who had at least some evidence of existing CB. It should also be noted that two out of five patients in Azulay et al. 1994 (24) had sensory impairment which could currently correspond to a differential characteristic with the diagnosis of MND and hence not fulfil the current diagnostic criteria for MMN (Table 11).

**Table 11. Key features of the included evidence from RCTs comparing intravenous Ig with placebo**

| Trial/Study                         | N             | Design/ duration  | Risk of bias | Patient population  | Key outcome(s)   |
|-------------------------------------|---------------|---|--------------|---|--|
| Azulay et al. 1994 (24)             | 5             | R, DB/<br>56 days (1.84 months)   | Some concern | MMN with CB associated with high titre of anti-GM1 antibodies.  | <ul style="list-style-type: none"> <li>• Change in disability;</li> <li>• Improvement in muscle strength.</li> </ul>   |
| Van den Berg et al. 1995 (25)       | 6             | OL, followed by R, DB/<br>26 months   | Low          | Patients with MMN with CB.  | <ul style="list-style-type: none"> <li>• Improvement in disability scale;</li> <li>• Improvement in muscle strength.</li> </ul>  |
| Federico et al. 2000 (26)           | 16            | R, DB, MC/<br>Not reported  | Low          | Naïve patients with asymmetric lower motor neuron syndrome with no sensory or bulbar signs and partial CB (>30%). | <ul style="list-style-type: none"> <li>• Change in disability using the NDS;</li> <li>• Improvement in maximal grip strength.</li> </ul>   |
| Leger et al. 2001 (27)              | 19            | R, DB/<br>7 months  | Low          | Naïve and previously treated patients with persistent CB.   | <ul style="list-style-type: none"> <li>• Improvement in muscle strength;</li> <li>• Overall response;</li> <li>• Self-evaluation score.</li> </ul>                                       |
| Hahn et al. 2013 (28)               | 44            | R, OL followed by DB, MC/<br>335 days (11.01 months)  | Low          | Probable or definite MMN, all previously treated and with definite CB.  | <ul style="list-style-type: none"> <li>• Change (deterioration) in disability in the upper limb portion;</li> <li>• Increased maximal grip strength in the more affected arm.</li> </ul> |
| <b>Meta-analysis</b>                |               |   |              |   |  |
| Improvement in disability           | N=60<br>k = 2 | Random effect model; overall pooled analysis and heterogeneity analysis presented.                    |              |   |  |
| Mean change in disability           | N=58<br>k = 2 | Random effect model; overall pooled analysis, subgroup analysis and heterogeneity analysis presented. |              |   |  |
| Improvement in muscle strength/grip | N=82<br>k = 4 | Random effect model; overall pooled analysis, subgroup analysis and heterogeneity analysis presented. |              |   |  |
| Mean change in muscle strength/grip | N=58<br>k = 2 | Random effect model; overall pooled analysis and heterogeneity analysis presented.                    |              |   |  |

Abbreviations: CB = conduction block; DB=double blind; Ig=immunoglobulin; k = number of studies included in the meta-analysis; N = number of patients included in the study or meta-analysis; MC=multi-centre; MMN = multifocal motor neuropathy; OL=open label (unblinded); R=randomised.

All five RCTs had similar baseline patient characteristics: adults, mainly males and with a wide range of duration of symptoms Table 12. All studies had a mix of patients who had been previously treated and naïve patients which may also complicate the interpretation of results. Only Leger et al. 2001 (27) divided the patients in groups, those who had never been treated with intravenous Ig and those who had presented with recurrent symptoms after successful treatment with intravenous Ig. However, that latter analysis was not presented within the main trial results for the outcomes ‘improvement in muscle strength’ and ‘self-evaluation score’.

**Table 12. Baseline demographic characteristics of RCTs**

| Characteristics of patients                             | Intravenous Ig arm | Placebo arm       |
|---|--------------------|-------------------|
| <b><sup>a</sup>Azulay et al. 1994(24) (n = 5)</b>       |                    |                   |
| Mean age at onset (range)                               | 48.4 (41 - 63)     |                   |
| Gender male, n (%)                                      | 4 (80)             |                   |
| Duration of symptoms (mean years)                       | 6.07               |                   |
| Mean baseline disability (Norris scale)                 | NR                 |                   |
| Presence of conduction block                            | Yes                |                   |
| Previously treated/treatment naïve                      | NR                 |                   |
| <b><sup>a</sup>Van den Berg et al. 1995(25) (n = 6)</b> |                    |                   |
| Mean age  | 47 (NR)            |                   |
| Gender male, n (%)                                      | 4(67)              |                   |
| Duration of symptoms (mean years)                       | 6                  |                   |
| Mean baseline disability (modified Rankin scale)        | 2                  |                   |
| Presence of conduction block                            | Yes                |                   |
| Previously treated/treatment naïve                      | NR                 |                   |
| <b>Federico et al. 2000(26) (n = 16)</b>                |                    |                   |
| Mean age (SD)   | 38.9 (2.8)         |                   |
| Gender male, n (%)                                      | 15 (94)            |                   |
| Duration of symptoms (mean years (SD))                  | 5.3 (1.2)          |                   |
| Mean baseline disability, (SD)                          | 28.6 points (6.3)  | 25.4 points (5.9) |
| Baseline grip strength (SD)                             | 21.9 Kg (3.4)      | 19.7 kg (3.2)     |
| Presence of conduction block                            | Yes                |                   |
| Previously treated/treatment naïve                      | NR                 |                   |
| <b>Leger et al. 2001(27) (n = 19)</b>                   |                    |                   |
| Mean age (SD)   | 57.1 (6.6)         | 51.9 (6.8)        |
| Gender, n (%) male                                      | 7 (70)             | 6 (66.7)          |
| Duration of symptoms (mean years)                       | 9.8 (8.7)          | 8.2 (5.6)         |
| Mean baseline muscle strength (SD) <sup>b</sup>         | 118.4 (11.2)       | 112.9 (19.2)      |
| Mean baseline self-evaluation score (SD) <sup>c</sup>   | 19.1 (2.0)         | 18.7 (2.9)        |
| Presence of conduction block                            | Yes                | Yes               |
| Previously treated/treatment naïve                      | Yes/Yes            | Yes/Yes           |
| <b><sup>a</sup>Hahn et al. 2013 (28) (n = 44)</b>       |                    |                   |
| Mean age (SD)   | 51.64 (10.25)      |                   |
| Gender male, n (%)                                      | 32 (72.7)          |                   |
| Duration of symptoms (mean years)                       | NR                 |                   |
| Mean baseline disability (SD)                           | NR                 |                   |
| Previously treated/treatment naïve                      | Yes/No             |                   |

Abbreviations: Ig= immunoglobulins; NR = not reported; SD = standard deviation

Note: <sup>a</sup> Characteristics of patients were not reported according to the two arms of study; <sup>b</sup> muscle strength was measured using the Medical Research Council (MRC) score with a maximum score of 150; <sup>c</sup> the maximum self-evaluation score was 25 (ranged from 0-5 for each five motor activities of daily life).

A summary of the features of the included single arm studies is presented in Table 13. Further details of all 24 included single arm studies is presented in Table 52 in Appendix C. Across the trials, there was no consistency between the trials in the definition of treatment response. In addition, the use of arbitrary cut-offs was used for the assessment of improvement (e.g. 1-2 point improvement in the Medical Research Council (MRC) score or in 1 or 2 muscles examined, 1 point improvement on a ordinal-based composite measure).

### SINGLE ARM STUDIES

Four retrospective studies described MMN patients who had received repeated Ig therapy over several years (1 - 8.2 years), suggesting that intravenous Ig can be considered a long-term treatment

option for MMN patients (19, 30, 31, 33). In these studies, the intravenous Ig regimen and frequency, and treatment response varied among patients. In terms of long-term treatment effect, some studies showed sustained remission (31) and others gradual progression of muscle weakness (19, 30, 33). Some variability was also observed in the studies regarding to continuing dose and frequency of administration such as 1.0 g/kg every 2 to 4 weeks, 2 g/kg every 1 to 2 months, or 1.0 g/kg every 3 weeks. The latter may suggest that the use of intravenous Ig is dependent on patients' condition and response and that lower doses may also be considered effective.

The follow-up period of the single arm studies was also variable with 13 reporting outcomes for a period of at least 1 year (up to a median of 7.25 years and a maximum of 8.2 years). One recent study (34) conducted by Chia et al 2019 in Malaysia (N=11) showed a high response rate at induction after 12 months treatment in both muscle strength (88.9%) and disability (77.8%) outcomes. The proportion of responder patients dropped to 33.3% after a follow-up of 13-24 months while the median duration of treatment was 48.4 (15-156) months. Two of the studies, Van den Berg et al (1998 and 2002) (29, 30) were a follow-up to one RCTs (35).

**Table 13. Summary characteristics of single arm studies**

|  |   |
|--|---|
| <b>Single arm studies</b>                            | Included (n=24); excluded (n=41)  |
| <b>Study designs</b>                                 | Case reports, retrospective studies, prospective open label non randomised studies, cross-sectional studies.  |
| <b>Outcomes</b>                                      | <p><b>Muscle strength</b></p> <ul style="list-style-type: none"> <li>• MRC score</li> <li>• MVIC</li> <li>• Grip strength</li> </ul> <p><b>Disability</b></p> <ul style="list-style-type: none"> <li>• Modified Rankin disability score</li> <li>• Overall Disability sum score (ODSS)</li> <li>• Guy's Neurological Disability Scale</li> <li>• Self-Evaluation Scales</li> <li>• Rasch-built Overall Disability Scale</li> <li>• ONLS disability scale</li> </ul> <p><b>Impact on conduction block</b></p> <p><b>Safety</b></p> <ul style="list-style-type: none"> <li>• Incidence of AEs</li> </ul> <p><b>QoL</b></p> <ul style="list-style-type: none"> <li>• SF-36 questionnaire.</li> <li>• EQ-5D</li> </ul> <p><b>Costs</b></p> <ul style="list-style-type: none"> <li>• Cost- minimisation</li> <li>• Cost of illness</li> <li>• Economic evaluation</li> </ul> |
| <b>Definition of respondents vs. non-respondents</b> | <ul style="list-style-type: none"> <li>• Increase &gt; 30% of the initial strength (total score) was obtained at the end of the study (Azulay et al. 1997);</li> <li>• Improvement by at least 2 points in MRC paresis sum score and (in addition) by at least one point either in the Guy's Neurological Disability Scale or the Individual Disability Score (Baumann et al 2009);</li> <li>• Improvement in muscle strength (defined as an increase of ≥1 MRC grade in at least 2 muscle groups without decrease in other muscle groups) in patients with MMN and disability. More severe weakness was defined as lower MRC sumscore than the median, and more severe disability as a lower than median ODSS score for arms and legs (Cats et al 2010);</li> </ul>  |

|                           |   |
|---------------------------|---|
| <b>Single arm studies</b> | Included (n=24); excluded (n=41)  |
|                           | <ul style="list-style-type: none"> <li>• Improvement of 2 points in MRC Sum Score (MRCSS) or by at least one point in modified Rankin score (mRS) within the first 12 months of treatment (Chia et al 2019);</li> </ul> <p>Overall, no systematic approach to translating statistical significant results (p-value) to clinical relevance of the finding were reported.</p> |

Abbreviations: AEs = adverse events; EQ-5D = Euroqol five dimensions; CB = conduction block; Ig= immunoglobulin; MMN = multifocal motor neuropathy; MRC = Medical Research Council scores; MVIC = Maximal voluntary isometric contraction; ODSS = overall disability sum score; ONLS = overall neuropathy limitations scale; QoL = quality of life.

## **B.5. OUTCOME MEASURES AND ANALYSIS**

Relevant outcomes were extracted from the included studies. It should be noted that outcomes were not measured consistently throughout the studies which could lead to difficulties in aggregating the data and interpretation of the overall results.

### **OUTCOMES FROM RCTS**

The outcomes measured in the included RCTs, along with the statistical methods used to analyse the results are presented in Table 51 Appendix B. The primary outcomes included in these studies were change/improvement in disability and improvement in muscle strength/grip. Four out of the five RCTs reported results for safety. All but one study, Hahn et al. 2013 (28), reported data for change in motor nerve conduction block. Two studies, Leger et al. 2001 and Hahn et al. 2013 (27, 28), also reported self-evaluated disability scores as secondary outcomes.

### **OUTCOMES FROM SINGLE ARM STUDIES**

The outcomes reported in the single arm studies are summarised in Table 52 in Appendix B. Overall, 13 of the 24 assessed single arm studies presented results with a follow-up period beyond 1 year (range from 1 - 7.25 years). While not all studies reported the safety of intravenous Ig, all reported efficacy measures as improvement in disability, muscle strength and/or provided a definition for a treatment responder.

## B.6. RESULTS OF THE SYSTEMATIC LITERATURE REVIEW

### IS IT SAFE?

#### **Summary – What is the comparative safety of intravenous Ig versus No intravenous Ig (BSC) in the treatment of MMN patients?**

Evidence from randomised trials showed that most adverse events (AEs) were mild and mainly typical of infusion reactions like headache, fever and chills. These events are generally characterised as being self-limiting and often resolved by reducing the rate or volume of infusion, or by implementing some preventive measures like prophylactic use of antihistamines. Only one RCT, Hahn et al 2013(28), 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 safety profile did not show important differences between the randomised and single arm studies. Similarly, infusion related AEs were frequent but generally mild and manageable with adjustments to infusion rate. Moderate and serious adverse events (SAEs) were less frequent and few patients discontinued treatment due to AEs.

Intravenous Ig products have been used in patients with MMN since the early 1990s, thus the safety profile is well understood, even with regard to rare events. The safety profile as presented in the Product Information should provide a comprehensive overview and understanding of the occurrence of adverse events, special warnings and precautions for use.

In summary, most AEs are mild and reversible, although the safety profile of intravenous Ig was worse than placebo.

Given that the ‘No IVIg with BSC’ was defined as the comparator, it can be said that the safety of intravenous Ig was worse than its comparator.

#### **Safety evidence from RCTs**

Overall, minor adverse effects were reported in four of the five RCTs (Table 14). Van den Berg et al. 1995(25) did not measure safety as an outcome. Some of the above mentioned AEs may not have been observed during the limited follow-up time of randomised controlled trials. The potential long-term AEs will be assessed from single arm studies.

The frequency of AEs in the RCTs ranged from 1 to 40%, but was usually less than 20%. Most AEs were mild and mainly typical of infusion reactions like headache, fever and chills. Headache was the most commonly reported AE followed by rash and shivering. These reactions are generally characterised as being self-limiting and are often resolved by reducing the rate or volume of infusion, or by implementing some preventive measures like premedication with an analgesics or antihistamines. Only one study, Hahn et al. 2013(28), reported one patient who suffered a serious adverse event due to pulmonary embolism that was attributed to the use of intravenous Ig. The same study also reported two patients who discontinued treatment; one due to muscular weakness and one due to decreased

range of joint motion. However, deterioration in muscle weakness and decreased range of joint motion were not considered a treatment related AE and thus not considered in the intention to treat (ITT) analysis.

**Table 14. 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)  |
|--|----------------------------------|---------------------------|-------------------------|--------------------------|
| <b>Azulay et al. 1994(24)</b>                              |                                  |                           |                         |                          |
| 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)       |
| <b>Van den Berg et al. 1995(25)</b>                        |                                  |                           |                         |                          |
|  | NR                               | NR                        | NR                      | NR                       |
| <b>Federico et al. 2000(26)</b>                            |                                  |                           |                         |                          |
| Total events   | 13/16 (81.2)                     | 1/16 (6.3)                | <b>13 (1.92, 87.99)</b> | <b>0.75 (0.52, 0.98)</b> |
| 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 (-0.0, 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)       |
| <b>Leger et al. 2001(27)</b>                               |                                  |                           |                         |                          |
| Headache   | 3/9 (33.3)                       | 0/9 (0)                   | NE                      | <b>0.33 (0.03, 0.64)</b> |
| 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)       |
| <b>Hahn et al. 2013(28)</b>                                |                                  |                           |                         |                          |
| One or more moderate or severe adverse events <sup>b</sup> |                                  |                           |                         |                          |
| 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)       |

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

Note: Bold text refers to statistically significant; <sup>a</sup>study reported that two patients have cutaneous rash and transient fever, but did not specify if patients were MMN or LMNS; <sup>b</sup>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).

### Safety evidence from single arm studies

Fourteen of the 24 included single arm studies reported safety outcomes (Table 15). 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 (low grade) and were manageable with adjustments to infusion rate. Moderate and SAEs tended to be less frequently reported. Overall, few patients discontinued treatment due to AEs.

**Table 15: Summary of adverse events reported in single arm studies.**

| Study ID                  | N  | AEs (n/N, %)   | Ref  |
|---------------------------|----|--|------|
| Chaudhry et al. 1993      | 9  | <ul style="list-style-type: none"> <li>• Transient headache (7/9, 77.8%)</li> <li>• Nausea 5/9 (55.5%) fever (3/9, 33.3%)</li> <li>• Rigors (1/9, 11.1%),</li> <li>• Diarrhoea (1/9, 11.1%)</li> </ul>   | (22) |
| Nobile-Orazio et al. 1993 | 5  | <ul style="list-style-type: none"> <li>• Mild headache with moderate fever (less than 38 °C) and itching after the first infusion (2/5, 40 %)</li> </ul>   | (36) |
| Jaspert et al. 1996       | 8  | <ul style="list-style-type: none"> <li>• Headache and sickness during the first two treatment cycles (1/8, 12.5%)</li> </ul>   | (37) |
| Azulay et al. 1997        | 18 | <ul style="list-style-type: none"> <li>• Headache, fever, or rash (8/18, 44.4%)</li> <li>• Aseptic meningitis occurred (1/8, 12.5%)</li> </ul>   | (38) |
| Grehl et al. 1997         | 7  | No severe side effects were observed during a total of 529 months of therapy. One patient suffered from headache and nausea for some hours after every intravenous Ig infusion.  | (39) |
| Van den Berg et al. 1998  | 7  | <p>Adverse effects after a full intravenous Ig course were:</p> <ul style="list-style-type: none"> <li>• Rash (2/7, 28.5%)</li> <li>• Headache (2/7, 28.5%)</li> <li>• Fever (1/7, 14.2%),</li> </ul> <p>Adverse effects during continuing intravenous Ig treatment:</p> <ul style="list-style-type: none"> <li>• Rash (2/7, 28.5%)</li> <li>• Headache (1/7, 14.2%)</li> <li>• Leukopenia (2/7, 28.5%)</li> <li>• Fatigue (1/7, 14.2%)</li> </ul> <p>One patient had a maculopapular rash on the trunk and distal limbs and another patient had an eczematous dermatitis on the palmar surface of the hands. In both patients the rash improved substantially after treatment with local corticosteroids but did not clear up completely during intravenous Ig infusions.</p> | (29) |
| Van den Berg et al. 2002  | 11 | Intravenous Ig was well tolerated in all patients over the years and side effects described previously (headache, rash, fatigue) and only caused minor inconvenience.  | (30) |
| Leger et al. 2008         | 40 | 150 adverse effects observed in 32/40 (80%) patients. These were in line with those previously described and only caused minor inconvenience.  | (19) |



| Study ID             | N  | AEs (n/N, %)  | Ref  |
|----------------------|----|---|------|
| Baumann et al. 2009  | 9  | <p>The following AEs were considered SAE: death, all events requiring hospitalization, myocardial infarction, stroke, thrombosis and embolic disease.</p> <p>AEs:</p> <ul style="list-style-type: none"> <li>• Fatigue (5/9, 55.5%)</li> <li>• Headache (4/9, 44.4%),</li> <li>• Nausea (2/9, 22.2%)</li> <li>• Hypertension (2/9, 22.2%)</li> <li>• Vertigo (1/9, 11.1%)</li> <li>• Abdominal pain (1/9, 11.1%)</li> </ul> <p>SAE:</p> <ul style="list-style-type: none"> <li>• Hospitalization due to infection of the IV line with septicaemia (1/9, 11.1%)</li> </ul> <p>Treatment discontinuation due to AEs:</p> <ul style="list-style-type: none"> <li>• Nausea (1/6, 16.6%).</li> </ul> <p>Overall in 35/48 (73%) of intravenous Ig cycles with increased dose at least one side effect was reported; in the 6 months before dose-increase at least one side effect was reported in 5/39 intravenous Ig cycles (13%).</p> | (40) |
| Cats et al. 2010     | 88 | Treatment discontinuation due to AEs: severe erythema and thromboembolic complication (2/88, 2.3%)  | (14) |
| Nobile-Orazio 2017   | 20 | <p>All reported adverse drug reactions (ADR) were mild, transient and possibly related to the study drug:</p> <p>All ADRs (4/20, 20%):</p> <ul style="list-style-type: none"> <li>• Headache (3/20, 15%)</li> <li>• Fever (1/20, 5%)</li> </ul> <p>There were no SAE or unexpected ADRs.</p>  | (41) |
| Kuwabara et al. 2018 | 13 | <p>AEs (12/13, 92.3%):</p> <ul style="list-style-type: none"> <li>• Nasopharyngitis (5/13, 38.5%)</li> <li>• Headache (3/13, 23.1%)</li> <li>• Contusion (3/13, 23.1%)</li> </ul> <p>ADR (9/13, 69.2%).</p> <p>SAEs (3/13, 23.1%), none were considered to relate to intravenous Ig.</p> <ul style="list-style-type: none"> <li>• Coronary artery stenosis (1/13, 7.7%)</li> <li>• Dysphagia (1/13, 7.7%)</li> <li>• Inguinal hernia (1/13, 7.7%)</li> </ul> <p>Treatment discontinuations due to AEs (2/13, 15.3%): dysphagia and decision of the investigator (slight decline of muscle strength).</p> <p>No death occurred during the study.</p>   | (32) |

| Study ID                       | N  | AEs (n/N, %)   | Ref  |
|--------------------------------|----|--|------|
| Not et al. 2012 <sup>1,2</sup> | 30 | <p>At least one adverse effect occurred in 27 patients (90%) representing 183 infusions (43%).</p> <p>The most common AEs:</p> <ul style="list-style-type: none"> <li>Hypertension 24/30 (80%; 131 infusions = 31%) requiring transient antihypertensive therapy in six studies. 80% of these patients did not have prior high blood pressure.</li> </ul> <p>Other minor side effects included:</p> <ul style="list-style-type: none"> <li>Headache 9/30 (30%; 49 infusions: 11.4%),</li> <li>Minor eczema type skin reactions 5/30 (16%, 20 infusions: 4.7%).</li> </ul> <p>SAEs 2/30 (6.6%):</p> <ul style="list-style-type: none"> <li>Acute congestive heart failure in a patient without previous cardiac history (leading to the discovery of non-obstructive cardiomyopathy) 1/30 (3.3%); aseptic meningitis 1/30 (3.3%).</li> <li>Aseptic meningitis 1/30 (3.3%).</li> </ul> <p>Uncatalogued</p> <ul style="list-style-type: none"> <li>Acute renal failure regressive after hydration alone occurred in Tegeline® (normal human immunoglobulin) treated patients 2/30 (6.6%)</li> </ul> | (42) |
| Rizk et al. 2001 <sup>1</sup>  | 1  | <ul style="list-style-type: none"> <li>Case report of non-cardiogenic pulmonary oedema within hours after receiving an infusion of intravenous Ig, a plasma derivative.</li> </ul> <p>Patient recovered spontaneously with only bed rest and nasal oxygen. Given the close temporal association between the intravenous Ig infusion and the onset of respiratory symptoms, the study concluded that this was a case of TRALI.</p>  | (43) |
| Abbas et al. 2018 <sup>3</sup> | NA | <p><b>Early AE:</b></p> <p><b>Mild:</b></p> <ol style="list-style-type: none"> <li>Local Infusion Site Reactions (rare &lt;1%; mild) <ul style="list-style-type: none"> <li>Swelling, bruising, bleeding, pain.</li> </ul> </li> <li>Constitutional Flu-Like Symptoms (common ~15%; mild) <ul style="list-style-type: none"> <li>Tension-type headache, fever, nausea, arthralgia, myalgia, malaise, chills, dizziness, mild hypertension.</li> </ul> </li> <li>Dermatological Reactions (common ~6%; mild-moderate) <ul style="list-style-type: none"> <li>Urticaria, pruritis. Less commonly delayed reactions include alopecia, erythema multiforme or very rarely a severe eczematous rash.</li> </ul> </li> </ol> <p><b>Severe:</b></p> <ol style="list-style-type: none"> <li>Anaphylaxis (very rare &lt;0.01%)</li> <li>Transfusion-Related Acute Lung Injury (very rare &lt;0.01%)</li> <li>Transfusion-Associated Circulatory Overload (very rare &lt;0.01%)</li> </ol>   | (44) |

| Study ID | N | AEs (n/N, %)  | Ref |
|----------|---|---|-----|
|          |   | <p><b>Delayed AE</b></p> <p><b>Severe</b></p> <ol style="list-style-type: none"> <li>1. Thromboembolic Events (rare ~1%, higher if risk factors; severe) <ul style="list-style-type: none"> <li>- Stroke, myocardial infarction, deep vein thrombosis, pulmonary embolism</li> </ul> </li> <li>2. Acute Kidney Injury (rare &lt;1%, higher if risk factors; mild-to-severe) <ul style="list-style-type: none"> <li>- Ranging from subclinical biochemical derangements to severe, fatal renal failure.</li> </ul> </li> <li>3. Aseptic meningitis (rare ~1%; moderate-to-severe)</li> </ol> <p><b>Mild to severe</b></p> <ol style="list-style-type: none"> <li>1. Laboratory Derangements (rare &lt;1%) <ul style="list-style-type: none"> <li>- Haemolysis (mild-to-severe)</li> <li>- Neutropenia (mild)</li> <li>- Pseudohyponatraemia and hyponatraemia (mild)</li> </ul> </li> <li>2. Blood-Borne Infection (very rare &lt;0.01%) <ul style="list-style-type: none"> <li>- Historical reports of hepatitis C transmission.</li> <li>- Theoretical risk of prion transmission is possible</li> </ul> </li> </ol> |     |

Abbreviations: ADR = adverse drug reaction; AEs = adverse events; CI = confidence interval; ID=identification Ig = immunoglobulin; N= number; SAE = serious adverse event; TRALI = transfusion-related acute lung injury.

Notes: <sup>1</sup>Studies providing information about safety excluded from the literature review; <sup>2</sup>The study reported safety of intravenous Ig for patients with demyelinating polyneuropathy; only 4 out of 30 patients had MMN; <sup>3</sup> Study is a systematic literature review of early and delayed complications observed in patients with CIDP (not MMN).

## IS IT EFFECTIVE?

### **Summary – What is the comparative efficacy of intravenous Ig versus No Ig with BSC in the treatment of MMN patients?**

The literature search found five randomised trials that assessed the efficacy in terms of improvement in disability and muscle strength of intravenous Ig compared to placebo (No intravenous Ig with BSC). All five RCTs reported some benefit associated with intravenous Ig, however the results should be interpreted with caution because of the limited number of patients recruited in each study, the limited follow-up and the cross-over study design.

When assessing the efficacy of each clinical effectiveness outcome, mainly being improvement in disability and muscle strength, some difficulties were found in comparing these results because different tools were used to measure the outcome. Only one study (Leger et al. 2001(27)) reported overall response to Ig treatment as an effectiveness measure.

Three of the five studies reported improvement in disability as an outcome measure, but of these only the study by Hahn et al. 2013(28) 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(27, 28) was of RR 1.81 (95% CI 0.74, 4.45), which means that intravenous Ig is superior to placebo, however no statistical differences were found ( $p=0.19$ ). These results were estimated under the assumption that the improvement was independent of the tools used to measure the outcome. Similarly, all five RCTs showed that intravenous Ig compared to placebo, resulted in an improvement in muscle strength but only found to be statistically significant in the study conducted by Hahn et al. 2013(28) (RR = 1.67; 95% CI 1.27, 2.18). The pooled treatment effect of RR 3.51 (95% CI 1.12, 11.05) reflects intravenous Ig being superior to placebo for improvement in muscle strength ( $p<0.03$ ).

The literature search showed that there are a number of single arm studies that provided relevant data on treatment effect. Overall, these studies were low level evidence consisting primarily of case series with generally small numbers of patients. These studies provide a before and after treatment effect which indirectly supports the clinical claim of superiority as suggested by the RCTs.

Most of the studies referred to above, fail to capture how these outcomes, disability and muscle strength, reflect an improvement in the quality of life (QoL) of patients with MMN. In fact, QoL was not measured in the RCTs. From the available single arm studies that reported QoL, it was observed that they all failed to report the baseline pre-treatment and after treatment QoL. The results from the available evidence show wide variability when comparing the mean absolute scores but they were generally consistent in the fact that QoL in patients with MMN was reduced with time, especially in the physical domains.

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.

A pooled analysis of all five RCTs was conducted in a meta-analysis for both outcome measures on effectiveness, disability and improvement in muscle strength/grip. As these outcomes were measured inconsistently across the different trials (mainly disability) a number of assumptions were made for

the meta-analysis. Therefore, this HTA did not use the pooled effect from the meta-analysis for the base case in the economic evaluation due to these inconsistencies and other reasons discussed further in Section B.4 and Section C. The software Revman 5 was used to conduct the meta-analysis using random and fixed effect models. Because the measure of statistical heterogeneity was similar between both models, the results for the random effect model are presented below (the results from the fixed effect model are presented in Appendix F).

Several qualitative aspects need to be considered to assess the poolability of the studies:

- The mean age at diagnosis was consistent for all studies as well as the male/female ratio. In addition, all studies enrolled patients who presented with some degree of CB. Overall, patient's characteristics were considered similar and hence poolable.
- Most studies enrolled patients who were treatment naïve and previously treated (this information was not provided for Azulay et al. 1994 and Van den Berg et al. 1995(24, 25)).
- The time point at which the outcomes were assessed was not consistent across the studies. For instance, the disability assessment was 28 days after the last treatment for three studies (Azulay et al. 1994, Federico et al. 2000 and Leger et al. 2001(24, 26, 27)), between 2-6 weeks in another study (Van den Berg et al. 1995) and day 8 ( $\pm 1$  day) for a 2-week treatment interval and day 15 ( $\pm 2$  days) for a 3 or 4-week treatment interval in the last study (Hahn et al. 2013(28)).
- The overall treatment effects were reported for different follow-up periods: 28 days after last treatment in three studies (Azulay et al. 1994, Federico et al. 2000 and Leger et al. 2001(24, 26, 27)), 1 month to 26 months (1 month for 3 patients, 3 months for 2 patients and 26 months for 1 patient) in one study (Van den Berg et al. 1995(25)) and approximately 48 weeks (11.05 months) after initial treatment in the most recent study (Hahn et al. 2013(28)).
- All five studies used different tools to measure the outcomes (disability and muscle strength). Overall, these tools were considered not comparable. While some studies used a disability specific tool such as the ODSS and NDS, others used self-assessment checklists. For muscle strength, some studies used MRC and others used either a digital/hand-held dynamometer or a computer analyser. A further discussion on the comparability of the tools and how this may impact the overall interpretation of the results, is presented in Table 23, Section C.2.4.

#### **EFFECTIVENESS ON DISABILITY**

The five RCTs used different tools to measure disability: the Norris scale, the modified Rankin scale (mRS), the Neurological Disability score (NDS) the Guy's Neurological disability scale (GNDS) and self-evaluation scales. Three of the five studies reported improvement in disability as an outcome measure, but of these only the study by Hahn et al. 2013(28) found statistically significant differences

(RR = 1.34; 95% CI 1.08, 1.67) (Table 16) between patients receiving intravenous Ig and placebo. Leger et al. 2001(27) was the only study that reported as an outcome measure the overall response to intravenous Ig treatment. This response is a composite of both a self-evaluation scale that captured improvement in activities of daily living (ADL) (disability) and muscle strength using the MRC score. Because improvement in disability (as measured by the self-evaluation scores) and improvement in muscle strength were not reported independently in the trial, it was assumed that the same number of patients who achieved the overall response also achieved improvement in the self-evaluation scale and muscle strength. Leger et al. 2001 also reported as an outcome measure the change (between baseline and month 4) in MRC score and self-evaluation score(27).

**Table 16. Results of disability across randomised controlled trials**

| Study ID                         | Risk of bias  | Intravenous Ig treatment<br>Mean/median<br>(SD/SEM) | Placebo treatment<br>Mean/median<br>(SD/SEM) | Relative risk<br>(95% CI) | Relative difference<br>(95% CI) |
|----------------------------------|---|---|--|---------------------------|---------------------------------|
| <b>Improvement in disability</b> |   |   |  |                           |                                 |
| 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) <sup>a</sup>                             | 2/9(22.2) <sup>a</sup>                       | 3.5 (0.98, 12.48)         | 0.56 (0.17, 0.94)               |
| Treatment naïve patients         | Low   | 2/4 (50) <sup>b</sup>                               | 2/5(40) <sup>b</sup>                         | 1.25 (0.29, 5.34)         | 0.10 (-0.55, 0.75)              |
| Pre-treated patients             |   | 5/5 (100) <sup>c</sup>                              | 0/4 (0) <sup>c</sup>                         | NE                        | 1 (1, 1)                        |
| Hahn et al. 2013 (28)            | Low   | 37/42 (88.1) <sup>e</sup>                           | 27/42 (64.3) <sup>e</sup>                    | <b>1.37 (1.07, 1.76)</b>  | 0.24 (0.06, 0.41)               |
|                                  |   | 39/42 (92.9) <sup>f</sup>                           | 29/42 (69) <sup>f</sup>                      | <b>1.34 (1.08, 1.67)</b>  | 0.24 (0.08, 0.40)               |
| Pooled result                    | <i>RR = 1.81 (95% CI 0.74, 4.45; p value = 0.19)</i>    |   |  |                           |                                 |
| <b>Mean change in disability</b> |   |   |  |                           |                                 |
| 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 <sup>g</sup>                                     | 0 <sup>g</sup>                               | NE                        | NE                              |
| Hahn et al. 2013 (28)            | Low   | 4.09 (0.95) <sup>h</sup>                            | 5.56 (0.84) <sup>h</sup>                     | NE                        | NE                              |
|                                  |   | 73.33 (94.60) <sup>i</sup>                          | 289.93 (96.99) <sup>i</sup>                  | NE                        | NE                              |
| Pooled result                    | <i>RR = -5.04 (95% CI -12.22, 2.14; p value = 0.17)</i> |   |  |                           |                                 |

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.

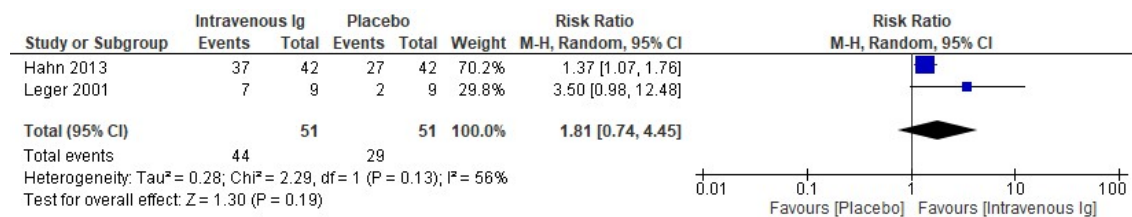
## Results from the meta-analysis

Results from the meta-analyses of the RCTs are presented as forest plots for improvement in disability and mean change in disability (Figure 8 and Figure 9). Previous systematic literature reviews on the use of intravenous Ig for the treatment of MMN considered reasonable to pool results from all available RCTs at the time of the analysis (1), which included the study by Azulay et al. 1994(24). Based on the arguments provided above, but mainly because the diagnosis criteria are not reflective of current practice, this study was excluded from the meta-analysis.

- The pooled treatment effect for the outcome improvement in disability was 1.81 (95% CI 0.74, 4.45), however it did not show a statistical difference ( $p=0.19$ ).
- The  $I^2$  statistic for the improvement in disability outcome represents moderate heterogeneity (45). This index represents the percentage of total variation in study estimates that is due to statistical heterogeneity and reflects the fact that there is some variability in the data.

### a. Improvement in disability

Figure 8. Forrest plot for the outcome improvement in disability using the random effect model.



Abbreviations: CI = confidence interval; Ig = immunoglobulin; M-H = Mantel-Haenszel.

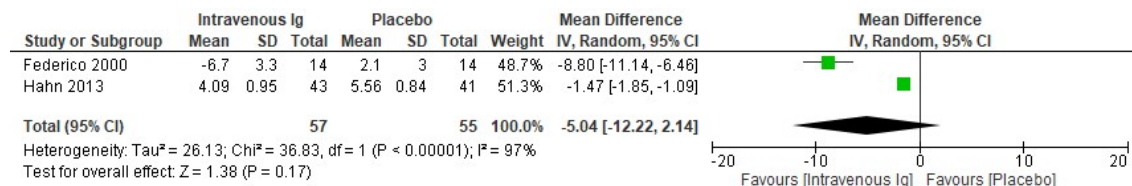
### b. Mean change in disability

Leger et al. 2001 and Hahn et al 2013 were the only studies that directly measured mean change in disability (27, 28), however both using different tools to measure disability (Table 16). Additionally, it should be noted from Hahn et al. 2013(28) that the disability outcomes using the GNDS and ODSS were only analysed as binary variables indicating whether the score of a patient deteriorated from baseline to the last cycle assessment at the end of each blinded period (1 or 2) and not reporting the

mean change. The study only reported mean change in disability using the self-evaluated patient global impression tool which represents the perceived deterioration since the last efficacy assessment. This outcome was used as a proxy for the outcome mean change in disability for the purpose of this analysis.

The estimated pooled treatment effect of -5.04 (95% CI -12.22, 2.14) reflects intravenous Ig being superior to placebo, however no statistical differences were found (p=0.17). The results from this analysis also showed considerable statistical heterogeneity (45). The latter may indicate that the assumptions made to use the self-evaluated patient global impression tool as a proxy to mean change in disability, as per the self-evaluation scale for five motor ADL used by Leger et al. 2001, was inappropriate. Hence, the results for this outcome measure in particular, may not be poolable (27).

**Figure 9. Forrest plot for the outcome mean change in disability using the random effect model.**



Abbreviations: CI = confidence interval; Ig = immunoglobulin; SD = standard deviation

Note: Leger et al. 2001 was excluded because their results were presented as median and not mean difference.

**EFFECTIVENESS MEASURED AS IMPROVEMENT IN MUSCLE STRENGTH**

All five RCTs showed that intravenous Ig compared to placebo resulted in an improvement in muscle strength (see Table 17), although the improvement was only statistically significant in the study conducted by Hahn et al. 2013(28) (RR = 1.67; 95% CI 1.27, 2.18).



**Table 17. Results of improvement and change in muscle strength across RCTs**

| Study ID                                      | Risk of bias  | Intravenous Ig treatment<br>Mean/median<br>(SD/SEM) | Placebo treatment<br>Mean/median<br>(SD/SEM) | Relative risk<br>(95% CI) | Risk difference<br>(95% CI) |
|---|---|---|--|---------------------------|-----------------------------|
| <b>Improvement in muscle strength/grip</b>    |   |   |  |                           |                             |
| 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) <sup>a</sup>                           | 0/16 (0) <sup>a</sup>                        | NE                        | 0.67 (0.46, 0.92)           |
| Leger et al. 2001 (27)                        |   |   |  |                           |                             |
| All patients                                  | Low   | 7/9 (77.8) <sup>b</sup>                             | 2/9(22.2) <sup>b</sup>                       | 3.5 (0.98, 12.48)         | 0.56 (0.17, 0.94)           |
| Treatment-naïve patients)                     |   | 2/4 (50) <sup>c</sup>                               | 2/5(40) <sup>c</sup>                         | 1.25 (0.29, 5.34)         | 0.10 (-0.55, 0.75)          |
| Pre-treated patients)                         |   | 5/5 (100) <sup>d</sup>                              | 0/4 (0) <sup>d</sup>                         | NE                        | 1 (1, 1)                    |
| Hahn et al. 2013 (28)                         | Low   | 40/42 (95.2) <sup>e</sup>                           | 24/42 (57.1) <sup>e</sup>                    | <b>1.67 (1.27, 2.18)</b>  | 0.38 (0.22, 0.54)           |
| Pooled result                                 | <b>RR = 3.51 (95% CI 1.12, 11.05; p value = 0.03)</b> |   |  |                           |                             |
| <b>Mean change in muscle strength or grip</b> |   |   |  |                           |                             |
| Azulay et al. 1994 (24)                       | Some concern  | 103.2 <sup>f</sup>                                  | -1.6 <sup>f</sup>                            | 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 <sup>g</sup>                                      | 3 <sup>h</sup>                               | NE                        | NE                          |
| Hahn et al. 2013 (28)                         | Low   | 3.75 (9.09)   | -31.38 (9.32)                                | NE                        | NE                          |

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.

<sup>a</sup>Subjective rating of patients.

<sup>b</sup>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.

<sup>c</sup>treatment naïve patients

<sup>d</sup>pre-treatment patients

<sup>e</sup>this represent the number of patients who remained stable or improved

<sup>f</sup>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.

<sup>g</sup>reported a median change between baseline score and score at month 4.

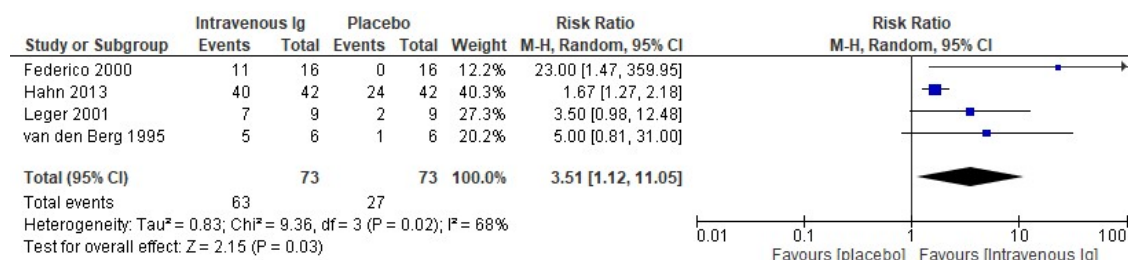
<sup>h</sup>reported a median change between baseline score and score at month 4. This estimate was reported as 1 in the previously published meta-analysis.

### Results from the meta-analysis

The results of the meta-analysis show that there is statistically significant improvement in muscle strength when patients are treated with intravenous Ig compared to placebo.

- Results from the meta-analyses of the RCTs are presented as a forest plot for improvement in muscle strength (Figure 10) comparing intravenous Ig versus placebo.
- The pooled treatment effect of 3.51 (95% CI 1.12, 11.05, p = 0.03) reflects intravenous Ig being superior to placebo in regard to improvement in muscle strength.
- The I<sup>2</sup> statistic for the improvement in muscle strength outcome represents moderate heterogeneity (45) which reflects the fact that there is some variability in the data.

**Figure 10. Forrest plot for the outcome improvement in muscle strength/grip using the random effect model.**



Abbreviations: CI = confidence interval; Ig = immunoglobulin; M-H = Mantel-Haenszel.

## QUALITY OF LIFE

From the clinical evidence presented above and the vast experience in the management of MMN patients with intravenous Ig, we can say that intravenous Ig has demonstrated to be effective in improving muscle strength and disability. However, all these studies fail to capture how these outcomes translate into an improvement in the QoL for patients with MMN.

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 the 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, this additional information allowed for a better understanding of 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, one abstract, one systematic literature review and 8 primary studies were found reporting QoL in patients with MMN (see Table 18) who had been treated with either forms of Ig (intravenous Ig or SCIg). The systematic literature review (46), evaluated the QoL in three chronic inflammatory neuropathies: CIDP, PDN and MMN. Of the studies reported in this review, all of which were identified in the literature search, seven provided some level of evidence of QoL in patients with MMN. Considering the primary studies only (n = 8), four assessed intravenous Ig only and four studies assessed Intravenous Ig and/or SCIg.

**Table 18. List of studies that assessed QoL of patients with MMN treated with intravenous Ig and/or SCIg**

| Author                               | Title   | Intervention comparator               |
|--------------------------------------|---|---------------------------------------|
| Katz et al. 2017 (abstract only)(47) | First Global MMN QoL Patient Survey Identifies Needs in Education and Treatment (P2.061)                                    | Intravenous Ig: 91.43%<br>SCIg: 8.57% |
| Rajabally et al. 2014(46)            | HRQoL in chronic inflammatory neuropathies: A systematic review.  | intravenous Ig and<br>SCIg            |
| Padua et al 2004(48)                 | Intravenous Ig treatment in autoimmune neurological disorders: pilot study on early effects on patients' QoL.               | Intravenous Ig                        |
| Padua et al. 2005(49)                | Intravenous Ig treatment in autoimmune neurological Disorders effects on QoL.   |                                       |
| Harbo et al. 2009(7)                 | SCIg versus Intravenous Ig in MMN: a randomized, single-blinded cross-over trial.   | Intravenous Ig<br>SCIg                |
| Eftimov et al. 2009 (50)             | SCIg therapy for MMN.   | Intravenous Ig<br>SCIg                |
| Misbah et al. 2011(51)               | A smooth transition protocol for patients with MMN going from Intravenous Ig to SCIg: an open-label proof-of-concept study. | SCIg                                  |
| Braine et al. 2012(52)               | A comparison between Intravenous Ig and SCIg.   | Intravenous Ig<br>SCIg                |
| Mahdi-rogers et al. 2013(53)         | Economic costs and QoL in chronic inflammatory neuropathies in southeast England.   | Intravenous Ig                        |
| Bozovic et al. 2019(54)              | QoL in patients with MMN from Serbia.   | Intravenous Ig                        |

Abbreviations: HRQoL = health-related quality of life; Ig = immunoglobulin; MMN = multifocal motor neuropathy; QoL = quality of life; SD = standard deviation; SCIg = subcutaneous immunoglobulin.

Table 19 summarises all primary studies with its corresponding QoL measurement tool, scores and level of significance. The most common QoL assessment tool used was the short version of the SF-36 questionnaire followed by the Life Quality Index (LQI) and the EQ-5D 3L. A common feature of these studies was that none of them reported the baseline pre-treatment QoL characteristics in these patients and how that may compare with normative values.

The overall results presented in Table 19 are variable and show wide discrepancies when comparing the mean absolute scores for the physical component summary (PCS) and mental component summary (MCS) of the SF-36. For example, the results for the PCS in patients treated with intravenous Ig ranged from  $37.0 \pm 6.8$  ( $p = 0.0014$ ) (48, 49) to  $64.8 \pm 22.3$  (54). These differences could be partly explained by differences in disease duration (time since diagnosis), treatment duration and potential differences in the clinical presentation and severity of the disease. However, all studies were consistent in the fact that QoL in patients with MMN was reduced with time, especially in the physical domains. It should be noted that limitations were found in these studies that therefore limits the interpretation of these results. For example, the studies by Padua et al. 2004 and 2005(48, 49), which are two versions of the same study, evaluated changes in QoL in 25 patients with autoimmune neurological diseases treated with intravenous Ig of which only three had MMN. According to Bozovic et al. 2019 ( $n = 17$ ), the arm disability was the most significant factor affecting the QoL which impacted both physical and mental domains (54). Finally, Mahdi-Rogers et al. 2013 estimated the costs and QoL of patients with MMN, CIDP and PDN in the UK who received treatment with intravenous Ig(53). The mean utility scores as per the EQ-5D for MMN patients was 0.72 (SD = 0.14), higher than the mean

score obtained for patients with all three diagnoses (0.65 (SD = 0.16)). It was found that the mean score in patients without intravenous Ig in all three diagnoses was 0.63 (SD = 0.23).

The studies that compared intravenous Ig versus SCIg, analysed QoL as a secondary outcome measure. Harbo et al. 2009 (7) is the only RCT that compared SCIg versus intravenous Ig and assessed HRQoL using the SF-36 questionnaire. This study did not find significant differences in QoL between the dose administration forms. Similar results were observed in a single arm open label study that enrolled 10 patients with definite MMN patients (50). Some differences were found by Braine et al. 2012 (52) between the intravenous Ig and SCIg patient group for the MCS, 84.16% versus 68.02% (p=0.03). Finally, Misbah et al. 2011 (51) measured QoL at screening and week 25 using a questionnaire to evaluate the patients' perceptions on SCIg, the Life Quality Index (LQI), and the Visual Analogue Scale (VAS). This study showed that there was improvement in the total LQI score in 6/8 patients, however baseline and follow-up scores were not presented.

**Table 19. QoL outcome measures in patients with MMN and CIDP.**

| Study                                   | QoL tool             | Intravenous Ig                  | Placebo                         | Significance                |
|---|----------------------|---------------------------------|---------------------------------|-----------------------------|
| <b>QoL studies in patients with MMN</b> |                      |                                 |                                 |                             |
| Padua et al. 2004 & 2005(48, 49)        | SF36 PCS score       | 37.0± 6.8                       | 32.5 ± 7.0                      | p = 0.0014                  |
|   | SF36 MCS score       | NR                              | NR                              | No significant differences. |
| Harbo et al. 2009(7)                    | SF36 PCS score       | 48.9 (95% CI 45.9, 51.9)        | NR                              | No significant differences. |
|   | SF36 MCS score       | 58.4 (95% CI 55.9, 60.9)        | NR                              | No significant differences. |
| Eftimov et al. 2009(50)                 | baseline SF-36 score | 92.2 (SD 14.4)                  | NR                              | NR                          |
|   | baseline LQI score   | 85 (SD 4.0)                     | NR                              | NR                          |
| Misbah et al. 2011(51)                  | LQI improvement      | 6/8 patients                    | NR                              | NR                          |
| Braine et al. 2012(52)                  | SF-36 v2             | 62.18%                          | NR                              | No significant differences. |
|   | LQI                  | 96.0±4.0%                       | NR                              |                             |
| Mahdi-Rogers et al. 2013(53)            | EQ-5D                | 0.72 (SD 0.14) MMN              | NR                              | NR                          |
|   |                      | 0.65 (SD 0.16) (MMN, CIDP, PDN) | 0.63 (SD 0.23) (MMN, CIDP, PDN) | NR                          |
| Bozovic et al. 2019(54)                 | SF-36 score          | 69.2 ± 19.9                     | NR                              | p > 0.05                    |
|   | SF36 PCS score       | 64.8 ± 22.3                     | NR                              |                             |
|   | SF36 MCS score       | 70.0 ± 19.5                     | NR                              |                             |

Abbreviations: CI = confidence intervals; CIDP = Chronic Inflammatory Demyelinating Polyneuropathy; EQ-5D = EuroQol 5 dimensions; HRQoL = health-related quality of life; Ig = immunoglobulin; LQI = life quality index; MCS = mental component summary; MMN = multifocal motor neuropathy; NR = not reported; PCS = physical component summary; PDN = paraproteinemic demyelinating neuropathy; QoL = quality of life; SD = standard deviation; SCIg = subcutaneous immunoglobulin; SD = standard deviation.

### C.1. OVERVIEW

The clinical evidence presented in Section B, suggests that the use of intravenous Ig has superior effectiveness and inferior safety compared to No intravenous Ig with BSC (referred to as placebo in the RCTs) in patients with MMN, hence a cost-utility analysis (CUA) is presented in Section D.

The immunomodulatory effect of intravenous Ig is expected to translate into improved muscle strength, reduced disability and overall improved quality of life. The clinical benefit derived from these outcomes is reflected in the increased time a patient remains stable/maintains improvement, however it does not lead to a cure of MMN. All patients will eventually discontinue treatment and their disease will enter into a slowly progressive disease phase which ultimately will deteriorate their QoL. It should be noted that the administration of intravenous Ig is not exempt of AEs which may also impact the QoL.

Intravenous Ig for the treatment of MMN is already used in Australia and in order to assess the applicability of the available clinical evidence to the Australian setting, the following aspects were considered:

#### **Applicability issues**

1. Are the inclusion/exclusion criteria defined in the randomised clinical trials consistent with the current MMN diagnostic criteria applied in Australia?
2. Is the Ig dosing and frequency of administration schedule in the clinical trials consistent with the current recommendation in Australia?
3. Does the patient profile in the clinical evidence match the demographic characteristics of patients with MMN in Australia?
4. Are the measurement scales used to assess muscle strength and disability in the trial setting consistent with those currently used in Australia?
5. Is the duration of Ig treatment in the clinical evidence consistent with use in the current Australian population?

#### **Extrapolation issues**

If the treatment duration in the trials is less than the expected duration of treatment in the current local setting, the need for extrapolation of the results is to be addressed subject to the following issue:

1. What is the duration of the treatment effect of intravenous Ig in patients with MMN and was the duration of effect expected in the Australian setting captured in the available clinical evidence?

### **Transformation issues**

Finally, because the clinical evidence does not report the clinical outcomes in a way suitable for an economic evaluation (as the combined effect of survival and quality of life; quality adjusted life years – QALYs), the transformation from trial based outcomes to QALYs is to be assessed as a transformation issue as follows:

1. How can the clinical evidence be transformed into a common patient-relevant outcome?
2. What are the sources that provide QoL weights (utility values) to derive QoL for patients with MMN applicable to the Australian context?

## **C.2. APPLICABILITY TRANSLATION ISSUES**

### **C.2.1 INCLUSION AND EXCLUSION CRITERIA VERSUS CURRENT VERSION 3 OF THE CRITERIA**

A summary of the inclusion criteria reported in the trials and Australian setting is presented in Table 20. A consistent difference across all five RCTs and the Australian setting is the inclusion of patients with CB within the clinical trials. The Criteria V3, which is aligned to the EFNS/PNS MMN guideline, states that CB is a characteristic that is typically present in patients with MMN but recognises that it may or may not present. Hence, in the Australian setting, patients diagnosed with MMN may or may not match the inclusion criteria defined in the RCTs. Given there is some evidence suggesting that patients with and without CB show a similar response to Ig treatment (2, 55), it is unlikely that this difference will result in a variation of the treatment effect in the current Australian setting.

Furthermore, it was also found that the RCTs did not take into account the baseline disability of patients as an eligibility criteria for Ig treatment initiation. From the evidence provided, it is unknown whether the patients treated in the trial setting would have the level of disability required in The Criteria V3. In Australia, patients need to present with an ONLS disability score of at least two points to qualify for Ig treatment.

Finally, Azulay et al. 1994 (24) shows two other distinct characteristics relative to the Australian setting: (1) only patients with a high titre of anti-GM1 were included – this is currently considered confirmatory evidence under The Criteria V3 rather than being essential for the diagnosis of MMN and; (2) recruited two patients (40%) who had sensory impairment which would now be considered an exclusion criteria for MMN in Australia. Given the small patient population in this study, this proportion is large enough to result in potential differences in terms of treatment effect when compared to the Australian setting. In contrast, the difference found with the remaining four RCTs, was considered minor hence unlikely to impact the treatment effect.

**Table 20. Differences between the clinical evidence from RCTs and the Australian setting**

|                               | Characteristic   |   |  |   |
|-------------------------------|--|---|--|---|
|                               | Inclusion/Diagnostic criteria  | Exclusion criteria  | Identified difference  | Outcome   |
| <b>Australian setting</b>     |  |   |  |   |
| NBA setting                   | Slowly progressive, asymmetric, predominately distal limb weakness without sensory impairment. Weakness often begins in the arms with a combination of weakness, wasting, cramps and fasciculations. The pattern of weakness follows the distribution of individual nerves (main difference with MND). Patients may or may not show (CB) and be positive for IgM anti-GM-1 antibodies (this is not essential for the diagnosis). Patients are eligible for intravenous Ig if they have a disability score of at least two points using the ONLS. | <ul style="list-style-type: none"> <li>• Presence of upper motor neuron signs;</li> <li>• Marked bulbar involvement;</li> <li>• Significant sensory impairment without an alternative explanation;</li> <li>• Diffuse symmetric weakness during the initial weeks.</li> </ul> | NA   | NA  |
| <b>RCTs Trial setting</b>     |  |   |  |   |
| Azulay et al. 1994 (24)       | Patients with motor neuron syndromes associated with high titre of anti-GM1 antibodies and CB.   | Patients with ALS.  | 2/5 (40%) had sensory impairment which could be a current exclusion criteria. Australian patients may or may not have CB and high titre of anti-GM1. | Differences could alter the interpretation of the treatment effect. |
| Van den Berg et al. 1995 (25) | Patients with progressive asymmetric weakness and atrophy without sensory involvement CB.  | Not reported.   | Australian patients may or may not have CB.  | Differences are unlikely to impact the Tx effect.                   |
| Federico et al. 2000 (26)     | Patients with asymmetric lower motor neuron syndrome with no sensory or bulbar signs and had evidence of partial CB (>30%) in motor nerves but normal sensory nerve conduction studies.  | Patients with ALS, CIDP and PDN.  | Trial patients had at least probable CB (>30%). Australian patients may or may not have CB.  | Differences are unlikely to impact the Tx effect.                   |
| Leger et al. 2001 (27)        | Patients presenting with progressive weakness with multifocal distribution, no bulbar involvement, no upper motor neuron signs and CB confined to motor axons. Fasciculation may also be present. Patients who had not received immune-suppressants and IVIg treatment for 2 months for treatment naïve (newly diagnosed) and 3 months for pre-treated patients with IVIg.   | Patients with severe concurrent medical conditions that might cause neuropathy or interfere with the treatment, were pregnant or were less than 18 years.   | Australian patients may or may not have CB.  | Differences are unlikely to impact the Tx effect.                   |



|                       | <b>Characteristic</b>   |  |  |   |
|-----------------------|---|--|--|---|
|                       | <b>Inclusion/Diagnostic criteria</b>  | <b>Exclusion criteria</b>  | <b>Identified difference</b>   | <b>Outcome</b>                                    |
| Hahn et al. 2013 (28) | Patients diagnosed with probable or definite MMN according to AANEM criteria, and are on a stable regimen of IVIg for ≥3 months at a dose of 0.4-2.0g per kg body weight every 2-5 weeks. | Co-existing neuropathy, Tx with other immunosuppressive agents 3 months prior to enrolment, history of thrombotic episodes, pregnancy, neutropenia, altered hepatic enzymes, certain malignancies, blood products 6 months prior to enrolment. | The AANEM defined definite and probable MMN as presenting with CB. (≥30%). Australian patients may or may not have CB. | Differences are unlikely to impact the Tx effect. |

Abbreviations: ALS = amyotrophic lateral sclerosis; AANEM = American Association of Electro-diagnostic Medicine; ALS = amyotrophic lateral sclerosis; CB = conduction block; IVIg = intravenous immunoglobulin; MMN = multifocal motor neuropathy; NA = not applicable; PDN = paraproteinemic demyelinating neuropathy; Tx = treatment.

### **C.2.2 IVIG DOSING AND FREQUENCY OF ADMINISTRATION.**

A potential translation issue can also occur if the doses and frequency of administration differ between the clinical trial setting and the population of interest. The doses were compared considering the recommended doses in The Criteria V3, those from each RCT and the average dose used per treatment cycle based on the utilisation data provided by the NBA for the period 1 July 2018 – 30 June 2019. The Criteria V3 suggests an initial induction dose of 2 g/kg divided into 2 - 5 doses and a maintenance dose of 0.4–1 g/kg every 2–6 weeks. The latter could be titrated to a maximum dose of 2 g/kg in a 4 week period based on individual response. It should be noted that the aim is to administer the lowest possible dose that achieves the appropriate clinical outcome for each patient.

A summary of the dosing and frequency of administration is presented in Table 21. The administered dose was consistent within the five RCTs, however they did not consider a differentiated induction and maintenance phase of treatment, both of which are recommended in the current Australian setting. This translates into patients from the clinical trial setting likely to have received, overall, higher intravenous Ig doses to those in Australia, which could lead to potential differences in treatment effect. Unlike the other three studies, Leger et al. 2001 and Hahn et al. 2013(27, 28), reflect the fact that there is an assessment treatment period phase where patients are exposed to the intervention/placebo before being catalogued as responders or non-responders and further actions are taken similar to that currently recommended in Australia (lasting 4 months). In addition, Hahn et al. 2013(28) suggests a dose range consistent with that recommended in The Criteria V3 for both the induction and maintenance phase of treatment (0.4–2 g/kg). However, the average monthly dose reported in this trial was 1.17 g/kg compared to the 0.64 g/kg per month as calculated from data provided by the NBA for the 1 July 2018- 30 June 2019 period. This difference likely reflects the lower doses recommended in The Criteria V3 during the maintenance phase and the fact that the aim is to administer the lowest possible dose. Overall, the fact that the RCTs did not differentiate between induction and maintenance dose is unlikely to impact the treatment effect in the Australian setting.

No major differences were identified in regard to the frequency of dosing, which generally lay in the range of 2-6 weeks as recommended in Australia, with Azulay et al. 1994(24) being the exception with dosing frequency set to 8 weeks. These differences are unlikely to impact the treatment effect observed in the RCTs compared to that in the Australian setting.

**Table 21. A comparison of the doses used and frequency of administration recommended in the Australian population for patients treated with intravenous Ig for MMN to that used in the clinical randomised evidence.**

|                               | Dose   | Frequency of dosing   | Monthly dose, g/Kg (SD) | Identified difference   | Outcome  |
|-------------------------------|--|---|-------------------------|---|--|
| <b>Australian setting</b>     |  |   |                         |   |  |
| NBA setting                   | Induction: 2 g/kg divided into 2-5 doses.<br>Maintenance: 0.4–1 g/kg | Induction: only once<br>Maintenance: 2–6 weeks  | 0.64 (NR) <sup>a</sup>  | NA  | NA   |
| <b>RCTs Trial setting</b>     |  |   |                         |   |  |
| Azulay et al. 1994 (24)       | 0.4g/Kg/day for 5 consecutive days.                                  | 8 weeks<br>Patients received two treatment courses.   | NR                      | No differentiated induction and maintenance dosing.   | Differences are unlikely to impact the Tx effect |
| Van den Berg et al. 1995 (25) | 0.4g/Kg/day for 5 consecutive days.                                  | The minimal time interval between two treatment courses was one month. Patients received four treatment courses.                        | NR                      | No differentiated induction and maintenance dosing.   | Differences are unlikely to impact the Tx effect |
| Federico et al. 2000 (26)     | 0.4g/Kg/day for 5 consecutive days.                                  | Overall, all patients received the two treatments (placebo and IVIg) alternatively after 28 days.                                       | NR                      | No differentiated induction and maintenance dosing.   | Differences are unlikely to impact the Tx effect |
| Leger et al. 2001 (27)        | 0.5g/Kg/day for 5 consecutive days.                                  | 4 weeks (once a month) for 3 months. Responders were re-treated for 3 additional months, non-responders were switched to alternate arm. | NR                      | No differentiated dosing but the on treatment phase somehow reflects the assessment for response phase as in Australia. | Differences are unlikely to impact the Tx effect |
| Hahn et al. 2013 (28)         | 0.4 – 2g/kg body weight divided over ≤5 consecutive days.            | Every 2- 4 weeks for 12 week periods (3 open label IVIg and 2 blinded IVIg/placebo periods).  | 1.17 (0.46)             | No differentiated dosing but the on treatment phase somehow reflects the assessment for response phase as in Australia. | Differences are unlikely to impact the Tx effect |

Abbreviations: IVIg = intravenous immunoglobulin; NA = not applicable; NR = not reported; RCTs = randomised controlled trials; Tx = treatment duration.

Note: <sup>a</sup>average per month as per the NBA data provided for the 1 July 2018- 30 June 2019 period (transformation from 0.41 g/kg per episode considering a total of 14.79 episodes per year for the 2019 financial year only).

### C.2.3 PATIENT DEMOGRAPHICS AND SETTINGS

Another potential translation issue arises when the patient demographics show differences that may influence the treatment effect. The aim is to assess how the demographic characteristics of patients treated with intravenous Ig for MMN in the Australian setting differ to those from the clinical evidence. The NBA provided data collected from BloodSTAR which is summarised in Table 22 and this was compared to those reported in the five RCTs. In general, comparable information was only available on age; patients in Australia are generally adults. Other characteristics such as mean weight (that influences the treatment dose) and disease duration (that may influence potential for response) were not consistently reported across the two populations. It is thus not possible to assess whether there are differences in these factors which influence the applicability of the data to the Australian treatment setting.

**Table 22. Demographics of the MMN population as per the RCTs versus the Australian population**

|                               | Age , years (range) | Mean weight, Kg (SD) | Disease duration (SD) |
|-------------------------------|---------------------|----------------------|-----------------------|
| <b>BloodStar</b>              | 59 (5-90)           | 81 (17)              | NR                    |
| <b>RCTs</b>                   |                     |                      |                       |
| Azulay et al. 1994 (24)       | 48.4 (41-63)*       | NR                   | 7.78 (4.5)            |
| Van den Berg et al. 1995 (25) | 47 (NR)             | NR                   | 6.00 (2.1)            |
| Federico et al. 2000 (26)     | 38.9 (NR)           | NR                   | 6.17 (4.8)            |
| Leger et al. 2001 (27)        | 54.6 (40-65)        | NR                   | 9.8 (8.7)             |
| Hahn et al. 2013 (28)         | 51.64 (31-72)       | NR                   | NR                    |

Abbreviations: KG = kilograms; NR = not reported; RCTs = randomised controlled trials; SD = standard deviation.

Note: \*age at onset.

### C.2.4 OUTCOME MEASUREMENT TOOLS

The different ways outcomes were measured may also reflect a potential translational issue if this is not consistent between the trials and current practice. In fact, the tools used to measure the two main clinical outcomes in MMN, muscle strength and disability, differ greatly between the trials and compared to the Australian setting as well. The measurement tools used to measure muscle strength and disability in the RCTs and Australian setting are summarised in Table 23.

The Criteria V3 does not specify a tool for measuring muscle strength however, for disability, the ONLS is recommended. Overall, in the current Australian setting, a patient needs to show an improvement (or remain stable) in terms of muscle strength and show an improvement in the ONLS to become eligible for continuing authorisation of intravenous Ig use. Four of five RCTs reported the effect of intravenous Ig for each outcome measure independently only and not as a composite outcome as it would be assessed in Australia for treatment continuation. Leger et al. 2001 was the only study that classified responders as those patients who had at least 1 more MRC point in two affected muscles plus 1 point less in two ADL (measure of disability) compared to baseline. The difference of this trial with the Australian setting is the disability tool used, a self-evaluation scale versus the ONLS respectively. Hahn et al. 2013, was the only study that used a tool similar to that used in Australia, the ODSS. The ODSS was the first scale designed to assess the limitations of patients with immune-mediated peripheral neuropathies which focused on upper and lower limb functions. The ODSS was

modified to include climbing stairs and running which transformed it into the ONLS. The latter, compared with the modified Rankin scale, the NDS and the GNDS is a more specific tool and would likely identify slight changes in disability compared to the other tools. Because different tools capture different aspects of the disease, it is likely that for the studies by Azulay et al. 1994 (24), Van den Berg et al 1995 (25), Federico et al. 2000 (26, 27) and Leger et al. 2001, those differences could alter the interpretation of the treatment effect in terms of disability compared to that observed in the Australian setting. On the other hand, for the study by Hahn et al. 2013 (28), differences are unlikely to impact the treatment effect in terms of disability.

**Table 23. Measurement tools to assess muscle strength, disability and overall response to treatment in the Australian setting compared to the clinical evidence.**

|                               | Muscle strength   | Disability  | Continuing authorisation/<br>Responder/non-responder  | Outcome  |
|-------------------------------|---|---|---|--|
| <b>The Criteria V3</b>        | Not specified.  | ONLS  | Improvement (after 4 months) or stabilisation (after 16 months) of weakness after previous evidence of deterioration in motor strength (very slow deterioration may occur); AND Improvement or stabilisation of disability as per the ONLS compared to the previous review score. | NA   |
| <b>RCTs</b>                   |   |   |   |  |
| Azulay et al. 1994 (24)       | Average strength (in newtons) of a maximal isometric contraction lasting 10 secs for two selected impaired muscles using a computerized analyser. | Norris scale  | NR  | Differences could alter the interpretation of the treatment effect in terms of disability. |
| Van den Berg et al. 1995 (25) | Hand held dynamometer and the MRC scale.  | Modified Rankin scale   | A patient improved if there was an increase of $\geq 50\%$ in $\geq 2$ muscles without a decrease of at least 25% in $> 1$ other muscle.  |  |
| Federico et al. 2000 (26)     | Maximal grip strength in both hands as measured by a hand dynamometer.  | Modified NDS  | A patient improved if there was improvement in NDS, grip strength and a subjective functional assessment.   |  |
| Leger et al. 2001 (27)        | MRC score.  | Self-evaluation scale scored from 0 (normal) to 5 (impossible) for five motor ADL.    | Responders if they had at least 1 more MRC point in two affected muscles plus 1 point less in two ADL compared to baseline.   | Differences are unlikely to impact the Tx effect in disability.                            |
| Hahn et al. 2013 (28)         | Muscle grip strength measured with a DynEx digital dynamometer.   | GNDS; ODSS; VAS and patient global impression of change at the end of each Tx period. | NR  |  |

Abbreviations: ADL = activities of daily life; GNDS = Guy's Neurological Disability Score; MRC = Medical Research Council scores; NA = not applicable; NDS = neurologic disability scale; NR = not reported; ODSS = overall disability sum score; ONLS = overall neuropathy limitations scale; Tx = treatment; VAS = visual analogue scale.

### C.2.5 TREATMENT DURATION

Finally, an applicability translation issue arises if the treatment duration in the clinical setting differs greatly to that expected in the current Australian population. The Criteria V3 does not specify a maximum duration of treatment, rather it guides treatment based on specific time points of clinical assessment to determine responsiveness and clinical benefit. Given that currently the mean treatment duration is not available from BloodSTAR, the duration reported in the RCTs was compared to that

sourced from single arm studies identified in Section B that reported a follow-up period greater than 1 year and treatment duration as one of its outcomes (Table 24).

The evidence from RCTs reported an intravenous Ig treatment duration that varied from 28 days (24) to approximately 12 months (28). This time period was pre-specified and not conditional on an assessment of treatment response, an important difference with the way intravenous Ig is currently delivered in Australia. Three of the RCTs (Azulay et al. 1994, Van den Berg et al. 1995 and Federico et al. 2000(24-26)) had a trial duration shorter than the current initial treatment phase (induction plus three maintenance cycles) recommended in The Criteria V3 to assess for responsiveness. For these three studies there are likely relevant applicability issues that may limit the interpretation of the reported results to the Australian setting. The trial duration in the Leger et al. 2001(27) study was 7 months but the clinical outcomes were reported for the 4-month assessment, which reflects the time period that currently informs responsiveness to Ig after the initial treatment phase (one induction plus three maintenance administrations delivered in 4 months) in Australia. The median treatment duration in Hahn et al. 2013 (28) was close to a year, however it may still not capture the expected treatment duration in current practice. From long-term single arm studies, it has been observed that the median duration of treatment, could vary from around 2 to 7 years (Table 24).

Overall, the clinical evidence from RCTs and single arm studies was variable and not entirely consistent with the expected duration of intravenous Ig treatment in Australia which limits its applicability to the current Australian population. In addition, none of the reviewed studies considered a weaning off trial phase as recommended in The Criteria V3, where responder patients enter an off-treatment phase until they relapse. Recommendations regarding time point for weaning off-treatment phase may have a direct impact on the total duration of treatment. Neither The Criteria V3 nor the published clinical evidence specify a time point at which this weaning off trial phase would be initiated and how long this phase is likely to last. The Criteria does however ask whether a trial of weaning has been considered each 12 months. For patients who relapse, The Criteria V3 suggests trial of weaning at 24 months in patients who are stable. However, based on expert opinion, it was suggested that it was more common in Australia to assess Ig treated patients for an end of dose effect (i.e. patient demonstrates an improvement in symptoms on the current dose). If the patient demonstrates such an improvement, a weaning off trial would not be recommended. In the case that a patient does not clearly have an end of dose effect (i.e. demonstrate no improvement or deterioration in symptoms (remains stable) on the current dose), weaning may be implemented. Weaning usually consists of a reduction in the actual dose and an increase in the dose interval. Some of these patients may cease treatment, but not all. Overall, if the proportion of patients initiating weaning is low, then it is unlikely that this aspect will have an impact on the overall treatment effect.

**Table 24. IVIg treatment duration from RCTs and single arm studies.**

|                              | Time points for measurement   | Median Tx duration; primary outcome time point.  |
|------------------------------|---|--|
| <b>RCTs</b>                  |   |  |
| Azulay et al. 1994(24)       | 0, 5, 28 and 56 days  | NR; 56 days  |
| Van den Berg et al. 1995(25) |   | Two intravenous Ig and 2 placebo treatments per patient.   |
| Federico et al. 2000(26)     | 1, 5 and 28 days after IVIg administration.   | NR; 28 days.   |
| Leger et al. 2001(27)        | Month 4 and 7.  | NR; 4 months.  |
| Hahn et al. 2013(28)         | Day 8 ( $\pm$ 1 day) of a 2-week treatment interval, and on day 15 ( $\pm$ 2 days) for those treated every 3-4 weeks. | 335 days (double blinded phase, intravenous Ig = 84 (13-91) days and placebo = 28 (7-86) days; 60 weeks. |
| <b>Single arm studies</b>    |   |  |
|                              | FUP duration median (range)   | Median Tx duration; time at discontinuation  |
| Azulay et al. 1997(38)       | 25.3 months (9 months and 4 years)  | 6.3 (range 2-15) <sup>a</sup> infusions every 53 days; NR.   |
| Cats et al. 2010(14)         | NR  | 6 years (0-17); NR.  |
| Chia et al. 2019(34)         | NR  | 48.1 (15-156) months; NR.  |
| Grehl et al. 1997(39)        | NR  | 26 (9-41) months <sup>a</sup> ; NR.  |
| Jaspert et al. 1996(37)      | NR (3 months - 4.5 years)   | 12 (2-32) months <sup>a</sup> ; NR.  |
| Kuwabara et al. 2018(32)     | 52 weeks (NR)   | NR.  |
| Leger et al. 2008(19)        | 2.2 $\pm$ 2.0 years   | At the end of FUP, 68% required periodic IVIg infusions to maintain good clinical condition; NR.         |
| Slee et al. 2007(56)         | 6.4 (1-16) years  | 3 (1-8) years; NR  |
| Terenghi et al. 2004(33)     | 8.2 (5-12) years  | NR; decline occurred after a mean period of 4.8 (3-7) years.   |
| Van den Berg et al. 1998(29) | 2-4 years   | NR; 50% progressed after a mean of 2.1 (1.5-3) years.  |
| Vucic et al. 2004(31)        | 7.25 (3.5-12) years <sup>a</sup>  | 7.25 (3.5-12) years <sup>a</sup> ; NR.   |

Abbreviations: FUP = follow-up period; NR = not reported; Tx = treatment.

Note: <sup>a</sup>mean; italic font represent numbers estimate during the evaluation using data reported in the trial.

### **C.3. EXTRAPOLATION TRANSLATION ISSUES**

#### **C.3.1 TREATMENT EFFECT DURATION**

The economic model in Section D assumes that while patients are receiving intravenous Ig they are stable in their disease and will discontinue treatment if they suffer an AE or if a weaning off trial phase is initiated. On the other hand, if a patient becomes a non-responder or requires treatment discontinuation, it was assumed this patient can only die due to other causes (further discussed in Section D.3).

The treatment duration reported from the RCTs presented in Section B and further described in Section C.2.5 (up to 12 months), does not represent the actual treatment duration likely to be observed in the Australian setting. In fact, it is likely that a responder patient will receive active treatment for many years. The latter means that an assumption needs to be made on how to best model treatment duration as a proxy for how long patients remain stable while on treatment (treatment effect duration) beyond the time period available from the RCTs. Based on the recommendations established in The Criteria V3, the model allows for patients on active treatment to initiate a weaning off trial phase where dose reductions and less frequent dose intervals may be



implemented before a proportion of patients cease treatment (off-treatment). This pathway of care has not been assessed in the available RCTs or single arm studies, hence an assumption had to be made to model the long-term impact of initiating weaning. It was advised by the Ig Review Reference group that MMN patients were rarely weaned, hence it was likely that a proportion of patients will receive treatment for a lifetime. In order to capture the long-term impact of patients that remain stable while on treatment and of patients that initiate weaning but eventually reinstate active treatment, an extrapolation of treatment duration (as a proxy to treatment effect duration) was required.

The effect of extrapolation is to extend the period from which patients derive clinical benefit (and quality of life) from the intervention therefore delaying the transition to the health state of continuing progression. Because it is unknown how patients progress over time, it was assumed that the treatment effect reported by Leger et al. 2001(27) was maintained constant throughout the assessed time horizon. It should be noted that, although extrapolating the treatment effect is likely to better represent the current Australian setting, it introduces a level of uncertainty in regard to the overall accrued health benefits given that some patients stop deriving treatment benefit later over time.

#### **C.4. TRANSFORMATION ISSUES**

##### **C.4.1 TRANSFORMATION OF CLINICAL OUTCOME TO A PATIENT RELEVANT OUTCOME**

###### **Transformation of clinical evidence into a common patient-relevant outcome**

The first aspect to be considered is the way that clinical outcomes were reported in the RCTs and whether these reflect how patients would be assessed in clinical practice in Australia. In fact, the only study that considered responders as a composite outcome, considering both improvement of muscle strength and reduced disability as it would in Australia, was Leger et al. 2001. Although this study used a different tool to measure disability, it was considered the evidence that best captured the fact that clinical response to treatment needs to consider both, disability and muscle strength. For this reason, this study was used in the base case analysis in the economic evaluation (Section D) to model the treatment effect after treatment initiation (4-month treatment phase). Although the study by Leger et al. 2001(27) measured response as a composite outcome as it would in Australia, it may still not capture the patient relevant outcome which is improvement in QoL. In fact, none of the RCTs captured how these clinical outcomes translate into an improvement in the QoL for patients with MMN.

This outcome measure (QoL) was sourced from other single arm studies (see Section B.6). The most commonly used questionnaire to capture potential differences in QoL due to treatment was the SF-36 followed by the LQI. It should be noted that most studies compared different forms of Ig administration (intravenous versus subcutaneous), and not the potential difference between receiving and not receiving Ig therapy. The latter was identified as one potential transformation issue.

### **Sources that provide QoL weights (utility values) to derive QoL for patients with MMN and their applicability to the Australian context**

The outcomes reported in the RCTs (mainly overall treatment response, improved muscle strength, reduced disability and adverse events) require transformation to become informative for an economic model. Because MMN is a disease that does not affect mortality but has an important QoL component, the quality adjusted life year (QALYs) was considered to be an appropriate outcome measure to capture the health benefit associated with the intervention.

A QoL outcome needs to be measured in a suitable way so that, directly or indirectly, the obtained scores can be transformed into utility values suitable for an economic evaluation. From the studies identified in the extended literature search described in Section B.6 (Table 19), only one reported direct utility values derived from using the EQ-5D questionnaire (53). This study evaluated patients with MMN, CIDP and PDN receiving treatment with intravenous Ig. Unfortunately, this study did not report utility values differentiated by diagnosis for when patients were off-treatment. It only reported utility values for MMN patients who received intravenous Ig therapy (0.72), all patients who received intravenous Ig therapy (0.65) and all patients who did not receive Ig therapy (0.63). In comparative terms, the utility value reported for MMN patients was lower than the average population in the UK of 0.86 (SD=0.28) (57) but higher than the score reported for patients with multiple sclerosis (0.55 (SD=0.33)) (58) and patients with Parkinson's disease (0.54 (SD=0.40)) (59).

Overall, all the studies described in Section B.6 did not report the change in QoL in patients before and after initiating treatment with intravenous Ig. For this reason, a manual search to identify studies that measured QoL in conditions similar to MMN that could also be useful to inform utility values to be used in the economic model in Section D, mainly CIDP, PDN and MND (Table 27) was conducted. The latter introduces an additional transformation issue.

The manual search identified three studies of which two were actually additional to the literature search reported in Section B.6 (Table 19). All three studies used the generic instrument EQ-5D to directly derive utility values. McCrone et al. 2003 (60) measured QoL at baseline (no treatment) and at 12 weeks in patients with CIDP who required treatment with intravenous Ig. 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, which has an underlying assumption that patients with MMN have a comparable QoL profile to patients with CIDP.

**Table 25. List of studies that reported QoL outcomes in patients with CIDP.**

| Study                        | QoL tool                    | Intravenous Ig  | Placebo  | Significance                         |
|------------------------------|-----------------------------|---|--|--------------------------------------|
| McCrone et al. 2003(60)      | EQ-5D                       | 0.69  | 0.57   | p = 0.072                            |
| Blackhouse et al. 2010(61)   | General UK population EQ-5D | Utility gains from intravenous Ig (McCrone et al 2003) were added to the background utility values. | Male   | Female                               |
|                              |                             |   | 35-44: 0.91<br>45-54: 0.85<br>55-64: 0.81<br>65-74: 0.78<br>75+ : 0.71 | 0.91<br>0.84<br>0.78<br>0.78<br>0.75 |
| Mahdi-Rogers et al. 2014(53) | EQ-5D                       | 0.62 (SD=0.23)  | NR   | NR                                   |

Abbreviations: EQ-5D = Euroqol 5 dimension; Ig = immunoglobulin; NR = not reported; SD = standard deviation.

The use of these sources to account for the potential for differences in QoL before and after initiating treatment with intravenous Ig in patients with MMN, is prone to uncertainty. The main limitation found was that the source that accounts for the incremental benefit of treatment, targeted patients with CIDP. Differences in QoL are likely to occur in these two patient populations due to the nature and natural history of the disease. In fact, the study by Mahdi-Rogers et al. 2014(53) that enrolled patients with different diagnoses (MMN, CIDP, PDN), identified differences within patients where the average utility for of all three diagnoses (0.65) was lower than the utility value reported specifically for patients with MMN (0.72). This difference could be interpreted as patients with CIDP and/or PDN may have a worse baseline QoL compared to patients with MMN. Due to the potential for uncertainties around these utility estimates, a sensitivity analysis was conducted to assess the potential impact on the results (Section D.6).

### **C.5. RELATIONSHIP OF EACH PRE-MODELLING STUDY TO THE ECONOMIC EVALUATION**

A summary of the pre-modelling studies and their relationship to the model conducted in Section D is presented in Table 26.

**Table 26. Summary of results of pre-modelling studies and their uses in the economic evaluation**

| Section       | Pre-modelling study                                   | Results used in Section D  | Overall impact in the results   |
|---------------|---|--|---|
| Applicability | Inclusion and exclusion criteria                      | <p>Some differences were found between the trial population and the Australian population in all five RCTs, mainly:</p> <ul style="list-style-type: none"> <li>All five RCTs considered the presence of CB within the inclusion criteria which differs to The Criteria V3. Because there is some evidence suggesting that patients with and without CB show a similar response to Ig, it is unlikely that this difference will result in a variation of the Tx effect.</li> <li>RCTs did not take into account the baseline disability as required in The Criteria V3 where patients are required to present with a level of significant disability (ONLS<math>\geq</math>2).</li> <li>Azulay et al. 1994(24) recruited patients who may not be considered MMN under the current diagnostic criteria.</li> </ul> | Overall, the differences were considered minor hence unlikely to impact the treatment effect.   |
|               | Intravenous Ig dosing and frequency of administration | <p>Some dosing and frequency of administration were found between the RCTs and the Australian setting, mainly:</p> <ul style="list-style-type: none"> <li>Induction and maintenance recommended were undifferentiated in the RCTs, which may lead to higher doses used in the clinical trial setting compared to Australia.</li> <li>Hahn et al. 2013(28) suggests a dose range consistent to that recommended in The Criteria V3 for both the induction and maintenance phase of Tx (0.4–2 g/kg). However, the average monthly dose was higher (1.17 g/kg) compared to that as informed by the NBA (0.41 g/kg) for the 2018-2019 period.</li> <li>The biggest difference in frequency was compared to Azulay et al. 1994(24) (8 weeks).</li> </ul>  | Overall differences were unlikely to impact the treatment effect. Potential treatment effect differences could arise from undifferentiated doses in RCTs compared to Australian clinical setting. |
|               | Patients demographics and settings                    | Although the patient characteristics is not available in a consistent manner to facilitate a proper comparison, it is unlikely that any difference would lead to differences in the outcomes of interest.  | Unlikely to impact the treatment effect.  |
|               | Outcome measurement tools                             | <p>The tools used to measure the two main clinical outcomes in MMN, muscle strength and disability, differ between the RCTs and compared to the Australian setting.</p> <ul style="list-style-type: none"> <li>4/5 RCTs reported the effect of intravenous Ig for each outcome measure independently only and not as a composite outcome as it would in Australia to assess for continuance of Tx.</li> <li>Similar to the ONLS (include climbing stairs and running), Hahn et al. 2013(28) used the ODSS. The ODSS compared to, the modified Rankin scale, the NDS and the GNDS is a more specific tool and would likely identify slighter changes in disability compared to the other tools.</li> </ul>  | Differences could alter the interpretation of the treatment effect. The pooled effect was not used in the economic model  |

|                |   |   |  |
|----------------|---|---|--|
|                | Treatment duration  | <p>Tx duration in the clinical setting differs to that expected in the current Australian population, mainly:</p> <ul style="list-style-type: none"> <li>• RCTs showed that Tx duration varied from 28 days to approximately 12 months. This time period was pre-specified and not conditional on an assessment of response, an important difference with the way intravenous Ig is currently delivered in Australia.</li> <li>• 3/5 of the RCTs had a trial duration shorter than the current initial Tx phase (induction plus three maintenance cycles) recommended in The Criteria to assess for responsiveness.</li> <li>• The median Tx duration in Hahn et al. 2013(28) was close to a year, however it may still not capture the expected Tx duration in current practice, which if extrapolated from long term data from single arm studies, could vary from around 2 to 7 years.</li> <li>• None of the reviewed RCTs considered a weaning off trial phase as recommended in The Criteria, which could directly impact the duration of treatment.</li> </ul> | <p>Differences could alter the interpretation of the treatment effect. Assumption on weaning was tested in a SA.</p> |
| Extrapolation  | Treatment effect duration   | <p>The Tx duration reported from the RCTs is unlikely to reflect the actual treatment duration in the Australian setting, hence an extrapolation is required. The treatment effect was kept constant throughout the whole time horizon in order to account for patients that remain as responders (hence stable in their disease).</p>  | <p>Likely to impact the overall results. Different time horizons were tested in a SA.</p>                            |
| Transformation | Transformation of clinical outcome to a patient relevant outcome  | <ul style="list-style-type: none"> <li>• Only one study considered responders as a composite outcome (improvement of muscle strength and reduced disability) as it would in Australia (27). This study was used in the base case analysis of the economic evaluation to model the treatment effect after treatment initiation.</li> <li>• None of the RCTs reported the impact of intravenous Ig on the QoL of patients as secondary outcomes.</li> </ul>   | <p>Unlikely to impact the treatment effect.</p>  |
|                | Sources that provide utility values to derive QoL for patients with MMN and their applicability to the Australian context | <p>MMN is a disease that does not affect mortality but has an important QoL component, hence QALYs were considered the appropriate outcome.</p> <p>Information on QoL in MMN patients is scarce and only available from single arm studies. This information had to be complemented with the incremental utility from CIDP to derive a baseline utility from patients who are not receiving intravenous Ig.</p>   | <p>Likely to impact the overall results. Utility values were tested in a SA.</p>                                     |

Abbreviations: CB = conduction block; GNDS = Guy's Neurological Disability Score; Ig = immunoglobulin; MMN = multifocal motor neuropathy; NBA = National Blood Authority; NDS = neurologic disability scale; QALYs = quality adjusted life year; ODSS = overall disability sum score; ONLS = overall neuropathy limitations scale; QoL = quality of life; RCT = randomised controlled trial; Tx = treatment.

## SECTION D

## ECONOMIC EVALUATION

### D.1. OVERVIEW

The clinical evaluation presented in Section B, suggested that intravenous Ig has superior effectiveness and inferior safety compared to 'No Ig with BSC' in patients with MMN based on the evidence profile presented in Section B.6. The framework used to classify the clinical evidence in Section B so that a decision could be made about the type of economic analysis to undertake in this Section, is presented in Table 27 below.

**Table 27. Classification of the comparative effectiveness and safety of the proposed therapeutic medical service compared with its main comparator and guide to the suitable type of economic evaluation**

| Comparative safety of IVIg | Comparative effectiveness of IVIg |                        |                           |                  |
|----------------------------|-----------------------------------|------------------------|---------------------------|------------------|
|                            | Inferior                          | Uncertain <sup>a</sup> | Non-inferior <sup>b</sup> | Superior         |
| Inferior                   | x                                 | ?                      | x                         | ? Likely CUA     |
| Uncertain <sup>a</sup>     | x                                 | ?                      | ?                         | ? Likely CEA/CUA |
| Non-inferior <sup>b</sup>  | x                                 | ?                      | CMA                       | CEA/CUA          |
| Superior                   | ? Likely CUA                      | ? Likely CEA/CUA       | CEA/CUA                   | CEA/CUA          |

Abbreviations: CEA = cost-effectiveness analysis; CMA = cost-minimisation analysis; CUA=cost-utility analysis; IVIg = intravenous immunoglobulins.

Notes: x = health forgone (at a cost). Under this situation, an economic evaluation is not warranted and the continued use of IVIg should not occur unless there are other supportive factors; ? = reflects uncertainties and any identified health trade-offs in the economic evaluation, as a minimum in a cost-consequences analysis; <sup>a</sup> 'Uncertainty' covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or the comparative safety considerations; <sup>b</sup> An adequate assessment of 'non-inferiority' is the preferred basis for demonstrating equivalence.

Based on this information, a cost-utility analysis was undertaken using data from Leger et al. 2001(27) as the main source of treatment effect (further arguments for the selection of this source are provided in Section C.4.1). Where data was not available and/or not reported by Leger et al. 2001, the model relied on data from Hahn et al. 2013(28) and other non-randomised single arm studies presented in Section B. Detailed information in regard to the model inputs is provided in Section D.4. The base case (Step 2) was generated using a modelled stepped evaluation detailed in Table 28.

**Table 28. Stepped economic evaluation**

| Steps              | Description  |
|--------------------|--|
| Step 1             | Presents a trial-based economic evaluation which spanned the randomised trial time horizon of 7 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.   |

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).

## **D.2. POPULATIONS AND SETTINGS**

The aim of the economic evaluation is to reflect the Australian MMN patient population, hence the modelled patient cohort was assumed to match that represented from the diagnostic criteria and treatment use recommended in The Criteria V3. The current approved indication is as first-line and maintenance therapy and for patients who relapse within six months of commencement of a trial off intravenous Ig in patients who fulfil the diagnostic criteria for MMN. Although the patient demographic characteristics were generally not well reported from the BloodSTAR database, a comparison of Australian MMN patients currently receiving intravenous Ig treatment with patients in the RCTs was presented in Section C.2.3. Based on the literature, it was assumed that more males than females are diagnosed with MMN in Australia (76.3% versus 23.7%) with an average age of 59 years (as per data provided by the NBA). It was assumed that patients diagnosed with MMN in Australia under The Criteria V3 match the patient population from the randomised study conducted by Leger et al. 2001 (27). This means that the treatment effect of intravenous Ig from this study was used in the base case analysis to determine the probability of a patient responding to IVIg after initial and subsequent maintenance treatment.

Based on the BloodSTAR database, a patient in Australia receives, on average, 0.41g/kg of intravenous Ig per treatment episode for MMN. This dose equates to an expected monthly dose of approximately 0.64 g/kg. This dose is consistent with that suggested in The Criteria V3 of 2 g/kg divided into 2-5 doses for the induction phase. This dose is also consistent with that recommended in the randomised clinical trials as described in Section C.2.2, however, the trial dose did not distinguish between induction and maintenance doses, which may result in higher doses used in the clinical trials compared to the Australian setting. The average intravenous Ig dose used in this population as reported by BloodSTAR is consistent with the recommendation from The Criteria V3, which specifies that the lowest possible dose that achieves the appropriate clinical outcome for the patient should be used. Based on this and the fact that there is substantial experience with the use of intravenous Ig in patients with MMN in Australia, the dose reported in the BloodSTAR database was used to capture utilisation in the economic and budget impact model. Although some differences in terms of dosing were found between the Australian setting and the RCTs (Section C.2.2), it was assumed that these would not impact the treatment effect.

In addition, The Criteria V3 does not specify in its recommendations a maximum duration of treatment, rather it guides treatment based on specific time points of clinical assessment to determine responsiveness and clinical benefit. For this reason, the modelled cohort of patients will receive treatment based on probabilities of discontinuation due to adverse events (hence no longer receiving intravenous Ig treatment) and the probability of being a responder and having had initiated a weaning off trial phase. The latter allows for a patient reinitiating treatment with no time limit at a constant probability.

### D.3. STRUCTURE AND RATIONALE OF THE ECONOMIC EVALUATION

A summary of the key characteristics of the economic evaluation is given in Table 29.

**Table 29. 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®   |

Abbreviations: BSC = best supportive care; Ig = immunoglobulin; QALYs = quality adjusted life years; NBA = National Blood Authority. SA=sensitivity analysis.

#### LITERATURE REVIEW

A systematic literature search was conducted in Embase, and Ovid MEDLINE® and Pubmed on 15 October 2019 to identify economic evaluations of intravenous Ig for the treatment of MMN. The aim of the literature search for economic evaluations was to identify relevant information such as model structure, potential health states, type of health states, utility weights and time horizon utilised in published studies to inform the current model.

A detailed literature search strategy is provided in Table 56 of Appendix G. A total of 14 studies were retrieved, none of which evaluated the cost-effectiveness of intravenous Ig for the treatment of MMN. It was agreed to broaden the search terms to identify economic evaluations of the use of intravenous Ig for the treatment of conditions similar to MMN, mainly CIDP, PDN and MND. This search was an updated search of the initial search to include keywords for CIDP, PND and MND plus an additional manual search to identify any possible study that could have been missed.

The extended search for economic evaluation studies on conditions similar to MMN identified four (60-63) studies of CIDP none of which could be used to inform the structure of the model. The literature search was complemented with those studies identified in Section C that assessed QoL.



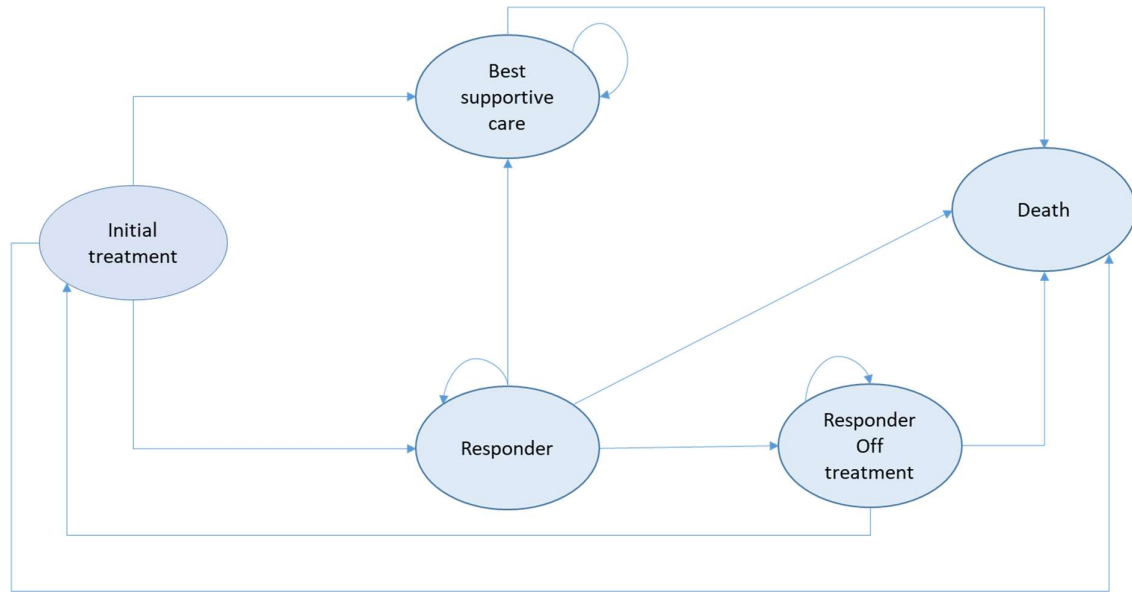
## STRUCTURE OF THE ECONOMIC EVALUATION

In the absence of any relevant economic evaluation applicable to MMN that could inform the current model, a Markov model was developed *de novo* in TreeAge Pro Software 2019 based on the natural history of MMN (refer to Section A.2) to evaluate the cost effectiveness of intravenous Ig therapy compared to BSC for the treatment of MMN. The information provided in The Criteria V3 was used to inform the structure of the Markov model, presented in Figure 11. There are five health states in the model:

1. Initial treatment;
2. Responder;
3. Responder off treatment;
4. Best supportive care (BSC);
5. Death (the absorbing health state).

All patients enter the model once they have been diagnosed with MMN and qualify for intravenous Ig therapy according to The Criteria V3. Once a patient receives the initial treatment phase, which consists of one induction plus three maintenance doses, the patient is assessed by a neurologist who determines whether that patient has responded or not to treatment with intravenous Ig. If responding, the patient transits to the health state 'Responder' while if not responding, the patient transits to the 'BSC' health state. While in the 'Responder' health state, a patient may discontinue due to an adverse event or discontinue because they initiate a weaning off trial phase. A patient in the 'BSC' health state only slowly progresses in their disease. Finally, if a patient initiates a weaning off trial phase, they may remain stable at the 'Responder off-treatment' health state or relapse and require reinitiating active treatment with intravenous Ig transitioning again to the 'Initial treatment' health state. From all health states, patients may die due to other causes which are determined by the Australian Life tables (64).

Figure 11. Decision analytic structure of the economic evaluation.



Notes: arrows represent the direction of each transition probability.

A description of each health state is provided in Table 30. The model compares two scenarios: where intravenous Ig is available (current practice) and BSC only (where intravenous Ig is not available).

**Table 30. Description of health states**

| Health state            | Description   |
|-------------------------|---|
| Initial treatment       | MMN patients who have been newly diagnosed, who have never trialled off from intravenous Ig therapy and/or who have relapsed (within and after six months) following weaning from intravenous Ig therapy. Patients remain here for an adjusted cycle of 4 months.   |
| Responder               | MMN patients who respond to initial treatment (either intravenous Ig or BSC) and remain on treatment. <ul style="list-style-type: none"> <li>• Patients in the intravenous Ig arm who remain on treatment are those who have shown benefit on therapy upon review by a neurologist. Benefit of intravenous Ig therapy is determined considering the clinical effectiveness assessment criteria as outlined in The Criteria V3 of The Criteria for MMN patients on first-line and maintenance therapy and MMN patients who have relapsed within six months of commencement of a trial off intravenous Ig therapy.</li> <li>• Patients in the no Ig with BSC arm who do not deteriorate (i.e. remain 'stable') on BSC after the initial treatment phase were assumed to remain 'stable' with no deterioration for only one cycle (6 months) after which they all transition to the 'BSC' health state.</li> </ul> |
| Responder off treatment | MMN patients who have previously responded to intravenous Ig and have initiated weaning/cessation of treatment. Thus, patients in this health state consist of those who remain in the weaning phase and those who have ceased treatment following weaning. Trial off weaning/cessation is considered annually for patients who are clinically stable to identify those who are in remission for cessation. Patients in the intravenous Ig arm who relapse either during weaning or after cessation of treatment reinstate intravenous Ig and transit back to the 'Initial treatment' health state.   |
| BSC                     | MMN patients who are not receiving intravenous Ig treatment but are on BSC. Patients in this health state include those who have responded to intravenous Ig but discontinue due to an adverse event or patients who have not responded to intravenous Ig or No intravenous Ig with BSC.  |
| Death                   | MMN patients who die from all causes.   |

Abbreviations: BSC = best supportive care; Ig = immunoglobulin; MMN = Multifocal motor neuropathy.

### MODEL ASSUMPTIONS

The economic evaluation was conducted from the perspective of the Australian health care system, hence only direct health care costs were included. MMN patients are assumed to enter the model at age 59 which is the average age of Australian patients receiving intravenous Ig therapy (9). 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. This means that any change to the patient's health state and potential associated costs, would only happen after each biannual follow-up visits. To reflect the duration of the initial treatment period as per The Criteria V3, all associated costs and benefits were adjusted to four months for the 'Initial treatment' health state. All costs and benefits associated with the remaining health states were calculated for a six-month period as per the defined model cycle length. A within cycle correction was applied to the model, where rewards are accumulated by the proportion of patients in a health state both at the beginning and the end of each cycle.

The following assumptions were implemented in the economic model:

- The model does not capture the fact that patients slowly deteriorate overtime because there is no adequate data to model the rate of deterioration in terms of utility values and as per the

natural history of the disease described in Section A. MMN patients that transit to the 'BSC' health state (not receiving active treatment with intravenous Ig) are assumed to have a constant utility associated value throughout the whole time horizon. This means that no decrement in QoL is attached and patients remain with the same baseline utility as when they first transited to that health state. This assumption was tested in a sensitivity analysis in Section D.6 assuming an annual utility decrement based on a study reporting QoL of untreated versus Ig treated patients. The limitations of this source are further discussed in Section D.4 all of which justify why this was not assumed in the base case analysis.

- MMN patients who do not receive active treatment with intravenous Ig (only BSC), but whose health does not deteriorate (i.e. remain 'stable') move to the respond health state, and are assumed to continue to remain 'stable' with no deterioration for a maximum of six months (1 cycle) after the initial treatment phase. After this period, all patients (100%) transit to 'BSC'. This assumption was based on evidence reported in the study by Leger et al. 2001(27), where two patients in the placebo arm remained as responders at 7 months when the clinical trial ended.
- Because the literature search did not identify any trials that implemented a weaning off trial phase, it was assumed that 5% of patients would transit to the 'Responder off-treatment' health state each cycle. This transition probability remained constant throughout the whole time horizon. This proportion was considered reasonable based on information provided by a clinical expert from the Ig Review Reference group as mentioned earlier in Section C.2.5. The effect of a higher proportion of patients initiating weaning and no patients initiating weaning (0%) was tested as a sensitivity analysis in Section D.6.
- The proportion of patients in the 'Responder off-treatment' health state likely to relapse and reinitiate treatment was assumed as 50% as per advice from the clinical expert of the Ig Review Reference group.
- Patients who re-initiate (pre-treated patients) treatment were assumed to have the same chance of not responding to treatment as would treatment naïve patients. This assumption was tested in a sensitivity analysis where pre-treated patients were assumed to have a higher probability of responding to treatment compared to treatment naïve patients.
- It was also assumed that all patients, independent of whether they are on intravenous Ig treatment or not, will require physiotherapy and rehabilitation services (BSC) once a month for the whole duration of their disease.
- The model included the costs and associated disutility of only serious adverse events that were reported in the RCTs. It was assumed that the proportion of MMN patients on intravenous Ig treatment who would experience this event is the same as that observed in

one of the RCTs (Hahn et al. 2013(28)), and that the event would be experienced once in the model. It was assumed that this event would lead to treatment discontinuation.

- To account for death from other causes, the life tables reported by the ABS were used (17). These were adjusted by the male/female ratio for patients diagnosed with MMN.

#### **D.4. INPUTS TO THE ECONOMIC EVALUATION**

A summary of all model inputs used in the base case and later in the sensitivity analysis and their corresponding sources, is presented in Table 31. From this table it is worth noting that the probability of discontinuation due to adverse events was based on the long-term trial by Cats et al. 2010(14) where the median duration of maintenance treatment was 6 years (range 0-17). By using this source and not the rate of discontinuation from the RCTs, we are representing the fact that if a patient does not experience an adverse event at the beginning of treatment they would be unlikely to have one later in time. This probability was kept constant during the whole time horizon of the economic model.

The following parameters were tested in a one way sensitivity analysis:

- Transition probabilities: lower and upper bound values were applied using estimates from literature and calculated values;
  - from the 'Responder' to the 'Responder off-treatment' health state (intravenous Ig arm);
  - from the 'Responder' to the 'BSC' health state (intravenous Ig arm);
  - from the 'Initial treatment' to the 'Responder' health state (No intravenous Ig arm);
  - probability of relapsing while being a 'Responder off-treatment' and reinitiating treatment at the 'Initial treatment' health state (intravenous Ig arm)/
- Cost per gram of intravenous Ig was varied by:
  - the lowest cost of intravenous Ig (imported intravenous Ig; \$44.94),
  - the highest cost of intravenous Ig (domestic intravenous Ig including cost of plasma fractionation; \$140.18),
- Utility weights: the incremental benefit predicted in the study by McCrone et al. 2003(60) (0.12) was varied by assuming a  $\pm 50\%$  from the baseline in relative terms (i.e.  $\pm 0.06$  incremental benefit).

In order to further test the impact on the ICER, several scenario analyses were conducted on the following parameters:

- Discount rate (assumed as 0%);
- Intravenous Ig price assuming the weighted average cost of intravenous Ig across all indications (\$94.51). Because the prices and proportions of domestic/imported Ig are expected to fluctuate overtime, this price was agreed to be used in all HTA reports assessing this technology;
- Age of entry into the model was varied by considering the average age of MMN patients in the RCTs which reflects age at diagnosis (48 years);
- Probability of treatment discontinuation due to AEs as per data from single arm studies;
- Potential for SCIg use assuming a 50:50 proportional use of both routes of administration under two scenarios:
  - differentiated costs between the forms of administration as per the NBA HTA conditions report) and;
  - cost of SCIg equals to the cost of intravenous Ig.
- Utility values: In order to capture the progressive nature of MMN symptoms over time irrespective of treatment, we applied a utility decrement per year in both treatment arms. The utility decrement was estimated from a published study (2) that reported the rate of progression in MMN patients treated with intravenous Ig compared to those who remained untreated. Progression of MMN was assessed using the weakness severity domain of the Neuropathy Impairment Score (NIS W) scale. The results showed a decrement in the NIS W scale of 1.3 points per year after initiating intravenous Ig therapy compared to 4.2 points per year prior to initiating treatment. Thus, untreated patients progressed in their disease 3.23 times more than those who received treatment with intravenous Ig. Because there is no mapping of the NIS W to utilities, we assumed a linear decline in the QoL of MMN patients irrespective of treatment received. In addition, a baseline yearly utility decrement of 0.01 was assumed for patients in the intravenous Ig arm and 0.032 for the untreated arm. It should be noted that the assumed utility decrement is not static, however there is no evidence available to capture this potential variation. To further assess uncertainties around this parameter, we presented an additional sensitivity analysis on the utility decrement by assuming a  $\pm 50\%$  from the baseline decline.
- Probability of treatment response in pre-treated patients: a 'memory' state was incorporated to the Markov model such that pre-treated patients (i.e. patients who reinstate treatment after relapse), would have a higher probability of responding to intravenous Ig compared to treatment naïve patients. It was assumed that pre-treated patients would have a higher

chance of responding to intravenous Ig compared to treatment naïve patients (0.929 as per Hahn et al. 2013(28) versus 0.778 as per Leger et al. 2001(27))

**Table 31 : Input parameters used in the economic model: base case and sensitivity analysis.**

| Parameter   | Base case model inputs | Range for univariate SA |       | Source   |
|---|------------------------|-------------------------|-------|--|
|   |                        | LB                      | UB    |  |
| <b>Transition probabilities</b>                                     |                        |                         |       |  |
| <b>Intravenous Ig arm</b>   |                        |                         |       |  |
| 'Initial treatment' to 'Responder'                                  | 0.778                  | 0.389                   | 0.929 | BC = Leger et al. 2001<br>SA LB = assumed 50% reduction from baseline)<br>SA UB: Hahn et al. 2013                                |
| 'Initial treatment' to 'BSC'  | 1-0.778-death          | NA                      | NA    | NA   |
| 'Responder' to 'Responder off treatment'                            | 0.05                   | 0.00                    | 0.25  | Assumption<br>SA UB = increased 20%.<br>SA LB = no patients initiate weaning.  |
| 'Responder' to 'BSC'  | 0.002                  | 0.00                    | 0.113 | Base = Cats et al. 2010<br>SA UB = Hahn et al. 2013<br>SA LB = assumed that patients do not discontinue due to AEs.              |
| 'Responder off treatment' to 'Initial treatment' due to relapse     | 0.50                   | 0.30                    | 0.70  | BC = advice from Ig Review Reference group.<br>SA = Assumption (20% variation)   |
| Remaining in 'Responder off treatment' (stable while off treatment) | 1-0.50-death           | NA                      | NA    | NA   |
| Death from all states   | NA                     | NA                      | NA    | ABS  |
| <b>No Ig with BSC arm</b>   |                        |                         |       |  |
| 'Initial treatment' to 'Responder'                                  | 0.222                  | 0.111                   | 0.69  | BC = Leger et al. 2001<br>SA LB = assumed 50% reduction from baseline)<br>SA UB: Hahn et al. 2013                                |
| 'Initial treatment' to 'BSC'  | 1-0.222-death          | NA                      | NA    | NA   |
| 'Responder' to 'Responder off treatment'                            | NA                     | 0                       | 0     | This transition does not occur in the comparator arm.  |
| 'Responder' to 'BSC'  | 1                      | NA                      | NA    | Patients with No intravenous Ig were assumed in the 'Responder' health state for only 1 cycle after which 100% transit to 'BSC'. |
| 'Responder off-treatment' to 'Initial treatment' due to relapse     | NA                     | 0                       | 0     | This transition does not occur in the comparator arm.  |
| Death from all states   | NA                     | NA                      | NA    | ABS  |
| <b>Utilities</b>  |                        |                         |       |  |
| 'Initial treatment'   | 0.60                   | 0.54                    | 0.66  |  |
| 'Responder'   | 0.72                   | 0.66                    | 0.78  |  |

| Parameter   | Base case model inputs | Range for univariate SA |          | Source   |
|---|------------------------|-------------------------|----------|--|
|   |                        | LB                      | UB       |  |
| 'Responder off-treatment'                         | 0.72                   | 0.66                    | 0.78     | BC = Mahdi-Rogers et al. 2013 (53) and McCrone et al. 2003 (60)<br>SA: assumed a $\pm 0.06$ relative to base line incremental benefit values.  |
| 'BSC'   | 0.60                   | 0.54                    | 0.66     |  |
| Adverse events (disutility)                       | -0.007                 | NA                      | NA       | Guy et al 2018 (65)  |
| <b>Costs</b>                                      |                        |                         |          |  |
| Cost per gram of intravenous Ig                   | \$60.41                | \$44.94                 | \$140.18 | BC = provided by the DoH (price does not include plasma fractioning).<br>SA LB: assumed the lowest price of intravenous Ig (imported Ig cost).<br>SA HB: assumed the highest price of intravenous Ig (domestic Ig cost including plasma fractioning) |
| <b>Parameters tested in scenario analysis</b>     |                        |                         |          |  |
| Discount rate                                     | 0.05                   | 0.00                    |          | MSAC Guideline (66)  |
| Intravenous IG price                              | \$60.41                | \$94.51                 |          | Weighted average cost of intravenous Ig across all indications.  |
| Age of entry to the model (years)                 | 59                     | 48                      |          | BC = NBA data<br>SA = average age at diagnosis from prevalence studies and RCTs respectively.  |
| 'Responder' to 'BSC': discontinuation due to AEs. | 0.002                  | 0.095                   |          | Average discontinuation rate from three single arm studies (14, 32, 40).   |
| Potential for SCIg use                            | No SCIg use.           | \$75.19                 |          | Differentiated costs between the forms of administration.  |
|   |                        | \$60.41                 |          | Cost of SCIg equal to the cost of intravenous Ig.  |

Abbreviations: ABS = Australian Bureau of Statistics; BC = base case; BSC = best supportive care; LB = lower bound; MSAC = Medical Services Advisory Committee; NA = not applicable; NBA = National Blood Authority; SA = sensitivity analysis; UB = upper bound.

### CLINICAL MANAGEMENT INPUTS

The clinical inputs and their associated assumptions relating to the clinical management of MMN, including the doses and administration pattern of intravenous Ig, are shown in Table 31.

The intravenous Ig utilisation estimates were obtained from the information provided by the NBA, where 372,875 grams of intravenous Ig were provided to 596 patients with MMN in the period from 1 July 2018 - 30 June 2019. Based on the above data and estimates, the current annual dose per patient was estimated to be 626 grams per patient (Section A, Table 3Table 3).



The recommended dosing of intravenous Ig in The Criteria Version 3 is 2g/kg divided in 2 to 5 doses in the induction phase and 0.4-1 g/kg 2-6 weekly, which is consistent with data supplied by the NBA (0.41 g/kg per episode) (Section A, Table 1 and Table 3).

#### **ADVERSE EVENTS AND CLINICAL OUTPUT INPUTS**

Differences in safety profile associated with intravenous Ig and No Ig with BSC were identified in the RCTs and reported in Table 14 (Section B). As the adverse events reported in RCTs and single arm studies were mostly mild and transient, or not related to the treatment with intravenous Ig, only cost and disutility related to SAEs were applied in the economic model. The RCTs and single arm studies reported only one SAE. The RCTs reported only one SAE, pulmonary embolism (PE), hence the economic model incorporates only the potential for patients experiencing PE as a SAE. Due to the small patient numbers and lack of detail in the RCT evidence, along with potential bias in the single arm studies, the incorporation of adverse event data into the economic analysis should be interpreted with caution.

#### **RESOURCE USE**

Resource use associated with the treatment of MMN patients was based on advice from the clinical expert on the Ig Review Reference group, clinical guidelines, published literature and previous MSAC reports. Several sources were used for the valuation of resources, mainly the MBS, PBS, NBA HTA conditions report and the Australian Refined Diagnosis Related Groups (AR-DRG). All costs were measured and valued in 2019 Australian prices. The total cost per item was calculated as a product of the unit price per item, quantity needed and frequency (proportion of patients likely to use it). Cost per health state was calculated as a sum of all the total costs per item under the health state. Details of cost estimation are presented in Table 56 in Appendix G.

The cost of 'Initial treatment', 'Responder' and 'Responder off-treatment' health states for the intravenous Ig treatment arm, includes the cost of specialist consultations (neurologist), pathology tests, diagnostics, intravenous Ig treatment and BSC. Pathology tests included cryoglobulin, renal function tests, complete blood count (CBC) with differential and serum creatinine. As diagnostic tests, neuromuscular electro-conduction studies on four nerves with or without electromyography were included.

Costs of intravenous Ig treatment included cost of the product itself, administration costs and cost of pre-medications for infusion reactions. The estimated cost per gram of intravenous Ig used in the base case analysis was \$60.41. Sensitivity analyses are presented assuming the lowest cost of intravenous Ig (imported intravenous Ig), the highest cost of intravenous Ig (domestic intravenous Ig including cost of plasma fractionation) and the weighted average cost of intravenous Ig across all indications. These costs were provided by the MSAC Ig Review Secretariat as agreed with the Applicant and the Ig Review Reference group to be consistent with other contracted assessments for Ig. In addition, because the costs and utilisation of resources for MMN will vary in the future, a sensitivity analysis was also

conducted by using the weighted average cost (imported and domestic Ig). The administration costs assumed that all patients were provided the service in an in-hospital outpatient setting considering that some patients would attend a public hospital (67%) and some would attend a private hospital (33%). This cost does not take into consideration the fact that some patients may require admission to hospital due to comorbidities, advanced age, doses required over multiple days and patient preference, thus it may represent an underestimation of the overall cost. It is unknown what proportion of patients with MMN require intravenous Ig to be delivered as inpatients.

The cost of the 'BSC' health state comprised of specialist consultation, physiotherapy, pathology, diagnostics and rehabilitation; and it applies to both treatment arms. The 'Initial treatment' and 'Responder' health states for the No Ig with BSC treatment arm comprises of the same components as for the 'BSC' health state. It should be noted that, as disease progresses to more severe stages, it is expected that some patients may require additional health resources given they would be at a higher risk of falls and prone to be affected by other disabilities due to muscle weakness. Such resources include the use of walking aids such as electric wheelchairs and walking frames, additional rehabilitation and physiotherapy sessions, social work services, residential admissions and home modifications for those with a high risk of falling but not admitted into residential care. The costs of these additional resources were not accounted for in the model as there is insufficient evidence to determine when these would be required and by what proportion of the patients. It was considered that the inclusion of these resources would have added more uncertainty to the model results.

Resource use associated with the treatment of PE was sourced from the MSAC 1566 report "Immunoglobulin Therapy for Myasthenia Gravis" (p. 147)(67). The resources included hospitalization, PE specialised consumables and equipment, fluid volume expanders and follow-up visits after discharge from hospital. The costs associated with the resource use were estimated based on AR-DRG (for hospitalisation), MBS and MSAC 1566 report. Detailed description of estimation of costs associated with PE is presented in Table 56 in Appendix G.

## **HEALTH OUTCOMES**

The utility values applied in the model are described in Section B.6 and Section C.4.1. MMN patients who respond to intravenous Ig either in the 'Responder' or 'Responder off-treatment' health states, were applied a utility value of 0.72 (53) for their time in those states. For the 'Initial treatment' and 'BSC' health states in each arm, it was assumed a baseline utility value of 0.6. This was calculated as a difference between the utility of responders (0.72) and the utility gained by CIDP patients who were treated with intravenous Ig reported by McCrone et al. 2003 (0.12) (60). Thus, it is assumed that a patient would gain 0.12 in utility from baseline under intravenous Ig treatment. Given the uncertainties around these point estimates, a sensitivity analysis was conducted in Section D.6.

The use of these constant parameters may not reflect the fact that intravenous Ig may delay progression of the disease and thus have an impact on the patient's QoL that does not necessarily remain constant over time. However, there is no evidence available in the literature that allows us to

capture this in the economic model. It is unknown what the rate of disease progression is after discontinuing treatment with intravenous Ig compared to that of patients who have never received active treatment. If patients progresses at a slower rate because they may still derive some benefit from the intervention, this assumption may bias the results against the use of intravenous Ig.

## **D.5. RESULTS OF THE ECONOMIC EVALUATION**

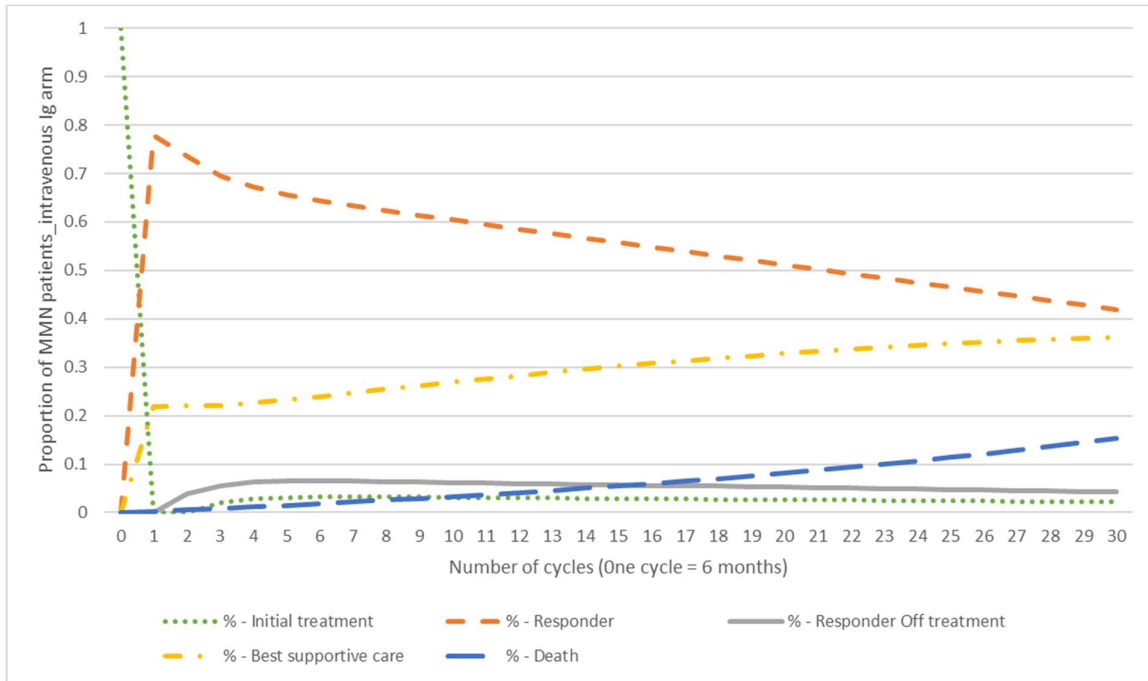
### **MARKOV TRACES**

Figure 12 shows the Markov traces that represent how MMN patients in the intravenous Ig arm moved through the different health states considering a life time horizon. The trace is consistent with the natural history of the disease described in Section A and also consistent with the advice from the Ig Review Reference group, who suggested that MMN patients are unlikely to discontinue treatment, hence would receive intravenous Ig for a long period of time. The model predicts that after 15 years of initiating treatment with intravenous Ig, approximately 41% of patients are still likely to be receiving active treatment. Because a low proportion of patients (5%) were assumed to initiate weaning, the lines representing the 'Initial treatment' and 'Responder off-treatment' health states, remain very low throughout the whole time horizon. As expected, the probability of death increases throughout the time horizon resulting in almost all individuals being dead when a lifetime horizon was tested (Markov traces of this scenario analysis are provided in Figure 20 and Figure 21 in Appendix G).

The predicted results from the model were compared to those observed in long term follow-up single arm studies as a way to validate the model. In the study by Chia et al. 2019 (34), nine of eleven patients (81%) received maintenance treatment with intravenous Ig for a median duration of treatment of 48.1 months (SD 46.3, range 15–156) months (4 years). After 4 years, our model predicts that 68.8% of patients would still receive treatment with intravenous Ig: 62.3% in the 'Responder' health state, 3.2% in the 'Initial treatment' health state and 3.2% in the 'Responder off-treatment' health state (i.e. 50% of total). Similarly, the long-term follow-up study by Cats et al 2010 (14), showed that at 6 years, 67 patients (76%) were still receiving maintenance treatment with intravenous Ig. In our model, at 6 years (12 cycles), it predicts that, 65% are still receiving active treatment: 59% in the 'Responder' health state, 3% in the 'Initial treatment' health state and 3% in the 'Responder off-treatment' health state. From these comparisons, our model could be predicting a treatment duration lower than expected which could lead to a higher actual ICER compared to that predicted in the model. However, this conclusion has to be interpreted with caution given the low number of patients in most studies and the wide range reported around the median treatment duration. Furthermore, the differences observed between these studies and the current model may be explained by the fact that patients who re-initiate (pre-treated patients) treatment have the same chance of not responding to treatment as would treatment naïve patients. This may not actually reflect real world patients as the probability of not responding after a previous response to treatment may be lower. This is a limitation of the current model given the available data.

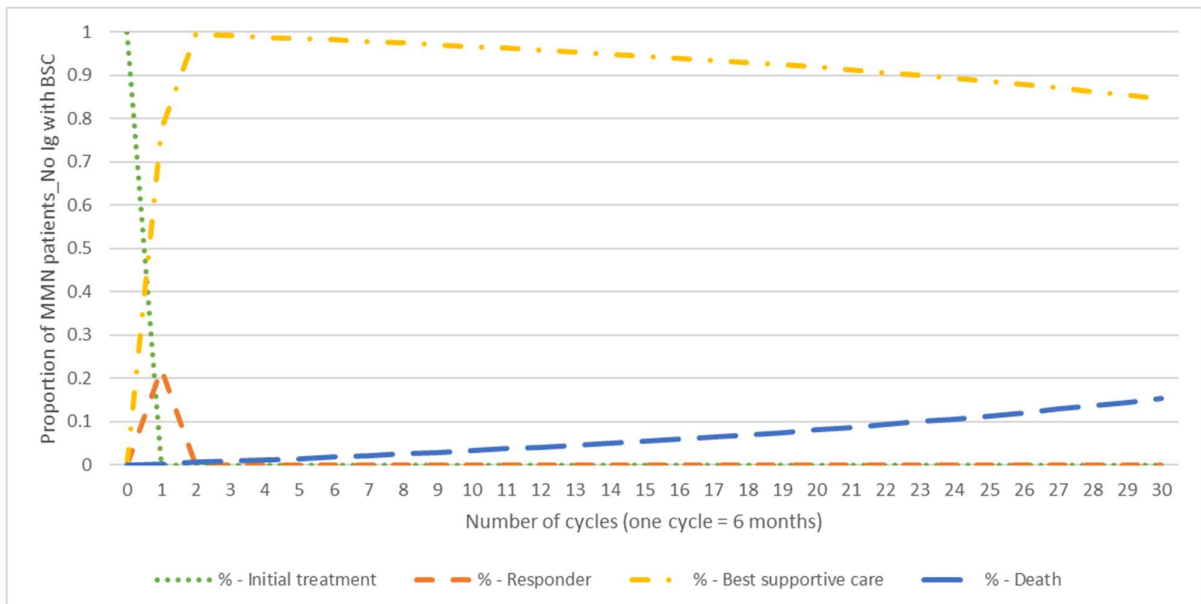
Similarly, Figure 13 represents how patients move through the model in the hypothetical scenario that intravenous Ig was not available for MMN patients in Australia.

**Figure 12. Markov traces for the base case analysis (15 years): intravenous Ig arm.**



Abbreviations: Ig = immunoglobulin; MMN = multifocal motor neuropathy

**Figure 13. Markov traces for the base case analysis (15 years): No Ig with BSC arm.**



Abbreviations: Ig = immunoglobulin; MMN = multifocal motor neuropathy.

## STEPPED ECONOMIC EVALUATION

The results of the stepped analysis of the base case economic evaluation are presented in Table 32. In Step 1, we present results for the trial-based evaluation reporting incremental costs per QALY after one cycle (6 months). Step 2 and Step 3 show the results in terms of cost per QALY gained using the modelled evaluation over 15 years and lifetime time horizon respectively.

The overall and incremental costs and outcomes calculated for the intravenous Ig and No Ig with BSC treatment arms in the economic model are shown in Table 32 where Step 2 represents the base case analysis. As expected, the cost of treating patients with intravenous Ig is higher than not providing active treatment, \$275,853 versus \$26,191 respectively considering a 15 year time horizon (Step 2). Because patients derive clinical and QoL benefits from treatment, the total accrued QALYs were higher for the intravenous Ig versus the No Ig with BSC arms (6.83 versus 6.04 QALYs respectively). This leads to a base case ICER of \$317,552/QALY gained. When assessing a lifetime horizon (Step 3) it was observed that an individual with MMN gained more QALYs compared to the 15 year time horizon (1.00 versus 0.79 QALYs). However, this benefit is offset by the incremental costs over the lifetime time horizon, resulting in a similar ICER (\$315,258 /QALY gained versus \$317,552/QALY gained). As a result, the ICER is somewhat independent of the time horizon.

**Table 32: Results of stepped economic evaluation**

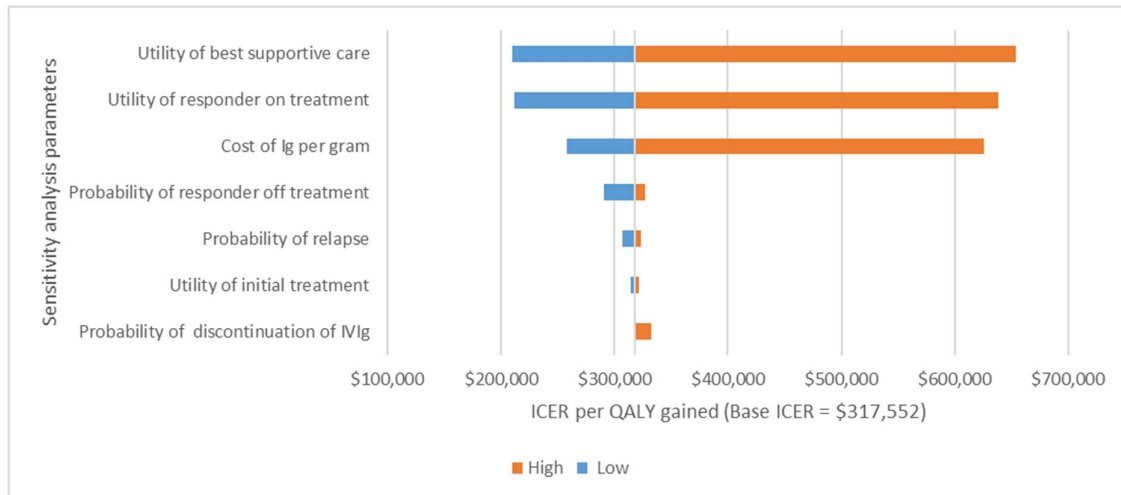
|   | Total costs | Incremental cost | Total Effectiveness | Incremental effectiveness | ICER (\$/QALY) |
|---|-------------|------------------|---------------------|---------------------------|----------------|
| <b>Step 1: trial-based evaluation, 7 months' time horizon</b>           |             |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

Abbreviations: ICER= incremental cost effectiveness ratio; Ig = immunoglobulin; QALY= quality adjusted life years

## D.6. SENSITIVITY ANALYSES

The results of the one-way sensitivity analyses are presented in Figure 14 while the results from the scenario analysis are presented in Table 33.

**Figure 14. Tornado diagram**



Abbreviations: AE=adverse events; Ig= immunoglobulin; ICER = incremental cost effectiveness ratio; IVIg= intravenous immunoglobulin; QALY = quality adjusted life year;

Notes:

<sup>1</sup>Probability of responder on treatment from initial treatment in no IVIg arm

<sup>2</sup>Utility of induction treatment

<sup>3</sup>Probability of no treatment from a responder on treatment (i.e. probability of discontinuation of Ig due to adverse events for the IVIg arm)

<sup>4</sup>Probability of responder on treatment from induction IVIG

<sup>5</sup>Probability of relapse from responder off treatment state/probability of induction treatment from responder off treatment state due to relapse IVIG arm

<sup>6</sup>Probability of responder off treatment from responder on treatment state (i.e. probability of initiating weaning/cessation of treatment) IVIG arm

<sup>7</sup>Cost of Ig per gram

<sup>8</sup>Utility of responder on treatment

<sup>9</sup>Utility of no treatment

**Table 33. Results of scenario analysis**

| Parameter   | Incremental cost (\$) | Incremental effectiveness | ICER (\$/QALY) | % change from base case |
|---|-----------------------|---------------------------|----------------|-------------------------|
| <b>Base case</b>  | 249,662               | 0.786                     | 317,552        | NA                      |
| Weighted average cost of Ig across all indications (\$94.51).   | 353,274               | 0.786                     | 449,338        | 42%↑                    |
| Assuming 50% SCIg and 50% Intravenous Ig use (equal price = \$60.41)  | 221,455               | 0.786                     | 281,675        | 11%↓                    |
| Discontinuation rate reported in NRS (0.095).   | 118,298               | 0.359                     | 329,662        | 4%↑                     |
| Assuming 50% Subcutaneous Ig and 50% intravenous Ig use (SCIg=\$75.19 per gram; intravenous Ig= \$60.41 per gram)                                 | 245,424               | 0.786                     | 312,161        | 2%↓                     |
| Discount rate (0%)  | 341,176               | 1.085                     | 314,560        | 1%↓                     |
| Mean age of MMN patients in RCTs (48 years)   | 256,695               | 0.809                     | 317,214        | 0.1%↓                   |
| Assuming pre-treated patients have a higher probability of responding to intravenous Ig compared to treatment naïve patients (0.929 versus 0.778) | 265,626               | 0.838                     | 316,938        | 0.2%↓                   |
| Deterioration in QoL over time: assuming annual decline of utility  | 249,662               | 2.533                     | 98,559         | 69%↓                    |

| Parameter  | Incremental cost (\$) | Incremental effectiveness | ICER (\$/QALY) | % change from base case |
|--|-----------------------|---------------------------|----------------|-------------------------|
| weight of 0.01 in the intravenous Ig arm and 0.032 in no intravenous Ig arm  |                       |                           |                |                         |
| Deterioration in QoL over time: assuming annual reduction of 0.005 in the intravenous Ig arm and 0.016 in no intravenous Ig arm <sup>2</sup> | 249,662               | 1.660                     | 150,429        | 53%↓                    |
| Deterioration in QoL over time: assuming annual reduction of 0.015 in the intravenous Ig arm and 0.048 in no intravenous Ig arm <sup>3</sup> | 249,662               | 3.407                     | 73,288         | 77%                     |

Abbreviations: ICER = incremental cost effectiveness ratio; Ig = immunoglobulin; NA = not applicable; NBA = National Blood Authority; RCT = randomised control trials; SC = subcutaneous.

Notes:

1. Base case rate of decline of utility weight over time.
2. Assuming - 50% of base case rate of deterioration.
3. Assuming +50% of base case rate of deterioration.

Overall, the ICER was most sensitive to the utility weights and to the price of intravenous Ig. It was noted that by assuming a deterioration in QoL of MMN patients over time had an important impact on the ICER (Table 34), however, this result should be considered with caution as there is uncertainty around the source used to capture this decline in QoL overtime (further details provided in Section D.4). The latter scenario analysis was based purely on assumptions.

To a lesser extent, the results were also sensitive to the probability of initiating weaning and relapsing after initiating weaning. The ICER was not sensitive to the assumption that pre-treated patients had a higher chance of responding to intravenous Ig compared to treatment naïve patients. Table 34 shows the key drivers of the cost-effectiveness results while

Table 57 in Appendix G shows the summary of the results for all conducted sensitivity analysis.

**Table 34: Key drivers of the economic model**

| Variable Description  | SA      |          | ICER (\$/QALY) |           | Impact |
|---|---------|----------|----------------|-----------|--------|
|   | Low     | High     | Low            | High      |        |
| <b>Base case</b>  | 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 |

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%.



## SECTION E

## FINANCIAL IMPLICATIONS

The financial implications and predicted use of intravenous Ig in patients with MMN were estimated for a 5-year period based on the calendar years 2019 to 2024. The budget impact model was built in Microsoft Excel. As described in Section A, intravenous Ig is already available for the treatment of MMN in Australia. In the hypothetical scenario if intravenous Ig were no longer available, it was assumed that it would be replaced with BSC. In that instance, all health services directly related to the use of intravenous Ig would be excluded but those required for active disease surveillance and other palliative treatments would be maintained.

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 2018-2019, where the data captures V2 and the ongoing implementation of The Criteria V3. The impact of fully implementing Version 3 may not be reflected from the available data as this version was implemented in October 2019. The transition from V2 to the Version 3 is expected to result in fewer MMN patients being approved (or being assessed) as eligible for treatment with intravenous Ig likely to be administered at a reduced dose. Therefore, there is some uncertainty in regard to how trends observed in previous years would represent the expected use of intravenous Ig for the treatment of MMN patients in Australia. In addition, as discussed in Section A, it is also possible that patients with a diagnosis different to MMN are currently being treated with intravenous Ig, hence leading to an overestimation of the number of eligible patients.

### E.1. JUSTIFICATION OF THE SELECTION OF SOURCES OF DATA

Several sources were used to estimate the financial implications associated with the use of intravenous Ig for the treatment of MMN patients. The main source to account for its yearly use was the 2018-2019 NBA report provided for the purpose of this assessment (9). The data provided in this report, show the number of patients treated with MMN, the grams of intravenous Ig used and the associated cost of intravenous Ig. Because there are other health resources to be considered, services were put together based on The Criteria V3, the EFNS clinical guideline and validated by the Ig Review Reference group. Each health resource was valued using the corresponding MBS/PBS schedule and AR-DRG as appropriate. A summary of the variables with their corresponding source and assumption is presented in Table 35.

**Table 35. 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 |

| Variable   | Data source  | Assumption  |
|--|--|---|
|  |  | 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 <sup>a</sup> (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.   |

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: <sup>a</sup>It was assumed that all patients received a prophylactic dose of antihistamines (promethazine) before receiving their corresponding intravenous Ig infusion.

The full year of data available for the total number of patients receiving intravenous Ig for MMN, total grams used and its associated cost is summarised in Table 36. The number of patients and the total grams per year increased at a relatively constant rate in the last 6 years from 2013-2019. The average grams per patient showed a similar trend, however, in the last period a slight decrease was observed, from 633 grams in 2017-18 to 626 in 2018-19. This decrease occurred despite the increase from 560 to 596 prevalent MMN patients under treatment with intravenous Ig in the period 2017-18 and 2018-19 respectively. This may be explained by the implementation of The Criteria V3.

**Table 36. Observed number of patients who received intravenous Ig, gram used and associated costs in patients diagnosed with MMN from 2013-19**

|                                 | 2013-14 | 2014-15 | 2015-16 | 2016-17 | 2017-18 | 2018-19 |
|---------------------------------|---------|---------|---------|---------|---------|---------|
| MMN prevalent cases             | 438     | 444     | 496     | 527     | 560     | 596     |
| Incident cases                  | 127     | 105     | 137     | 126     | 125     | 123     |
| Total grams issued/administered | 239,791 | 256,041 | 293,458 | 331,147 | 354,434 | 372,875 |
| Average grams per patient       | 547     | 577     | 592     | 628     | 633     | 626     |
| Average cost per gram of IVIg   | NA      | NA      | NA      | NA      | \$70.13 | \$69.46 |

Abbreviations: Ig = immunoglobulin; MMN = multifocal motor neuropathy; NA = not applicable.

Source: NBA National Reports on the issue and use of immunoglobulin Ig 2015-16 and the HTA Conditions Report 1, 2 and 3 provided by the NBA on 06 January 2020 ('Phase 2 HTA conditions data.xlsx' workbook).

It should be noted that the data presented in Table 36 do not take into account; patients diagnosed with MMN but still not eligible to receive intravenous Ig, or patients who have previously received Ig but have discontinued due to AEs or because they are no longer responders. However, as these groups could occur in either the No Ig with BSC or the intravenous Ig groups, absence of estimates for these patient pools will not impact the overall incremental budget impact results. It is expected that all of these patients would still require BSC to account for the monitoring of their disease and other health

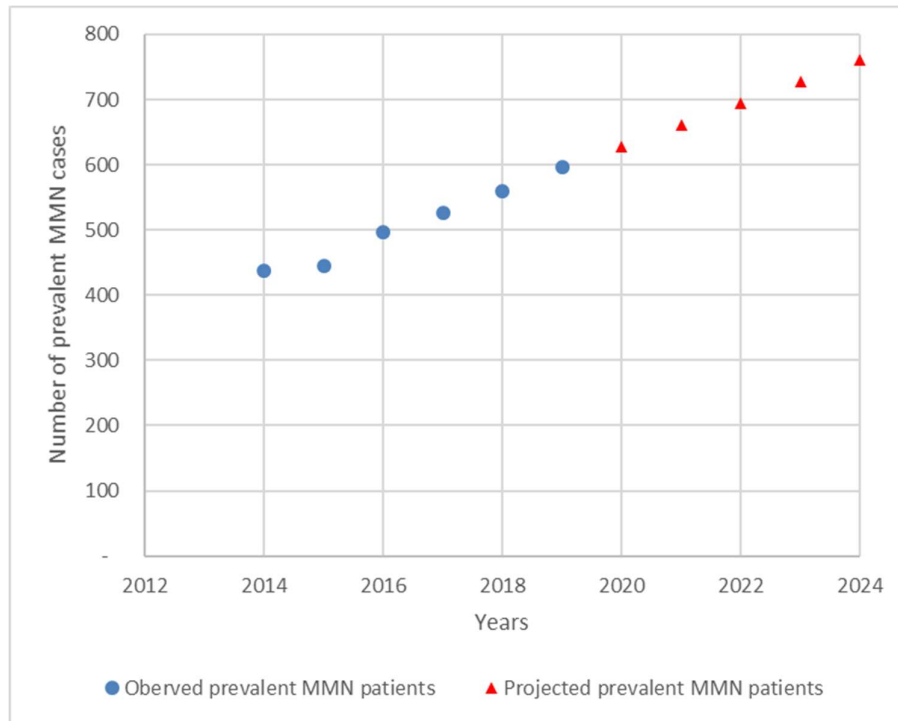
care services such as physiotherapy or rehabilitation. It was also noted from the observed data that the number of new MMN patients diagnosed each year (incident cases) compared to the difference in prevalent cases reported the following year do not match. These numbers may partly represent misdiagnosed cases of MND. It is expected that the number of new MMN patients under intravenous Ig treatment is likely to reduce in the coming years as The Criteria V3 introduces further restrictions for treatment initiation and continuation and expands on the exclusion criteria for treatment (further details are provided in Section A.2).

**E.2. USE AND COSTS OF INTRAVENOUS IGG FOR THE TREATMENT OF MMN**

**NUMBER OF MMN PATIENTS ELIGIBLE TO RECEIVE INTRAVENOUS IGG**

Patient numbers were projected using linear extrapolations fitted to the observed data (Figure 15). The observed data for the number of prevalent MMN cases were linearly projected based on the constant increase observed in the previous period (between 2014 – 2017). This projection resulted in a total of 761 MMN patients projected to receive intravenous Ig by 2024.

**Figure 15. Patient number projections**



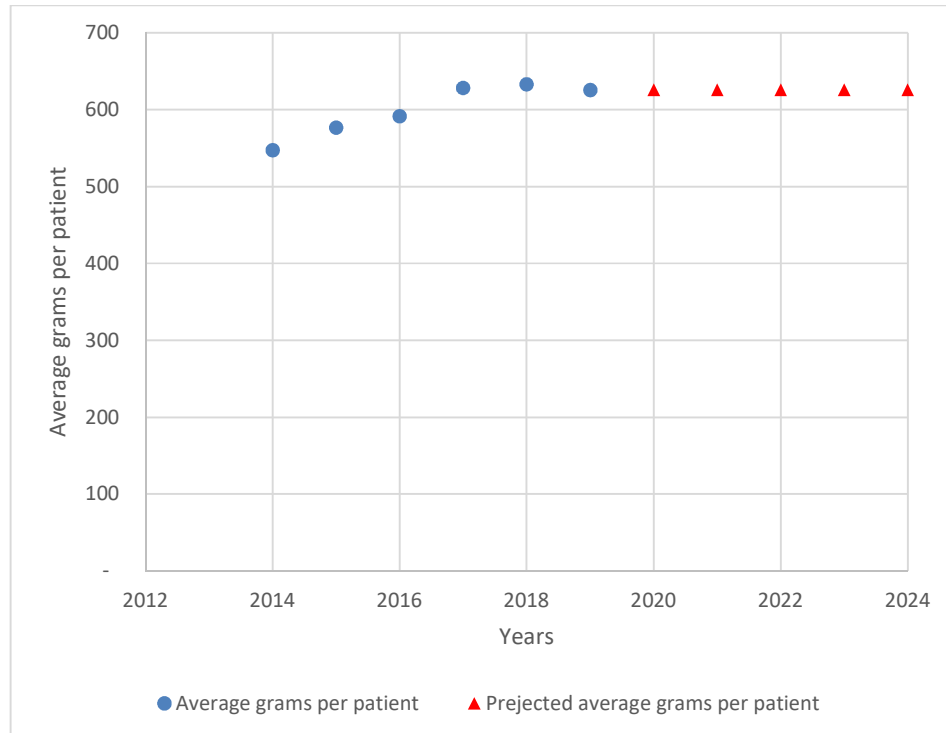
Abbreviations: MMN = multifocal motor neuropathy.  
 Source: NBA National Reports on the issue and use of immunoglobulin Ig 2015-16 and the HTA Conditions Report 1, 2 and 3 provided by the NBA on 06 January 2020 ('Phase 2 HTA conditions data.xlsx' workbook).

**ESTIMATED INTRAVENOUS IGG GRAMS PER PATIENT**

Figure 16 shows the average grams per patients from the observed data and the projected constant average assumed throughout the 5-year time horizon. Average grams per patient were not

linearly projected (but instead kept constant at 626 grams) as it was assumed a potential dose per patient reduction due to the implementation of The Criteria V3. This assumption was based on the fact that a slight reduction in dose per patient was observed in the last year despite the increased number of prevalent cases under Ig treatment. A linear projection of the utilised grams per episode was tested as a sensitivity analysis in Section E.6

**Figure 16. Observed and estimated average intravenous Ig grams per MMN patient.**



Abbreviations: MMN = multifocal motor neuropathy.

Source: NBA National Reports on the issue and use of immunoglobulin Ig 2015-16 and the HTA Conditions Report 1, 2 and 3 provided by the NBA on 06 January 2020 ('Phase 2 HTA conditions data.xlsx' workbook).

To estimate the total number of intravenous Ig grams per year, the average grams per patient, was multiplied by the projected number of patients (Table 37). Overall, the total grams increased from 392,544 grams in year 1 to 476,177 grams in year 5 (21% increase).

**Table 37. Projected intravenous Ig grams per year**

|                                 | Year 1         | Year 2         | Year 3         | Year 4         | Year 5         | Total over 5 years |
|---------------------------------|----------------|----------------|----------------|----------------|----------------|--------------------|
| MMN prevalent cases             | 627            | 660            | 694            | 727            | 761            | 3,469              |
| Average grams per patient       | 626            | 626            | 626            | 626            | 626            | 3,130              |
| <b>Total grams administered</b> | <b>392,544</b> | <b>413,452</b> | <b>434,361</b> | <b>455,269</b> | <b>476,177</b> | <b>2,171,803</b>   |

Abbreviations: MMN = multifocal motor neuropathy.

Source: Projections from observed data from the HTA Conditions Report 1, 2 and 3 provided by the NBA on 06 January 2020 ('Phase 2 HTA conditions data.xlsx' workbook).

## ESTIMATED COST OF INTRAVENOUS Ig

The base case cost per Ig gram was provided by the DoH and corresponds to the domestic price without considering plasma fractioning (\$60.41). The total cost was estimated by multiplying the average cost per gram by the total grams administered per year (Table 38). Considering that the National Blood Agreement estimates that 63% of the product is funded by the Commonwealth and 37% by the states and territories, it was estimated that the overall cost to the Commonwealth increased from \$14,930,687 in year 1 to \$18,295,725 in year 5, resulting in a total cost of \$82,852,456 over a 5-year time horizon.

A sensitivity analysis was conducted assuming the international price (\$44.94) as the lower bound and domestic price with plasma fractioning (\$140.18) as the upper bound. An additional sensitivity analysis was conducted assuming the agreed weighted average price for domestic and international Ig as per NBA data for the period 2018-2019 (\$94.51). The results of these analysis are presented in Section E.6.

**Table 38. Cost of intravenous Ig for the treatment of MMN patients, observed and projected estimates.**

|  | Year 1       | Year 2       | Year 3       | Year 4       | Year 5       | Total over 5-years |
|--|--------------|--------------|--------------|--------------|--------------|--------------------|
| Cost per gram of intravenous Ig                | \$60.41      | \$60.41      | \$60.41      | \$60.41      | \$60.41      | \$60.41            |
| Domestic IVIg (grams)                          | 97,269       | 102,400      | 107,802      | 113,488      | 119,474      | 540,434            |
| Imported IVIg (grams)                          | 295,274      | 310,850      | 327,246      | 344,508      | 362,681      | 1,640,559          |
| Total cost Domestic intravenous Ig             | \$5,872,559  | \$6,178,668  | \$6,500,733  | \$6,839,585  | \$7,196,101  | \$32,587,646       |
| Total cost imported intravenous Ig             | \$17,826,944 | \$18,756,179 | \$19,733,850 | \$20,762,482 | \$21,844,733 | \$98,924,188       |
| Overall costs                                  |              |              |              |              |              |                    |
| IVIg cost to the Commonwealth <sup>a</sup>     | \$14,930,687 | \$15,708,954 | \$16,527,787 | \$17,389,303 | \$18,295,725 | \$82,852,456       |
| Intravenous Ig cost to the states <sup>a</sup> | \$8,768,816  | \$9,225,893  | \$9,706,796  | \$10,212,765 | \$10,745,108 | \$48,659,379       |
| Total cost                                     | \$23,699,504 | \$24,934,847 | \$26,234,583 | \$27,602,068 | \$29,040,833 | \$131,511,835      |

Abbreviations: Ig = immunoglobulin; MMN = multifocal motor neuropathy; NBA = National Blood Authority.

Notes: <sup>a</sup> The National Blood Agreement states that 63% of products are funded by the Commonwealth and 37% by the states and territories. Source: Projections from observed data from the HTA Conditions Report 1, 2 and 3 provided by the NBA on 06 January 2020 ('Phase 2 HTA conditions data.xlsx' workbook) and cost per gram of intravenous Ig was provided by the DoH.

## E.3. CHANGES IN USE AND COST OF OTHER MEDICAL SERVICES

### INTRAVENOUS Ig ADMINISTRATION RELATED COSTS

All patients who currently receive intravenous Ig for the treatment of MMN administered by intravenous infusion, require services to be delivered in the hospital setting (Table 39). In order to estimate the intravenous Ig administration cost, the average number of treatment episodes for the two latest periods were used to account for the projected years assuming these remained constant

thereafter. From these, the average number of treatment episodes per patient was estimated, resulting in an average of 14.77 episodes per year (this number corresponds to the average number of episodes reported for the period 2017-2018 (14.75) and 2018-2019 (14.79)). These were used as a proxy for average number of IV infusions per year in order to capture the additional costs associated with the administration of intravenous Ig. The costing of each treatment episode was consistent with that estimated in Section D for the purpose of the economic evaluation (See Table 31) and maintained constant throughout the 5-year time horizon.

**Table 39. Administration cost of intravenous Ig per treatment episode.**

| Items per episode   | Quantity | Frequency | Price    | Cost            |
|---|----------|-----------|----------|-----------------|
| Public hospital (outpatient)                                | 1        | 67%       | \$461.00 | \$308.87        |
| Private hospital (outpatient) <sup>a</sup>                  | 1        | 33%       | \$500.00 | \$165.00        |
| Pathology tests during intravenous Ig infusion              | 1        | 100%      | \$208.90 | \$208.90        |
| Portacath <sup>b</sup>                                      | 1        | 10%       | \$276.75 | \$27.68         |
| <b>Total intravenous Ig administration cost per episode</b> |          |           |          | <b>\$710.45</b> |

Abbreviations: Ig = immunoglobulin.

Note: Frequency for private vs private hospital showed as proportions; <sup>a</sup>The unit price corresponds to an assumption; <sup>b</sup> it was assumed that a portacath is required by 50% of patients over 5 years (MBS item 34528).

The estimated costs associated with the administration of intravenous Ig are summarised in Table 40. Over the time horizon of 5 years, it is estimated that a total of \$36,396,455 would be spent on administration purposes.

**Table 40. Estimated costs associated to the administration of intravenous Ig.**

|   | Year 1             | Year 2             | Year 3             | Year 4             | Year 5             | Total over 5 years  |
|---|--------------------|--------------------|--------------------|--------------------|--------------------|---------------------|
| Number of episodes per year                       | 8,536              | 8,536              | 8,536              | 8,536              | 8,536              |                     |
| MMN prevalent cases                               | 627                | 660                | 694                | 727                | 761                |                     |
| Number of episodes per patient/year               | 14.77              | 14.77              | 14.77              | 14.77              | 14.77              |                     |
| Total Intravenous administration cost per episode | <b>\$710.45</b>    | <b>\$710.45</b>    | <b>\$710.45</b>    | <b>\$710.45</b>    | <b>\$710.45</b>    |                     |
| <b>Administration costs</b>                       | <b>\$6,578,498</b> | <b>\$6,928,895</b> | <b>\$7,279,291</b> | <b>\$7,629,687</b> | <b>\$7,980,084</b> | <b>\$36,396,455</b> |

Abbreviations: IVIg = intravenous immunoglobulin; MMN = multifocal motor neuropathy.

Source: Estimations conducted during the assessment; HTA Conditions Report 1, 2 and 3 provided by the NBA on 06 January 2020 ('Phase 2 HTA conditions data.xlsx' workbook).

## **DISEASE MONITORING AND PATIENT FOLLOW-UP RELATED COSTS**

Disease and treatment monitoring is a critical step to ensure treatment success and overall patient safety. It was assumed that patients treated with intravenous Ig require monitoring of their disease every 6 months to assess treatment continuation although the requirement of the Criteria is every 12 months after the initial review. Patients are required to be reviewed by a neurologist to assess and document clinical efficacy before continuation of intravenous Ig therapy can be authorised. It was assumed, the patient undertakes pathology tests and other physical tests at each review to be assessed for treatment response. In addition, a patient undergoes neuromuscular electro-diagnosis conduction studies once a year (i.e. every other review). It was also assumed that each patient,

independent of whether they are on intravenous Ig treatment or not, would require physiotherapy and rehabilitation services once a month for the whole duration of their disease. A summary of the estimated costs associated with BSC and follow-up is presented in Table 41. The total estimated cost for BSC and follow-up was \$3,018.08 per patient per year.

**Table 41. Estimated costs associated to follow-up/BSC of MMN patients treated with intravenous Ig per year per patient.**

| Items per follow-up                  | Quantity per year | Frequency | Item price | Annual cost       |
|--------------------------------------|-------------------|-----------|------------|-------------------|
| Specialist consultation <sup>1</sup> | 2.00              | 100%      | \$124.93   | \$249.85          |
| Pathology tests <sup>2</sup>         | 2.00              | 100%      | \$417.80   | \$835.60          |
| Diagnostic imaging <sup>3</sup>      | 1.00              | 100%      | \$227.55   | \$227.55          |
| <b>BSC</b>                           |                   |           |            |                   |
| Physiotherapy <sup>4</sup>           | 12.00             | 100%      | \$63.25    | \$759.00          |
| Rehabilitation <sup>5</sup>          | 12.00             | 100%      | \$78.84    | \$946.08          |
| <b>Total follow-up costs</b>         |                   |           |            | <b>\$3,018.08</b> |

Abbreviations: BSC = best supportive care; Ig = immunoglobulin; MMN = multifocal motor neuropathy.

Abbreviations: BSC = best supportive care; IVIg = intravenous immunoglobulin; MMN = multifocal motor neuropathy.

Note:

<sup>1</sup>Average price for the following MBS item numbers: 6013, 6007, 6015 and 6011;

<sup>2</sup>includes: CBC count (65070), cryoglobulin (71059), glucose testing (701), renal function test (12527), serum creatinine level (66500);

<sup>3</sup>Neuromuscular electrodiagnosis conduction studies on 4 or more nerves with or without electromyography OR recordings from single fibres of nerves and muscles OR both examinations (MBS item 11018);

<sup>4</sup>MBS item 10960;

<sup>5</sup> Average of the following MBS items: 880, 385, 386, 387, 388.

Source: Estimations conducted during the assessment.

The estimated annual BSC and follow-up costs over 5 years are summarised in Table 42Table 40. A total of \$4,555,235 would be spent on BSC and follow-up over 5 years.

**Table 42. Estimated costs associated to disease monitoring and patients follow-up per year.**

|  | Year 1             | Year 2             | Year 3             | Year 4             | Year 5             | Total over 5 years |
|--|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|
| MMN prevalent cases                      | 627                | 660                | 694                | 727                | 761                |                    |
| Total BSC and follow-up cost per patient | \$3,018.08         | \$3,018.08         | \$3,018.08         | \$3,018.08         | \$3,018.08         |                    |
| <b>Total follow-up costs</b>             | <b>\$823,339</b>   | <b>\$867,193</b>   | <b>\$911,047</b>   | <b>\$954,901</b>   | <b>\$998,755</b>   | <b>\$4,555,235</b> |
| <b>Total BSC costs</b>                   | <b>\$1,069,199</b> | <b>\$1,126,149</b> | <b>\$1,183,098</b> | <b>\$1,240,048</b> | <b>\$1,296,998</b> | <b>\$5,915,491</b> |

Abbreviations: BSC = best supportive care.

Source: Estimations conducted during the assessment.

### **CHANGES IN COSTS ASSOCIATED WITH AEs CAUSED BY THE USE OF INTRAVENOUS IG**

It was assumed that a patient undergoing intravenous Ig treatment is at a higher risk of experiencing a PE. All other AEs were considered minor and likely to be managed through reducing the rate of infusion or by using over the counter (OTC) medications. It was also assumed that a patient suffering a PE would require hospitalisation and all costs would be incurred by Medicare and hospital funding (AR-DRG). The annual cost per PE event per patient per year was estimated at \$7,619.90. The incidence of PE was sourced from Hahn et al. 2013(28), assumed constant at 5% and that this event would lead to treatment discontinuation.

A summary of all health care budget related costs is presented in Table 43. The estimated total cost to the MBS over 5 years was estimated at \$48,068,815.

**Table 43. Estimated costs to the health care budget**

|   | Year 1             | Year 2             | Year 3             | Year 4              | Year 5              | Total over 5 years  |
|---|--------------------|--------------------|--------------------|---------------------|---------------------|---------------------|
| Intravenous Ig administration costs         | \$6,578,498        | \$6,928,895        | \$7,279,291        | \$7,629,687         | \$7,980,084         | \$36,396,455        |
| Follow-up costs                             | \$823,339          | \$867,193          | \$911,047          | \$954,901           | \$998,755           | \$4,555,235         |
| BSC   | \$1,069,199        | \$1,126,149        | \$1,183,098        | \$1,240,048         | \$1,296,998         | \$5,915,491         |
| Total cost of AE                            | \$217,190          | \$228,759          | \$240,327          | \$251,895           | \$263,464           | \$1,201,635         |
| <b>Total cost to the health care budget</b> | <b>\$8,688,226</b> | <b>\$9,150,994</b> | <b>\$9,613,763</b> | <b>\$10,076,532</b> | <b>\$10,539,300</b> | <b>\$48,068,815</b> |

Abbreviations: AE = adverse event; BSC = best supportive care; IVIg = intravenous immunoglobulin; MBS = Medicare Benefits Schedule. Source: Estimations conducted during the assessment. HTA Conditions Report 1, 2 and 3 provided by the NBA on 06 January 2020 ('Phase 2 HTA conditions data.xlsx' workbook); MBS schedule.

#### **E.4. FINANCIAL IMPLICATIONS FOR THE MBS**

The financial implications to the MBS that would result from the delisting of intravenous Ig are summarised in Table 44. As expected, ceasing the supply of intravenous Ig in this population would lead to a reduction of the overall costs, as the associated administration costs would no longer be required. Patients would still receive BSC which includes monitoring of the disease, as well as other services such as physiotherapy and rehabilitation.

**Table 44. Total costs to the MBS associated with delisting IVIg as a treatment option for MMN patients.**

|                       | 2015-16           | 2016-17             | 2017-18             | 2018-19             | 2019-20             |
|-----------------------|-------------------|---------------------|---------------------|---------------------|---------------------|
| <b>Intravenous Ig</b> |                   |                     |                     |                     |                     |
| MBS Cost              | \$8,688,226       | \$9,150,994         | \$9,613,763         | \$10,076,532        | \$10,539,300        |
| <b>No Ig with BSC</b> |                   |                     |                     |                     |                     |
| MBS Cost              | \$1,892,537       | \$1,993,341         | \$2,094,145         | \$2,194,949         | \$2,295,753         |
| <b>Net cost</b>       | <b>-6,795,689</b> | <b>-\$7,157,653</b> | <b>-\$7,519,618</b> | <b>-\$7,881,583</b> | <b>-\$8,243,547</b> |

#### **E.5. FINANCIAL IMPLICATIONS FOR THE GOVERNMENT HEALTH BUDGET**

##### **OTHER GOVERNMENT IMPACTS**

As part of the administration of intravenous Ig costs, it was assumed that all patients receive prophylactic antihistamines as a preventative measure for infusion reactions. The use of antihistamines impacts the PBS and a summary of the overall costs is presented in Table 45.

**Table 45. Estimated costs associated with the use of premedications for intravenous Ig related infusion reactions**

|                                     | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Total over 5 years |
|-------------------------------------|--------|--------|--------|--------|--------|--------------------|
| MMN prevalent cases                 | 627    | 660    | 694    | 727    | 761    |                    |
| Number of episodes per patient/year | 14.77  | 14.77  | 14.77  | 14.77  | 14.77  |                    |



|  | Year 1           | Year 2           | Year 3           | Year 4           | Year 5           | Total over 5 years |
|--|------------------|------------------|------------------|------------------|------------------|--------------------|
| Total prophylactic medications <sup>a</sup> cost per episode | \$35.07          | \$35.07          | \$35.07          | \$35.07          | \$35.07          |                    |
| <b>Pre-medication costs<br/>Cost to the PBS</b>              | <b>\$324,737</b> | <b>\$342,034</b> | <b>\$359,331</b> | <b>\$376,628</b> | <b>\$393,924</b> | <b>\$1,796,654</b> |

Abbreviations: Ig = immunoglobulin; MMN = multifocal motor neuropathy; PBS = Pharmaceutical Benefit Scheme.

Note: <sup>a</sup>In hospital use of promethazine hydrochloride 50 mg/2 mL injection

Source: HTA Conditions Report 1, 2 and 3 provided by the NBA on 06 January 2020 ('Phase 2 HTA conditions data.xlsx' workbook).

The net financial implications for the government budget associated with the funding of intravenous Ig for the treatment of MMN patients in Australia are presented in Table 46. Overall, the net reduction in government costs of ceasing supply of intravenous Ig for the treatment of MMN would result in a 5-year cost reduction of -\$170,906,578.

**Table 46. 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 <sup>a</sup>          | \$14,930,687         | \$15,708,954         | \$16,527,787         | \$17,389,303         | \$18,295,725         | \$82,852,456          |
|  | IVIg cost to the states <sup>a</sup>                | \$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           |
|  | <b>Total</b>  | <b>\$32,712,467</b>  | <b>\$34,427,875</b>  | <b>\$36,207,677</b>  | <b>\$38,055,227</b>  | <b>\$39,974,058</b>  | <b>\$181,377,304</b>  |
| 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          |
|  | <b>Total</b>  | <b>\$1,892,537</b>   | <b>\$1,993,341</b>   | <b>\$2,094,145</b>   | <b>\$2,194,949</b>   | <b>\$2,295,753</b>   | <b>\$10,470,726</b>   |
| <b>Net costs (Intravenous Ig versus No Ig)</b> |   |                      |                      |                      |                      |                      |                       |
|  | 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         |
|  | <b>Total net costs</b>                              | <b>-\$30,819,929</b> | <b>-\$32,434,534</b> | <b>-\$34,113,532</b> | <b>-\$35,860,278</b> | <b>-\$37,678,305</b> | <b>-\$170,906,578</b> |

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: <sup>a</sup> The National Blood Agreement states that 63% of products are funded by the Commonwealth and 37% by the states and territories.

Source: Projections from observed data from the HTA Conditions Report 1, 2 and 3 provided by the NBA on 06 January 2020 ('Phase 2 HTA conditions data.xlsx' workbook).

## E.6. IDENTIFICATION, ESTIMATION AND REDUCTION OF UNCERTAINTY

The results of sensitivity analyses exploring uncertainty in the assumptions used to determine the financial implications are presented in Table 47. The financial estimates were most sensitive to the cost of intravenous Ig, mainly when the lower imported cost (\$44.94) was used for the total grams utilised by all MMN patients. The higher impact compared to using the higher cost of the domestic product is because in Australia most patients use imported product. Following the intravenous Ig cost,

the costs were also sensitive to linearly projecting the total numbers of grams used per patient, which for the base case were maintained constant.

An epidemiological approach could have also been conducted by using prevalence estimates from the international literature. The study conducted by Cats et al. 2010(14) was suggested by the Ig Review Reference Group at the Ig review meeting (09 October 2019), because the study was conducted in a systematic way and their findings are widely used. In addition, the clinical criteria used for intravenous Ig therapy for MMN in this study was consistent with the clinical criteria as per The Criteria V3 for the use intravenous Ig therapy for MMN in Australia. However, by using this estimate (0.6 per 100,000 population), the total number of prevalent cases with a definite diagnosis would equate to 151 patients, which greatly differs from the data provided by the NBA and discussed above. The differences observed between the two sources could be partly explained due to patients treated according to The Criteria V2 having been categorised in all the diagnostic categories of MMN: definite, probable and possible. On the other hand, as discussed in Section A, this could also be a result of misdiagnosing MND as MMN. The latter was supported by a clinical expert during the meeting held on 25 March 2020 where it was suggested that the number of MMN cases from the NBA data likely represented an overestimate of the target population. It should also be noted that The Criteria V3 is more sensitive in differentiating between MMN and MND compared to V2 due to the new requirements for initial and continuing treatment. The Criteria V3 requires that newly diagnosed MMN patients on intravenous Ig therapy be reviewed at 4 months to eliminate non-responders and to also trial-off treatment for MMN patients in remission on maintenance therapy. The full implementation of The Criteria V3 may reduce the misdiagnosing of MND as MMN and thus reduce the number of treated patients.

**Table 47. 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   | -\$30,700,757 | -\$32,309,014 | -\$33,981,664 | -\$35,722,063 | -\$37,533,742 | -\$170,247,241     |

|   |               |               |               |               |               |                |
|---|---------------|---------------|---------------|---------------|---------------|----------------|
| public hospitals                                    |               |               |               |               |               |                |
| 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 |

Abbreviations: AE = adverse event; Ig = immunoglobulin.

By using the NBA utilisation data on Ig for MMN, the estimated prevalence of MMN was 2.3 per 100,000 population for the end of the year 2019. Similarly, the corresponding incidence of MMN in Australia was estimated as 0.5 per 100,000 persons (Table 48). However, as stated above, these estimates may not truly represent the prevalence of MMN in Australia. In addition, The Criteria V3 requires MMN patients to demonstrate progressive muscle weakness and disability according to the adjusted ONLS (see Table 4) in order to be eligible to receive intravenous Ig. Hence, those who do not exhibit these symptoms are not being captured in the NBA utilisation data for intravenous Ig use in patients with MMN.

**Table 48: Incidence and prevalence of MMN in Australia using data on the use of intravenous Ig therapy from the National Blood Authority based on The Criteria Version 2 and 3.**

|  | 2013-14    | 2014-15    | 2015-16    | 2016-17    | 2017-18    | 2018-19    |
|--|------------|------------|------------|------------|------------|------------|
| Australian population                              | 23,475,686 | 23,815,995 | 24,190,907 | 24,601,860 | 24,982,688 | 25,364,307 |
| New patients diagnosed treated with intravenous Ig | 127        | 105        | 137        | 126        | 125        | 123        |
| Total patients                                     | 438        | 444        | 496        | 527        | 560        | 596        |
| Estimated incidence per 100,000                    | 0.5        | 0.4        | 0.6        | 0.5        | 0.5        | 0.5        |
| Estimated prevalence per 100,000                   | 1.9        | 1.9        | 2.0        | 2.1        | 2.2        | 2.3        |

Abbreviations: Ig = immunoglobulin; MMN = multifocal motor neuropathy

Note: the total population of Australia used in estimating the prevalence rate of MMN was the estimate for the end of June quarter (end of each financial year) to correspond with data reported by MSAC on usage of Ig for MMN. E.g. at the end of 2014 June quarter the total population of Australia was 23,475,686 according to data accessed from the Australian Bureau of Statistics on 14/01/2020 at 11:15am.

These data reflect usage under The Criteria V2, prior to the introduction of key changes in The Criteria V3 which aimed to address leakage. This number is likely to be less using the qualifying criteria for Ig therapy for MMN under of the current Version 3 of the Criteria due to the differences in the qualifying criteria between The Criteria Version 2 and Version 3, with the latter being more sensitive in diagnosing true MMN patients eligible for Ig therapy.

Source: [http://stat.data.abs.gov.au/Index.aspx?DatasetCode=ERP\\_QUARTERLY#](http://stat.data.abs.gov.au/Index.aspx?DatasetCode=ERP_QUARTERLY#) accessed on 14/01/2020 at 11:15am (note that ABS Stat beta is continuing to be developed and data is continuously updated hence numbers may change); Table 30, p. 25 of the 1590 MMN draft Referral form and Updated Phase 2 HTA conditions data 23 Dec 2019.

The calculated prevalence of MMN in Australia using the NBA data resulted in a higher estimate compared to other estimates reported in the literature (see Table 5), potentially indicating use in a non-MMN population.

## APPENDIX A

## PEOPLE INVOLVED IN THE REPORT

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The project team comprised of:

Professor Stephen Goodall (Project leader);

Constanza Vargas (Senior Researcher and contact point with the DoH);

Dr Philip Haywood (Clinical lead);

Dr Rebecca Addo (Research fellow);

Milena Lewandowska, (Research fellow);

Liz Chinchin (literature searching and proofreading);

Professor Rosalie Viney (Advisor);

Associate Professor Richard De Abreu Lourenco (Advisor).

# APPENDIX A

# SEARCH STRATEGIES

## BIBLIOGRAPHIC DATABASES

| Electronic database  | Time period searched                             |
|--|--|
| Embase,  | 1974 to 11 October 2019                          |
| Ovid MEDLINE ® and Epub Ahead of print, In-Process & Other Non-Indexed Citations, Daily and Versions | 1946 to 11 October 2019                          |
| Pubmed   | Date of inception of database to 11 October 2019 |
| The Cochrane Library   | Date of inception of database to 15 October 2019 |

## ADDITIONAL SOURCES OF LITERATURE (INCLUDING WEBSITES)

| Source  | Location  |
|---|---|
| clinicaltrials.gov                                      | <a href="https://clinicaltrials.gov/">https://clinicaltrials.gov/</a>             |
| International Clinical Trials Registry Platform (ICTRP) | <a href="https://apps.who.int/trialsearch/">https://apps.who.int/trialsearch/</a> |

**Table 49. Search terms used in the systematic literature search for intravenous Ig treatment for MMN patients**

| Electronic database  | Search strategy/terms   |
|--|---|
| Embase, vid MEDLINE ® and Epub Ahead of print, In-Process & Other Non-Indexed Citations, Daily and Versions. | 1 multifocal motor neuropath*.mp. (2119)  |
|  | 2 Immunoglobulins, Intravenous/ or Intravenous immunoglobulin* or ivig.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy] (141961) |
|  | 3 1 and 2 (1126)  |
|  | 4 exp clinical trial/ (2279960)   |
|  | 5 exp "clinical trial (topic)"/ or exp clinical trial as topic/ (641983)  |
|  | 6 controlled study.de. (7015974)  |
|  | 7 ((clinical or controlled) adj (trial* or study or studies)).ab,ti. (1669338)  |
|  | 8 exp comparative study/ (3196621)  |
|  | 9 prospective study/ (1074972)  |
|  | 10 8 or 9 (4108338)   |
|  | 11 (random* or controlled or 'control group' or 'control groups').ab,ti. (4254392)  |
|  | 12 10 and 11 (614477)   |
|  | 13 4 or 5 or 6 or 7 or 12 (9896517)   |
|  | 14 3 and 13 (428)   |
|  | 15 randomized controlled trial.de. (1067989)  |
|  | 16 ("randomized controlled trial (topic)" or randomized controlled trials as topic).de. (297904)  |
|  | 17 randomization.de. (84727)  |
|  | 18 single blind procedure.de. (37038)   |
|  | 19 double blind procedure.de. (167444)  |
|  | 20 triple blind procedure.de. (235)   |
|  | 21 crossover procedure.de. (61258)  |
|  | 22 open study.de. (37112)   |
|  | 23 parallel design.de. (11100)  |
|  | 24 (placebo or placebos).de. (378937)   |
|  | 25 placebo effect.de. (10205)   |

| Electronic database  | Search strategy/terms  |
|----------------------|--|
|                      | <p>26 major clinical study.de. (3568633)</p> <p>27 latin square design.de. (364)</p> <p>28 quasi experimental study.de. (6077)</p> <p>29 (random* adj (trial* or study or studies)).ab.ti. (300042)</p> <p>30 ((assigned or allocated or allocation) adj random*).ab.ti. (15666)</p> <p>31 (random* adj2 (comparison or comparative)).ab.ti. (23491)</p> <p>32 ((single or double or treble or triple) adj (blind* or mask* or dummy)).ab.ti. (398777)</p> <p>33 ('cross over' or crossover or 'open label' or 'open trial' or 'parallel design' or placebo*).ab.ti. (732760)</p> <p>34 ('comparison group' or 'comparison groups' or quasiexperimental or 'quasi experimental' or pseudoexperimental or 'pseudo experimental').ab.ti. (66385)</p> <p>35 (matched adj (communities or schools or population* or pair or pairs)).ab.ti. (26477)</p> <p>36 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 (5435753)</p> <p>37 3 and 36 (258)</p> <p>38 meta analysis.de. (279503)</p> <p>39 (meta analysis as topic or "meta analysis (topic)").de. (58632)</p> <p>40 ('meta analysis' or 'meta analyses' or 'meta analytical' or metanaly*).ab.ti. (355095)</p> <p>41 38 or 39 or 40 (457386)</p> <p>42 3 and 41 (15)</p> <p>43 systematic review.de. (336880)</p> <p>44 ("systematic review (topic)" or systematic review as topic).de. (24475)</p> <p>45 ((quantitative* or systematic* or methodologic*) and (review* or overview*)).ti. (258734)</p> <p>46 ((quantitative* or systematic* or methodologic*) and (review* or overview*)).ab. (477930)</p> <p>47 cochrane*.jn. (34518)</p> <p>48 (evidence based medicine and review).de. (58994)</p> <p>49 43 or 44 or 45 or 46 or 47 or 48 (709008)</p> <p>50 3 and 49 (51)</p> <p>51 pooled analysis.de. (34)</p> <p>52 (pooled adj4 analys?s).ab.ti. (46848)</p> <p>53 51 or 52 (46852)</p> <p>54 3 and 53 (0)</p> <p>55 14 or 37 or 42 or 50 or 54 (485)</p> <p>56 remove duplicates from 55 (367)</p> |
| The Cochrane Library | <p>ID Search Hits</p> <p>#1 Intravenous immunoglobulin* 2851</p> <p>#2 Multifocal motor neuropath* or MMN 466</p> <p>#3 MeSH descriptor: [Immunoglobulins] explode all trees 22872</p> <p>#4 #1 or #3 24338</p> <p>#5 #2 and #4 66</p> <p>Results:</p> <ul style="list-style-type: none"> <li>- Cochrane Database of Systematic Reviews Issue 10 of 12, October 2019 - 18 records</li> <li>- Cochrane Central Register of Controlled Trials Issue 10 of 12, October 2019 - 48 records</li> </ul>   |

## APPENDIX B

## STUDIES INCLUDED IN THE SYSTEMATIC REVIEW

Table 50. List of included studies

| Study ID                                 | Title  | Citation  | Ref. |
|--|--|---|------|
| <b>Randomised controlled trials</b>      |  |   |      |
| Azulay et al. 1994                       | Intravenous immunoglobulin treatment in patients with motor neuron syndromes associated with anti-GM1 antibodies: A double-blind, placebo-controlled study | Neurology 44: 429-432   | (24) |
| Van den Berg et al. 1995                 | Treatment of multifocal motor neuropathy with high dose intravenous immunoglobulins: a double blind, placebo controlled study                              | Journal of Neurology, Neurosurgery, and Psychiatry 59 (3): 248-252        | (25) |
| Federico et al. 2000                     | Multifocal motor neuropathy improved by intravenous Ig: Randomised, double-blind, placebo controlled study   | Neurology 55 (9): 1256-1262   | (26) |
| Leger et al. 2001                        | Intravenous immunoglobulin treatment in MMN. A double blind, placebo-controlled study  | Brain 124 (1):145-153   | (27) |
| Hahn et al. 2013                         | A controlled trial of intravenous immunoglobulin in multifocal motor neuropathy  | Journal of Peripheral Nervous System 18 (4): 321-330                      | (28) |
| <b>Non-randomised single arm studies</b> |  |   |      |
| Chaudrhy et al. 1993                     | Multifocal motor neuropathy: response to human immunoglobulin  | Annals of Neurology;33:237-242  | (22) |
| Nobile-Orazio et al. 1993                | High-dose intravenous immunoglobulin therapy in multifocal motor neuropathy  | Neurology 43:537-54   | (36) |
| Leger et al. 1994                        | Human immunoglobulin treatment of multifocal motor neuropathy and polyneuropathy associated with monoclonal gammopathy                                     | Journal of Neurology Neurosurgery and Psychiatry 57 (Supplement):46-49    | (68) |
| Comi et al. 1994                         | Clinical and neurophysiological assessment of immunoglobulin therapy in five patients with multifocal motor neuropathy                                     | Journal of Neurology, Neurosurgery, and Psychiatry; 57 (Supplement):35-37 | (69) |
| Van den Berg et al. 1995                 | Improvement of multifocal motor neuropathy during long-term weekly treatment with human immunoglobulin   | Neurology 45: 987-988   | (70) |
| Jaspert et al. 1996                      | Multifocal motor neuropathy: Clinical and electrophysiological findings  | Journal of Neurology 243: 684-692   | (37) |
| Azulay et al. 1997                       | Long term follow-up of multifocal motor neuropathy with conduction block under treatment   | Journal of Neurology Neurosurgery and Psychiatry;62:391-394               | (38) |
| Grehl et al. 1997                        | Long-term therapy with high-dose intravenous immunoglobulins (intravenous Ig) in inflammatory neuropathies   | European Journal of Neurology 4, 266-273                                  | (39) |

| Study ID                  | Title  | Citation   | Ref. |
|---------------------------|--|--|------|
| Van den Berg et al. 1998  | The long-term effect of intravenous immunoglobulin treatment in multifocal motor neuropathy  | Brain 121, 421–428   | (29) |
| Katz et al. 2002          | Axonal multifocal motor neuropathy without conduction block or other features of demyelination   | Neurology 58:615-620   | (47) |
| Nobile-Orazio et al. 2002 | Multifocal motor neuropathy: clinical and immunological features and response to intravenous Ig in relation to the presence and degree of motor conduction block                             | Journal of Neurology Neurosurgery and Psychiatry;72:761–766    | (71) |
| Van den Berg et al. 2002  | Disease severity in multifocal motor neuropathy and its association with the response to immunoglobulin treatment  | Journal of Neurology 49 : 330–336                              | (72) |
| Van den Berg et al. 2002  | Multifocal motor neuropathy: long-term clinical and electrophysiological assessment of intravenous immunoglobulin maintenance treatment  | Brain 125, 1875-1886   | (30) |
| Vucic et al. 2004         | Multifocal motor neuropathy. Decrease in conduction blocks and reinnervation with long-term intravenous Ig   | Neurology 3:1264–1269  | (31) |
| Delmont et al. 2006       | Multifocal motor neuropathy with and without conduction block: A single entity?  | Neurology 67: 592-596  | (55) |
| Slee et al. 2007          | Multifocal motor neuropathy. The diagnostic spectrum and response to treatment   | Neurology 69:1680–1687   | (56) |
| Leger et al. 2008         | Intravenous immunoglobulin as short- and long-term therapy of multifocal motor neuropathy: A retrospective study of response to intravenous Ig and of its predictive criteria in 40 patients | Journal of Neurology, Neurosurgery and Psychiatry 79:93–9      | (19) |
| Baumann et al. 2009       | Intravenous immunoglobulin dose increase in multifocal motor neuropathy: a prospective six month follow-up   | Journal of Neurology 256:608–614                               | (40) |
| Cats et al. 2010          | Correlates of outcome and response to intravenous Ig in 88 patients with multifocal motor neuropathy   | Neurology 75:818–825   | (14) |
| Vlam et al. 2013          | Pharmacokinetics of intravenous immunoglobulin in multifocal motor neuropathy  | Journal of Neurology Neurosurgery and Psychiatry 85:1145–1148. | (73) |
| Nobile-Orazio et al. 2017 | High-dose Ig VENA is well tolerated and efficacious in patients with multifocal motor neuropathy   | Neurological Sciences 38:899–902                               | (41) |
| Goedee et al. 2018        | Nerve ultrasound for the identification of treatment-responsive chronic neuropathies without nerve conduction abnormalities  | Muscle and Nerve 60(4): 415-419                                | (74) |



| Study ID             | Title  | Citation   | Ref. |
|----------------------|--|--|------|
| Kuwabara et al. 2018 | Intravenous immunoglobulin for maintenance treatment of multifocal motor neuropathy: A multi-centre, open-label, 52-week phase 3 trial | Journal of Peripheral Nervous System 23:115–119. | (32) |
| Chia et al. 2019     | Clinical and functional change in multifocal motor neuropathy treated with intravenous Ig  | Journal of Clinical Neuroscience 69: 114-119     | (34) |

Abbreviations: Ig = immunoglobulins.

**Table 51. Profiles of studies included in the systematic literature review**

| Authors<br>Study ID<br>Publication<br>Year | Study design<br><br>Risk of bias                             | Eligibility criteria   | Study population<br>characteristics   | Description<br>Intervention   | Description<br>Comparator   | Relevant outcomes<br>assessed<br>Duration of follow-<br>up  | Measurement of outcomes,<br>time point of outcome<br>measurement reported, and<br>methods of analysis   |
|--|--|--|---|---|---|---|---|
| Azulay et al.<br>1994 (24)                 | Double-blind,<br>placebo-<br>controlled,<br>cross-over trial | <u>Inclusion criteria:</u><br>Patients with motor neuron syndromes associated with high titre of anti-GM1 antibodies and also had electrophysiological evidence of motor conduction block.<br><i>Two of these patients had sensory impairment.</i><br><u>Exclusion criteria:</u><br>Patients with amyotrophic lateral sclerosis. | N = 5<br>Mean age of onset: 48.4 (range: 41 to 63)<br>Gender, n (%) male: 4 (80)<br>Duration of symptoms (mean years): 6.07<br>Baseline average disability: NR<br>Presence of conduction block: Yes<br>Previously treated: NR | Intravenous Ig treatment administered as 0.4g/Kg/day for 5 consecutive days. Patients were switched over to the alternative treatment after 8 weeks. Patients received a total of two treatment courses | Saline solution for 5 consecutive days. Patients were cross over after 8 weeks. Patients received a total of two treatment courses. | <u>Outcomes</u><br>Primary:<br>• Change in disability<br>• Improvement in muscle strength<br>Secondary:<br>• Side effects (safety)<br><br><u>Duration of follow-up</u><br>56 days | <u>Measurement of outcome</u><br>Evaluation was performed before and on days 5, 28, and 56 after drug administration.<br>• Disability was measured using the derived Norris scale (score of 63 to 0).<br>• Muscle strength was tested by a computerized analyser (Myocomp, Meditronic instrument). Average strength (expressed in newtons) of a maximal isometric contraction lasting 10 secs for two selected impaired muscles was computed. Two muscles (impaired muscles) with a preserved contraction was selected at the beginning of the study for strength assessment. Muscle strength was obtained by |

| Authors<br>Study ID<br>Publication<br>Year | Study design<br>Risk of bias                                     | Eligibility criteria   | Study population characteristics  | Description of Intervention   | Description of Comparator  | Relevant outcomes assessed<br>Duration of follow-up  | Measurement of outcomes, time point of outcome measurement reported, and methods of analysis   |
|--|--|--|---|---|--|--|--|
|  |  |  |   |   |  |  | <p>summing the strength values. <i>A patient was considered improved if muscle score increased &gt;50% of the initial value.</i></p> <p><u>Time point of assessment</u><br/>28 days after last treatment</p> <p><u>Statistical method of analysis</u><br/>Analysis of variances. Scheffe F-test</p>  |
| Van den Berg et al. 1995 (25)              | Open trial followed by a single patient double blind placebo RCT | <p><u>Inclusion criteria:</u><br/>Patients who had progressive asymmetric weakness and atrophy without sensory involvement, and with electrophysiological evidence of conduction block.</p> <p><u>Exclusion criteria:</u><br/>Not reported. <i>Inferred as patients with upper motor neuron findings or those with a diagnosis of chronic inflammatory demyelinating polyneuropathy.</i></p> | <p>N = 6<br/>Mean age of onset: 47)<br/>Gender, n (%) male: 4 (67)<br/>Duration of symptoms (mean years): 6<br/>Baseline average disability: 2<br/>Presence of conduction block: Yes<br/>Previously treated: NR</p> | <p>Intravenous Ig treatment administered as 0.4g/Kg/day for 5 consecutive days. Patients received alternative treatment once they return to the clinically pre-treatment state. The minimal time interval between two treatment courses was kept at one month. Overall, patients received a total of four treatment course.</p> | <p>Pasteurised plasma solution for 5 consecutive days. Patients received alternative treatment once they return to the clinically pre-treatment state. The minimal time interval between two treatment courses was kept at one month. Overall, patients received a total of four treatment course.</p> | <p><u>Outcomes</u></p> <ul style="list-style-type: none"> <li>Improvement in disability scale</li> <li>Improvement in muscle strength</li> </ul> <p><u>Duration of follow-up</u><br/>26 months</p> | <p><u>Measurement of outcome</u><br/>Patients were examined after each treatment or treatment effects on days 1, 6 and then weekly thereafter. .</p> <ul style="list-style-type: none"> <li>Disability was measured with the modified Rankin scale<sup>c</sup>.</li> </ul> <p>Muscle strength was evaluated with a hand held dynamometer and the MRC<sup>d</sup> scale. Patients were examined before and after each treatment, and then weekly at the outpatient clinic by the same physician. The muscles examined for strength were the flexors and extensors of the neck, elbow, wrist, hip, knees, and feet; abductors of the upper arm; hand grip;</p> |

| Authors<br>Study ID<br>Publication<br>Year | Study design<br><br>Risk of bias                   | Eligibility criteria  | Study population<br>characteristics  | Description<br>Intervention  | of<br>Description<br>Comparator  | of<br>Relevant outcomes<br>assessed<br><br>Duration of follow-<br>up   | Measurement of outcomes,<br>time point of outcome<br>measurement reported, and<br>methods of analysis   |
|--|--|---|--|--|--|--|---|
|  |  |   |  |  |  |  | <p>abductor; and opponens of the thumb. A patient was considered improved when there is a presence of an increase of 50% or more in at least 2 muscles without a decrease of at least 25% in more than one other muscle.</p> <p><u>Time point of assessment</u><br/>Different time points; between 2-6 weeks.</p> <p><u>Statistical method of analysis</u><br/>Description as either a positive or negative improvement.</p>  |
| Federico et al. 2000 (26)                  | Double-blind, placebo controlled, cross-over trial | <p><u>Inclusion criteria:</u><br/>Patients with asymmetric lower motor neuron syndrome with no sensory or bulbar signs and had evidence of partial conduction block (&gt;30%) in motor nerves but normal sensory nerve conduction studies.</p> <p><u>Exclusion criteria:</u><br/>Patients with ALS, chronic inflammatory demyelinating polyneuropathy and</p> | <p>N = 16<br/>Mean age of onset (SD): 38.9 (2.8)<br/>Gender, n (%) male: 15 (94)<br/>Duration of symptoms (mean years (SD)): 5.3 (1.2)<br/>Baseline average disability (SD): intravenous Ig = 28.6 points (6.3), placebo = 25.4 points (5.9)<br/>Baseline grip strength (SD): intravenous Ig = 21.9 Kg (3.4), placebo = 19.7 Kg (SD = 3.2)</p> | <p>Intravenous Ig treatment administered as 0.4g/Kg/day for 5 consecutive days. Patients who remained unchanged or deteriorated were crossed over into the alternate arm on day 28. Patients who improved were not crossed over to the alternate arm until their measures of benefits returned to baseline levels.</p> | <p>5% dextrose or 0.9% saline administered daily for 5 consecutive days. Patients who remained unchanged or deteriorated were crossed over into the alternate arm on day 28. Patients who improved were not cross over to the alternate arm until their measures of benefits returned back to baseline levels.</p> | <p><u>Outcomes</u><br/>Primary:</p> <ul style="list-style-type: none"> <li>• Change in NDS (disability) in response to intravenous Ig treatment</li> <li>• Improvement in maximal grip strength</li> </ul> <p>Secondary:</p> <ul style="list-style-type: none"> <li>• Side effects (safety)</li> <li>• Patient self-rated overall functional ability and strength</li> </ul> | <p><u>Measurement of outcome</u><br/>Evaluation was performed on days 1, 5 and 28 after drug administration.</p> <ul style="list-style-type: none"> <li>• Overall disability tests included a modified NDS<sup>®</sup> (from Dyck et al.1982). It comprised of a summed score of strength in 26 muscle groups (0 = normal, 1 = mildly weak, 2 = moderately weak, 3 = severely weak, 4 = paralysis); the summed score of sensation in all four limbs; and assessment of</li> </ul> |

| Authors<br>Study ID<br>Publication<br>Year | Study design<br><br>Risk of bias                  | Eligibility criteria  | Study population<br>characteristics                         | Description<br>Intervention  | Description<br>Comparator  | Relevant outcomes<br>assessed<br><br>Duration of follow-<br>up | Measurement of outcomes,<br>time point of outcome<br>measurement reported, and<br>methods of analysis   |
|--|---|---|---|--|--|--|---|
|  |   | paraproteinemic neuropathy.   | Presence of conduction block: Yes<br>Previously treated: No | Overall, all patients received the two treatments alternatively after 28 days. | Overall, all patients received the two treatments alternatively after 28 days. | <u>Duration of follow-up</u><br>Not reported                   | tendons reflexes (0 = normal, 1 = reduced, 2 = absent) and tremor (0 = absent, 1 = present).<br><i>A patient is said to have improved on day 28 if there is NDS reduction of <math>\geq 10</math>.</i><br><ul style="list-style-type: none"> <li>Maximal grip strength in both hands (best of the 3 trials) was measured by a hand dynamometer. This was performed by same blinded neurologist on days 1, 5, and 28. <i>A patient is said to have improved on day 28 if there is improvement of grip strength of <math>\geq 10</math>kg.</i><br/>Overall a patient is said to be improved in this study if he/she experienced improvement in NDS, grip strength and subjective functional assessment.</li> </ul> <u>Time point of assessment</u><br>28 days after last treatment<br><br><u>Statistical method of analysis</u><br>Paired one-tailed Student's T-test |
| Leger et al.<br>2001(27)                   | Double-blind, placebo controlled cross over trial | <u>Inclusion criteria:</u><br>Patients diagnosed with MMN based on clinical | N = 19<br>Mean age of onset: 54.6 (range: 40-65)            | Intravenous Ig treatment administered as 0.5g/Kg/day for 5                     | 1% human albumin, lyophilized once a month for 3 months.                       | <u>Outcomes</u><br>Primary:                                    | <u>Measurement of outcome</u><br>Evaluation was performed b at baseline, 4 and 7 months.  |

| Authors<br>Study ID<br>Publication<br>Year | Study design<br><br>Risk of bias | Eligibility criteria  | Study population characteristics  | Description of Intervention   | Description of Comparator   | Relevant outcomes assessed<br>Duration of follow-up  | Measurement of outcomes, time point of outcome measurement reported, and methods of analysis  |
|--|----------------------------------|---|---|---|---|--|---|
|  |                                  | <p>(progressive weakness with multifocal distribution, with no bulbar involvement and no upper motor neuron signs. Symptoms are prominent in the arms) and electrophysiological (multifocal conduction block confined to motor axons. Fasciculation may also be present) diagnostics who had not received immune-suppressants and intravenous Ig treatment for 2 months for treatment naïve (newly diagnosed) and 3 months for pre-treated patients with intravenous Ig.</p> <p><u>Exclusion criteria:</u><br/>Patients with severe concurrent medical condition that might cause neuropathy or interfere with the treatment, were pregnant or were less than 18 years.</p> | <p>Gender, n (%) male:<br/>Duration of symptoms (mean years): 9.04 (range: 1.3-31.7)<br/>Baseline average disability (SD)<sup>a</sup>: intravenous Ig arm = 118.4 (11.2), placebo arm = 112.9 (19.2)<br/>Baseline self-evaluation score<sup>b</sup> (SD): intravenous Ig arm = 19.1 (2), placebo arm = 18.7 (2.9)<br/>Presence of conduction block: Yes<br/>Previously treated: Yes (9 out of 19)</p> | <p>consecutive days. Responders remained on the same treatment after 3 more months and non-responders crossed over to the alternative treatment for the following 3 months.</p> | <p>Responders remained on the same treatment after 3 more months and non-responders crossed over to the alternative treatment for the following 3 months.</p> | <ul style="list-style-type: none"> <li>Improvement in muscle strength</li> <li>Secondary: <ul style="list-style-type: none"> <li>Overall response</li> <li>Self-evaluation scale (assessing change in disability)</li> <li>Side effects (safety)</li> </ul> </li> </ul> <p><u>Duration of follow-up</u><br/>7 months</p> | <ul style="list-style-type: none"> <li>Muscle strength was measured using the MRC score. MRC score was measured in 28 muscles (7 x 2 in the upper limbs, 5 x 2 in the lower limbs and 4 in the neck). Primary endpoint was a difference in MRC score between baseline and 4 months. Change in MRC was calculated as medians with 95% CI within each category of patients (intravenous Ig and Placebo), and between intravenous Ig patients and placebo patients. Changes were considered significant if CI did not include zero. <i>A patient is said to respond to intravenous Ig on the MRC scale at month 4 if he/she had at least 1 more MRC point in two affected muscles Maximum mean overall MRC score in this study was 140; 0 (total paralysis) to 140 (normal strength)</i></li> <li>Self-evaluation scale scored from 0 (normal) to 5 (impossible) for five motor ADL chosen for each</li> </ul> |

| Authors<br>Study ID<br>Publication<br>Year | Study design<br><br>Risk of bias   | Eligibility criteria  | Study population<br>characteristics  | Description<br>Intervention  | of<br>Description<br>Comparator  | of<br>Relevant outcomes<br>assessed<br>Duration of follow-<br>up  | Measurement of outcomes,<br>time point of outcome<br>measurement reported, and<br>methods of analysis   |
|--|--|---|--|--|--|---|---|
|  |  |   |  |  |  |   | <p>patient together with the examiner at baseline.<br/>Maximum score = 25</p> <p><i>Overall, patients were considered as responders at month 4 if they had at least 1 more MRC point in two affected muscles plus 1 point less in two ADL compared to baseline.</i></p> <p><u>Time point of assessment</u><br/>Analysis presented were for the difference between baseline and month 4 (i.e. 28 days after end of treatment course)</p> <p><u>Statistical method of analysis</u><br/>Fischer's exact test for muscle strength</p> |
| Hahn et al.<br>2013 (28)                   | Phase III randomised withdrawal, double-blind, placebo-controlled, cross-over study. | <u>Inclusion criteria:</u><br>Patients diagnosed with probable or definite MMN according to American Association of Electro-diagnostic Medicine criteria, and are on a stable regimen of intravenous Ig for ≥3 months at a dose of 0.4- | N = 44<br>Mean age of onset (SD): 51.64 (10.25)<br>Gender, n (%) male: 32 (72.7)<br>Duration of symptoms (mean years): NR<br>Baseline average disability: NR | Intravenous Ig treatment was administered as 0.4 – 2g/kg body weight every 2- 4 weeks. Each treatment was divided over ≤5 consecutive days.<br>Each blinded period lasted for 12 weeks. All 44 patients received | 0.25% human albumin with normal saline from BUMINATE 25%, or human albumin 200g/l Baxter solution for infusion. Each blinded period lasted for 12 weeks. The same treatment protocol applied as in the intravenous Ig arm. | <u>Outcomes</u><br>Primary:<br>• Change (deterioration) in disability in the upper limb portion<br>• Increased maximal grip strength in the more affected arm<br>Secondary: | <u>Measurement of outcome</u><br>Day 8 (±1 day) of a 2-week treatment interval, and on day 15 (±2 days) for those treated every 3-4 weeks.<br><br>• Disability as determined by the upper limb portion of Guy's Neurological Disability Score (GNDS <sup>1</sup> ): ranges from 0 and 5 (unable   |

| Authors<br>Study ID<br>Publication<br>Year | Study design<br><br>Risk of bias | Eligibility criteria  | Study population characteristics                                       | Description of Intervention  | Description of Comparator   | Relevant outcomes assessed<br><br>Duration of follow-up  | Measurement of outcomes, time point of outcome measurement reported, and methods of analysis  |
|--|----------------------------------|---|--|--|---|--|---|
|  |                                  | <p>2.0g per kg body weight every 2-5 weeks.</p> <p><u>Exclusion criteria:</u><br/>Patients with any co-existing neuropathy, receiving treatment with other immunosuppressive agents, a history of thrombotic episodes, pregnant females, with neutropenia</p> | <p>Presence of conduction block: NR</p> <p>Previously treated: yes</p> | <p>intravenous Ig treatment before randomisation and at the end of each treatment course (or sequence), also for a 12-weeks period (making it a total of three 12-weeks periods of open-label intravenous Ig treatment for all patients). To limit potential axonal damage associated with intravenous Ig withdrawal, patients were permitted to switch from blinded treatment to the next open-label intravenous Ig treatment period without breaking the blind (referred as "accelerated switch") as soon as deterioration interfered significantly with daily activities or if grip strength declined by 50% in the more affected hand. If baseline function was not regained after the switch to open-label intravenous Ig, a dose increase and/or administration of</p> | <p>The median treatment duration during the double-blinded cross-over period was 28 days (range: 7-86).</p> | <ul style="list-style-type: none"> <li>• Decline of <math>\geq 30\%</math> in grip strength in the more and less affected arm</li> <li>• Maximal grip strength in the less affected arm</li> <li>• Overall disability sum score (increased ODSS of at least one grade represents a clinically relevant worsening of disability)</li> <li>• Time required for 9-hole board test with the dominant and non-dominant hand</li> <li>• Patient global impression of change score</li> <li>• Visual analogue scale of disability</li> <li>• Safety and tolerability</li> </ul> <p><u>Duration of follow-up</u><br/>Not reported.</p> | <p>to use either arm for any purposeful movements). Effect of intravenous Ig was assessed for each blinded period by comparing the results to the most recent corresponding observations on open-label intravenous Ig (served as baseline value) GNDS for the upper limbs was analysed as a binary variable indicating whether the score of a subject deteriorated from the blinded periods' baseline (1 or 2) to the last cycle assessment at the end of the blinded periods (1 or 2).</p> <ul style="list-style-type: none"> <li>• Muscle Maximal grip strength in the more affected hand measured with a DynEx digital dynamometer. Effect of intravenous Ig was assessed for each blinded period by comparing the results to the most recent corresponding observations on open-label intravenous Ig (served as baseline value). Mean grip strength of the three trials in the more affected hand, the</li> </ul> |

| Authors<br>Study ID<br>Publication<br>Year | Study design<br>Risk of bias | Eligibility criteria | Study population characteristics | Description of Intervention  | Description of Comparator | Relevant outcomes assessed<br>Duration of follow-up | Measurement of outcomes, time point of outcome measurement reported, and methods of analysis  |
|--|------------------------------|----------------------|----------------------------------|--|---------------------------|---|---|
|  |                              |                      |                                  | <p>intravenous Ig at a shortened dosing interval was permitted ("rescue" treatment) and no further blinded treatment was administered.</p> <p>Median total duration of intravenous Ig treatment per patient was 335 days (11.01 months).<br/>Median monthly dose of 1.2g/kg body weight.<br/>Median treatment duration during the double-blinded cross-over period was 84 days (rang: 13-91)</p> |                           |   | <p>relative change (%) from the blinded periods baseline (defined as the most recent observation from the previous open-label intravenous Ig treatment period) to the end of the blinded period (1 or 2) was analysed using a Fixed effects ANOVA model reflecting the cross-over study design, with factors for sequence (placebo followed by intravenous Ig or intravenous Ig followed by placebo), subject nested within sequence, period (1 or 2), treatment (intravenous Ig or placebo), and baseline for the relative change. The contrast to be tested was the treatment effect of intravenous Ig vs. placebo</p> <p><u>Time point of assessment</u><br/>Day 8 (<math>\pm 1</math> day) for a 2-week treatment interval and day 15 (<math>\pm 2</math> days) for a 3 or 4-week treatment interval</p> <p><u>Statistical method of analysis</u><br/>McNemar's test for disability</p> |



| Authors<br>Study ID<br>Publication<br>Year | Study design<br>Risk of bias | Eligibility criteria | Study population<br>characteristics | Description<br>Intervention | of<br>Description<br>Comparator | of<br>Relevant outcomes<br>assessed<br>Duration of follow-<br>up | Measurement of outcomes,<br>time point of outcome<br>measurement reported, and<br>methods of analysis |
|--|------------------------------|----------------------|-------------------------------------|-----------------------------|---------------------------------|--|---|
|  |                              |                      |                                     |                             |                                 |  | Fixed effects ANOVA model<br>for muscle grip strength.  |

Abbreviations: ALS = amyotrophic lateral sclerosis; GNDS = Guy's Neurological Disability Score; MMN = multifocal motor neuropathy; MRC = medical research council; NDS = neurologic disability scale; NS = not specified; SD = standard deviation

Note: Italicised text were added during the report writing.

a = Disability was measured using the Medical Council Research score; maximum score was 150

b = The maximum self-evaluation score was 15

c = *The modified Rankin scale is measured on a scale of 0 to 5 where, 0 = no symptoms at all; 1 = no significant disability despite symptoms: able to carry out all usual duties and activities; 2 = slight disability: unable to carry out all previous activities but able to look after own affairs without assistance; 3 = moderate disability: requiring some help, but able to walk without assistance; 4 = moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance; 5 = severe disability: bedridden, incontinent, and requiring constant nursing care and attention. (Was initially designed and used for stroke)(75)*

d = *MRC scale is measured using the scale: 0 = No visible contraction 1 = Visible contraction without movement of the limb (not existent for hip flexion) 2 = Movement of the limb but not against gravity. 3 = Movement against gravity over (almost) the full range 4 = Movement against gravity and resistance 5 = Normal (76)*

e = *NDS was designed for deficits affecting the peripheral nervous system(77).*

f = *Guy's Neurological Disability Score (GNDS): ranges from 0 (no upper limb problem), 1 (problems in one or both arms, not affecting the ability to do any of the functions listed), 2 (problems in one or both arms, affecting some but not preventing any of the functions listed), 3 (problems in one or both arms, affecting all or preventing one or two of the functions listed), 4 (problems in one or both arms preventing three or all of the functions listed), and 5 (unable to use either arm for any purposeful movements)(78).*

Table 52. Profiles of single arm studies included in the systematic literature review.

| Authors<br>Study ID<br>Publication<br>Year | Study design                          | Risk of bias<br>(L=low,<br>M=medium,<br>H=high) | Eligibility criteria   | Study population<br>characteristics           | Description of<br>Intervention   | Relevant<br>outcomes<br>assessed   | Measurement of outcomes,<br>time point of outcome<br>measurement reported, and<br>methods of analysis                            |
|--|---------------------------------------|---|--|---|--|--|--|
| Chaudhry et al.<br>1993(22)                | Retrospective<br>study                | M   | Chronic, progressive, asymmetrical predominantly distal limb weakness, muscle wasting, reflex loss, and electrophysiological evidence of multifocal motor demyelination with PMCB. Patients with sensory symptoms or significant sensory abnormalities, either clinically or electrophysiologically were excluded. | 9 patients with MMN;<br>Mean age: 44 years    | HIG: 1.6g - 2.4 g/kg over a period of 2 to 5 days. Six of the 9 patients have received repeated treatments at intervals varying from 2 to 4 months   | Improvement in disability<br><br><br><br><br><br><br>Improvement in muscle strength<br><br>CB<br><br>AEs | Reported as ranging from dramatic to mild.<br><br><br><br><br><br>Hand-held dynamometer, a pinch and grip meter<br><br>EMG; CMAP |
| Nobile-Orazio et al. 1993(36)              | Prospective, open, uncontrolled trial | M   | Chronic or stepwise progressive asymmetric limb weakness with a multineuropathic distribution affecting the muscles of at least two distinct motor nerves and lasting at least two months; and minimal or no sensory loss or symptoms and absence of clinical signs of upper motor neurone involvement.            | 23 patients with MMN;<br>Mean age: 39.4 years | Intravenous Ig for 6 to 12 months: 0.4 g/kg, for 5 consecutive days. No additional therapy was given to patients during the first 3 to 5 months. Afterward, oral cyclophosphamide (1.5 to 3 mg/kg/d) was added in two patients | Improvement in disability  | MRDS   |

|                       |                                      |   |   |  |  |   |   |
|-----------------------|--------------------------------------|---|---|--|--|---|---|
|                       |                                      |   |   |  | (nos. 1 and 2) in order to reduce the frequency of maintenance Intravenous Ig infusions.         | Improvement in muscle strength<br><br>CB<br>AEs   | MRC<br><br>Electrodiagnostic studies; CMAP                            |
| Comi et al. 1994 (69) | Prospective, open uncontrolled trial | M | Asymmetrical weakness and muscle atrophy without relevant sensory loss, which lasted for at least six months; neurological disability | 5 patients with MMN; 3 previously treated steroids, plasma exchange or cyclophosphamide<br>Mean age: 39.6 years (range 23-52). | HIG 0-4 g/kg for 5 consecutive days. All patients had at least 2 intravenous Ig administrations. | Improvement in disability<br><br><br><br><br><br>Improvement in muscle strength<br><br>CB | MRC<br><br><br><br><br><br>MRC<br><br>Electrophysiological test; CMAP |
| Leger et al. 1994(68) | Retrospective study                  | M | NR  | 6 patients with MMN and CB;<br>Age: 34-50 years  | 2g/kg 3-5 days for at least 6 months followed by maintenance treatment.                          | Improvement in muscle strength<br><br><br><br><br>CB                                      | MRC<br><br><br><br>Motor nerve conduction studies; CMAP               |

|                              |                                       |   |   |   |   |  |   |
|------------------------------|---------------------------------------|---|---|---|---|--|---|
| Van den Berg et al. 1995(70) | Case report                           | M | NA  | 1 patient; Age: 37  | HIG treatment in two treatment courses of 0.4 g/kg for 5 consecutive days followed by one HIG infusion (0.4 g/kg) every week for 11 months  | Improvement in muscle strength<br><br>CB           | MRC<br><br>Electrodiagnostic studies, CMAP  |
| Jaspert et al. 1996(37)      | Prospective, open, uncontrolled trial | M | CB  | 8 patients with MMN, 7 patients with asymmetrical paresis; 2 patients previously treated with corticosteroids | High-dose intravenous Ig treatment; initial dosage 0.4 g/kg body weight per day for 5 days; 0.4 g/kg body weight repeated after 4 weeks but only for 1 day. Afterwards, intravenous Ig dosage and the interval between treatment cycles were adjusted to the individual clinical course of the patient. | Improvement in muscle strength<br><br>CB<br><br>AE | MRC<br><br>Electrophysiological examination |
| Azulay et al. 1997(38)       | Retrospective study                   | M | Progressive, asymmetric neuropathy mainly affecting the upper limbs with/without mild sensory loss and CB | 18 patients with MMN; 4 patients had been treated   | 0.4 g/kg/day, for three to five consecutive days at intervals   | Improvement in muscle strength                     | MVIC  |

|                              |                                       |   |  |  |   |  |   |
|------------------------------|---------------------------------------|---|--|--|---|--|---|
|                              |                                       |   |  | previously with steroids without any improvement; Mean age: 45.8 years | determined for each patient after the first evaluation. A mean of 6-3 (range 2 to 15) infusions were performed per patient during a period of nine to 48 months with a mean follow up of 25-3 months. | CB<br>AEs  | Electrophysiological examination                  |
| Grehl et al. 1997(39)        | Prospective, open, uncontrolled trial | M | NR   | 7 patients with MMN  | During the first intravenous Ig course 0.4g/kg per day for 5 days   | Improvement in disability<br><br>Improvement in muscle strength<br><br>CB<br>AEs | MRDS<br><br>MRC<br><br>Neurophysiological studies |
| Van den Berg et al. 1998(29) | Prospective, open, uncontrolled trial | L | Asymmetrical lower motor neuron syndrome with onset distally in one limb, areflexia or hyporeflexia, absent upper motor neuron features, and evidence of CB. All patients were previously untreated and presented with a decline in muscle strength before intravenous Ig. | 7 patients with MMN  | 2 Intravenous Ig treatments (0.4 g/kg for 5 consecutive days) and 2 placebo treatments (pasteurized   | Improvement in disability  | MRDs  |

|                               |                                       |   |   |   |   |   |   |
|-------------------------------|---------------------------------------|---|---|---|---|---|---|
|                               |                                       |   |   |   | plasma solution for 5 consecutive days) in random order. Treatments were blinded for the patient and the physician by the participating pharmacist. | Improvement in muscle strength<br><br>CB<br><br>AEs | Hand-held dynamometer<br><br>Electrophysiological studies, CMAP |
| Katz et al. 2002(47)          | Prospective, open, uncontrolled trial | M | Slowly progressive/ non-progressive, asymmetric, purely motor neuropathy multifocal weakness with preferential involvement of individual peripheral nerves by clinical examination.<br><br>Motor unit potentials or spontaneous activity suggestive of a neuropathic process. | 9 patients with MMN;<br>Mean age: 39 years    | Initial intravenous Ig 2g/kg, maintenance dose 0.4 g/kg   | Improvement in muscle strength<br><br><br><br>CB    | MRC<br><br><br><br>Electrodiagnostic studies, CMAP              |
| Nobile-Orazio et al. 2002(71) | Prospective, open, uncontrolled trial | M | Chronic or stepwise progressive asymmetric limb weakness with a multineuropathic distribution affecting the muscles of at least two distinct motor nerves and lasting at least two months; and (b) minimal or no  | 23 patients with MMN;<br>Mean age: 38.2 years | Intravenous Ig 2 g/kg over 4-5 consecutive days, followed by periodic maintenance intravenous Ig infusions at a dose                                | Improvement in disability                           | MRDS  |

|                              |                                       |   |  |   |   |   |   |
|------------------------------|---------------------------------------|---|--|---|---|---|---|
|                              |                                       |   | sensory loss or symptoms and absence of clinical signs of upper motor neurone involvement  |   | of 1–1.2 g/kg over 2-3 consecutive days at the time of clinical worsening;                                  | Improvement in muscle strength<br><br>CB  | MRC<br><br>Electrophysiological examination, CMAP                             |
| Van den Berg et al. 2002(72) | Prospective, open, uncontrolled trial | M | Presence of asymmetric limb weakness at onset, or a distribution of muscle weakness at examination with at least two peripheral nerves affected and at least one muscle group demonstrating disabling weakness of MRC grade 4 or less; electrophysiological evidence of motor conduction block in at least one nerve according to previously published criteria ; the patient had not received any immunological treatment previously. | 34 patients with MMN;<br>Mean age: 33.5 years | Full course of intravenous Ig 0.4 g/kg for 5 days.  | Improvement in disability<br><br><br><br><br><br><br><br>Improvement in muscle strength<br><br>CB | MRDS<br><br><br><br><br><br>MRC<br><br>Electrophysiological examination, CMAP |
| Van den Berg et al. 2002(30) | Prospective, open, uncontrolled trial | L | Asymmetrical limb weakness at onset or motor involvement with a motor nerve distribution in $\geq 2$ peripheral nerve sites, predominant upper limb involvement, disabling weakness  | 11 patients with MMN;<br>Mean age: 38.8       | Intravenous Ig 0.4 g/kg for 6 days followed by one intravenous Ig infusion every week during the first year | Improvement in disability   | GNDS  |

|                       |   |   |  |  |  |   |   |
|-----------------------|---|---|--|--|--|---|---|
|                       |   |   | of MRC grade $\leq 4$ in at least one muscle; (ii) definite/probable motor CB; (iii) response to intravenous Ig; and (iv) intravenous Ig maintenance treatment lasting at least 4 years.   |  | of intravenous Ig maintenance treatment. The dosage and frequency of intravenous Ig infusions during the remainder of the follow-up were tailored to each patient on the basis of functioning in daily life.   | Improvement in muscle strength<br><br>CB<br><br>AEs | MRC<br><br>Electrophysiological examination, CMAP |
| Vucic et al. 2004(31) | Prospective (with retrospective collection of data), open, uncontrolled trial | L | MMNCB criteria: (1) asymmetric limb weakness ( $\leq$ grade 4 on the MRC) in $\geq 2$ more motor nerves; and 2) evidence of CB $\geq 2$ motor nerves at sites distinct from common entrapment or compression syndromes, with normal mixed and sensory NCS. All patients had to have showed response to intravenous Ig and had been given it for $\geq 2$ years. The criteria for inclusion in this study were 1) response to intravenous Ig treatment; and 2) intravenous Ig treatment given for at least 2 years. | 10 patient; Mean age: Mean age: 46.1 years | Initial treatment: intravenous Ig (2 g/kg) given every 4th week. Each course was administered for 5 consecutive days (0.4 g/kg/day). If after the last course no functional decline had occurred after the expected clinical improvement, the dose of intravenous Ig during the next course was decreased, by 0.4 g/kg/4 weeks, to a | Improvement in disability                           | MRDS  |



|  |  |  |  |  |   |  |  |
|--|--|--|--|--|---|--|--|
|  |  |  |  |  | <p>new maintenance level of 1.6 g/kg given over 4 days. If a functional decline had occurred, then the treatment was repeated at the dose of 2 g/kg in 5 days for one or several courses until strength level was stable. The monthly intravenous Ig dose then was gradually adjusted so that no functional decline occurred before the next treatment. Should the threshold for maximum clinical efficacy be crossed (e.g., the patient's strength declined before the upcoming treatment), the next dose then was increased by 0.4 g/kg. Changes in intravenous Ig dose were made in steps of 0.4 g/kg every 4th week. All patients received maintenance intravenous Ig</p> |  |  |
|--|--|--|--|--|---|--|--|

|                         |                     |   |   |   |  |                                |                                    |
|-------------------------|---------------------|---|---|---|--|--------------------------------|------------------------------------|
|                         |                     |   |   |   | treatment every 4 weeks  | Improvement in muscle strength | MRC                                |
|                         |                     |   |   |   |  | CB                             | EMG CMAP                           |
| Delmont et al. 2006(55) | Retrospective study | M | Chronic asymmetric purely motor weakness with a peripheral nerve distribution mainly affecting the upper limbs.   | 33 patients with 20 with CB; 13 no CB; Mean age: 44.3 years | intravenous Ig (0.4 g/kg, for 5 days. Patients were usually given 3 days of intravenous Ig every 6 to 8 weeks depending on the duration of their improvement after the first infusion.   | Improvement in muscle strength | MRC                                |
|                         |                     |   |   |   |  | CB                             | Electrophysiological studies, CMAP |
| Slee et al. 2007(56)    | Retrospective study | M | Asymmetric onset of purely LMN accompanied by one or more of 1) neurophysiologic evidence of motor CB, 2) clinical observation of markedly weak but un-wasted muscles, 3) markedly differential weakness between muscles innervated by the same motor nerve, 4) intravenous Ig responsiveness. Patients were excluded if had objective sensory abnormality or upper motor neuron signs. Minor subjective sensory symptoms and isolated neurophysiologic sensory potential abnormality was | 47 patients with MMN; Mean age: 42 years                    | Intravenous Ig 0.4 g/kg per day for 5 days. Maintenance intravenous Ig therapy began if the neurologist and patient agreed that meaningful subjective and objective improvement had occurred. Selected patients were converted to domiciliary intravenous Ig | Improvement in disability      | Self-nominated disability score    |

|                         |                                      |   |   |  |   |   |   |
|-------------------------|--------------------------------------|---|---|--|---|---|---|
|                         |                                      |   | permitted if unlikely to be clinically relevant.  |  | administration. No further intravenous Ig was administered to patients without improvement at the initial post-intravenous Ig assessment.   | CB  | EMG CMAP                                |
| Leger et al. 2008(19)   | Retrospective study                  | M | ENMC diagnostic criteria for MMN (except for upper age limit: 80years and CSF analysis).  | 40 patients (22 naïve and 18 previously treated); Mean age; 42 years | Monthly intravenous Ig 2 g/kg over 3–5 days for at least 6 months, maintenance infusions (at the same dose), if needed by recurrent clinical worsening  | Improvement in muscle strength<br><br>CB<br>AEs | MRC<br><br>Electromyography examination |
| Baumann et al. 2009(40) | Prospective, open uncontrolled trial | M | MMN diagnosed according to AAEM criteria, repetitive intravenous Ig treatment for at least 1 year, stable intravenous Ig dose during the last 6 months, persistent paresis and CB, and stable symptoms and findings for at least six months | 9 patients with MMN; Mean age: 59.4 years                            | Individual intravenous Ig dose given over the last six months was retrospectively analysed. In step one, dose was increased to 1.2 g/kg per month given over 3 consecutive days planned for 6 cycles. If patients' motor function did not improve after 2 | Improvement in disability<br>AE                 | GNDS                                    |

|                      |  |   |  |   |   |  |   |
|----------------------|--|---|--|---|---|--|---|
|                      |  |   |  |   | cycles, they entered step two: Dose was increased to 2 g/kg per month given over 5 consecutive days.  | Improvement in muscle strength<br>CB<br>AE                                   | MRC<br><br>Electrophysiological Studies, CMAP |
| Cats et al. 2010(14) | A national cross-sectional descriptive study | M | Definite, probable, or possible MMN, based on the criteria published by Van den Berg 2000 (PMID: 11117549). Normal sensory nerve conduction in segments with motor CB and normal distal sensory nerve action potential amplitudes at the first nerve conduction study. | 88 patients with MMN; Mean age: 40 years ranging (22-66). | intravenous Ig 2g/kg. Median duration of maintenance treatment was 6 years (range 0–17) Dose gradually increased over the years from 12 to 17 g/week. | Improvement in disability<br><br>Improvement in muscle strength<br>CB<br>AEs | ODSS<br><br>MRC<br><br>CMAP                   |
| Vlam et al. 2014(73) |  | M | Definite or probable conduction block; axonal loss in combined nerves; decreased distal compound muscle action; presence of anti-monosialotetrahexosylganglioside (GM1) IgM antibodies   | 23 patients with MMN; Mean age: 41 years                  | Intravenous Ig 2g/kg  | Improvement in muscle strength   | MRC   |

|                          |                                       |   |   |  |   |  |                       |
|--------------------------|---------------------------------------|---|---|--|---|--|-----------------------|
| Nobile-Orazio 2017(41)   | Retrospective study                   | M | MMN according to European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) criteria   | 20 patients with MMN; 49 (31–70) years; 12 (60%) and 8 (40%) had been diagnosed with definite or probable MMN; | Intravenous Ig 0.4 g/kg/day for 5 days followed by maintenance dose individualised according to the clinical needs of each patient, and ranging from a minimum 25 g to a maximum of 80 g every 2–5 weeks. | Improvement in disability<br><br>Improvement in muscle strength<br><br>AEs | ONLS<br><br>MRC       |
| Goedee et al. 2018(74)   | Case report                           | M | Newly referred and treatment-naïve patients at the neuromuscular outpatient clinic at the University Medical Centre Utrecht (UMCU) who were seen between January 2014 and January 2016.4 They did not meet the inclusion criteria of the ongoing study to evaluate the diagnostic accuracy of HRUS in patients with inflammatory neuropathies4 because their NCS showed no electrodiagnostic features of demyelination. | 1 patient with MMN; Age: 50 years  | Intravenous Ig 2g/kg; treatment effects assessed at intervals of 3 to 4 weeks after initial doses   | Improvement in muscle strength<br><br>CB                                   | MRC<br><br>CMAP, SNAP |
| Kuwabara et al. 2018(32) | Prospective, open, uncontrolled trial | L | Definite (8 patients) or probable (5 patients) MMN according to the EFNS/PNS clinical diagnostic criteria. Inclusion criteria: patients requiring intravenous Ig Tx; no   | 13 patients with MMN (12 previously treated,   | Intravenous Ig 0.4 g/kg/d for consecutive 5 days  | Improvement in disability  | GNDS                  |

|                      |                     |   |  |  |  |   |      |
|----------------------|---------------------|---|--|--|--|---|------|
|                      |                     |   | additional immunotherapy, or if already treated, not increasing dose of agents for MMN from 30 days prior to consent; at week 4 an MRCSS improved by $\geq 1$ point or more in 2 or more muscles; age 20 years or older. | 1 naive); Mean age: 60 years   | was administered as the induction treatment, After 3 weeks, intravenous Ig was then administered 1.0 g/kg/d for 1 day, or 0.5 g/kg/d for consecutive 2 days as the maintenance treatment. The maintenance intravenous Ig was administered every 3 weeks from week 4 to week 49 in the maintenance period, with observation conducted until week 52. If additional treatment for MMN was needed, the patient dropped out. | Improvement in muscle strength<br><br>AEs | MRC  |
| Chia et al. 2019(34) | Retrospective study | M | MMN fulfilling EFNS/PNS criteria for definite and probable MMN   | 11 patients with MMN, 9 with definite, 2 with probable MMN; Mean age: 39.5 years | Intravenous Ig 2 g/kg as per actual body weight, with mean dose of 146 gm divided over 5 infusion days. On average, each patient received 5.5  | Improvement in disability                 | MRDS |

|  |  |  |  |  |   |                                |     |
|--|--|--|--|--|---|--------------------------------|-----|
|  |  |  |  |  | (range 4–7, SD 1.0) cycles of treatment over 24.7 weeks (SD 9.1) duration before treatment regime change. This was equivalent to an average of 129.9 gm intravenous Ig per month or 1.82 gm/kg/month (SD 0.3) | Improvement in muscle strength | MRC |
|--|--|--|--|--|---|--------------------------------|-----|

Abbreviations: AEs=adverse events; CB=conduction block; CMAP= compound muscle action potentials; EFN/PNS= European Federation of Neurological Societies/Peripheral Nerve Society; EMG= Needle electromyography; GM1= anti-monosialotetrahexosylganglioside; GNDS= Guy's Neurological Disability Score; HIG= human immunoglobulin; IgM= Immunoglobulin M; Ig= immunoglobulin; MMN=Multifocal motor neuropathy; MMNCB= Multifocal motor neuropathy with conduction block; MRC=Research Council; MRDS= modified Rankin disability scale; MVIC= Maximal voluntary isometric contraction; NA=not available; NCS= Nerve conduction study NR= not reported; ODSS= overall disability sum score; ONLS= Overall Neuropathy Limitations Scale; PMCB=partial motor conduction block; SNAP= sensory nerve action potential; UMCU=University Medical Centre Utrecht LMN=lower motor neuropathy.

## APPENDIX C

## EVIDENCE PROFILE TABLES

Table 53: Risk of bias assessment of randomised controlled studies using the Cochrane risk of bias tool

|   | Azulay et al. 1994 (24)   | Van den Berg et al. 1995 (25)   | Federico et al. 2000 (26)   | Leger et al. 2001 (27)   | Hahn et al. 2013 (28)  |
|---|---|---|---|--|--|
| <b>Selection bias</b>   |   |   |   |  |  |
| <b>Random sequence generation -</b><br>biased allocation to interventions due to inadequate randomisation   | Some concerns<br><br>Authors did not mention any form of randomisation  | Low<br><br>Authors noted that patients were randomised but did not state the randomisation method | Low<br><br>Treatment order was assigned to each patient individually using a random number generator.   | Low<br><br>The method of randomisation was not stated in the article even though authors noted that patients were randomised.                          | Low<br><br>Randomisation was carried out using a randomisation code by the sponsor.          |
| <b>Allocation concealment –</b><br>biased allocation to interventions due to inadequate concealment of allocations prior to assignment                          | Some concerns<br><br>Nurses who administered treatment were independent of the study, however, this information is insufficient to assess concealment as it remains unclear if nurses and other study personnel were blinded to treatment or not. | Low<br><br>Patients and physicians were blinded to the treatment                                  | Low<br><br>Actual treatment protocol was blinded to neurologist, electromyographer and treating nurses  | Low<br><br>Authors noted that study was double-blinded, although sufficient information was not presented on how and who was blinded.                  | Low<br><br>All patients, investigators and the sponsor were blinded during the entire study. |
| <b>Performance bias</b>   |   |   |   |  |  |
| <b>Blinding of participants and personnel –</b> performance bias due to knowledge of the allocated interventions by participants and personnel during the study | Some concerns<br><br>Nurse who administered treatment was independent of the study but there is insufficient information to assess if participants and other personnel were blinded.  | Low<br><br>Patients and physicians were blinded to the treatment                                  | Low<br><br>Study participants, neurologist, electromyographer and treating nurses were blinded to treatment. It should be noted that there could be a potential for unmasking of treatment order in some patients given the | Low<br><br>Authors noted that study was double-blinded, although insufficient information was presented on how and who was blinded. However, it can be | Low<br><br>Study personnel, sponsors and patients were blinded during the study period.      |



|   | Azulay et al. 1994 (24)   | Van den Berg et al. 1995 (25)  | Federico et al. 2000 (26)  | Leger et al. 2001 (27)   | Hahn et al. 2013 (28)  |
|---|---|--|--|--|--|
|   |   |  | AE profile of intravenous Ig the adverse effects, even though authors note that blinding code was broken at the end of the trial. In addition, the study protocol allowed for patients who remained unchanged or deteriorated to cross over into the second arm on day 28. Patients who improved on day 28 did not enter the second arm until the above measures returned back to the baseline levels. This could lead to unmasking. | inferred from this statement in the paper 'all patients had a double-blind clinical evaluation', that evaluators and patients were blinded to the treatment. The potential for unmasking due to AEs was disregarded by the authors.              |  |
| Detection bias  |   |  |  |  |  |
| <b>Blinding of outcome assessment</b> – detection bias due to knowledge of the allocated interventions by outcome assessors | Some concerns<br><br>Study did not state if outcome assessors were aware or not of the treatment. | Low<br><br>Assessors were blinded to the intervention                                | Low<br><br>Assessors were blinded to the intervention. The blinding code was broken only at the end of the trial.  | Low<br><br>Outcome assessors were blinded to the intervention.   | Low<br><br>Outcome assessors were blinded to the intervention.   |
| <b>Attrition bias</b>   |   |  |  |  |  |
| <b>Incomplete outcome data</b> – attrition bias due to amount, nature or handling or incomplete outcome data.               | Low<br><br>Data was available for all study participants and all data were analysed.              | Low<br><br>Data was available for all study participants and all data were analysed. | Low<br><br>All patients completed both treatment arms; however, follow-up data was not available for 2 patients for the NDS outcome, 1 patient for grip strength, and 6 patients for electro-physiologic measures (this outcome is not considered for the evaluation hence assessment is done disregarding it). The reason for   | Low<br><br>One patient in the naïve group was lost to follow-up. This patient received intravenous Ig treatment for the first treatment course and was lost to follow-up during the treatment course period, hence evaluation was not conducted. | Low<br><br>Two patients discontinued treatment; one was due to adverse events and the other due to relocation from study site. These patients were excluded from most of the analysis. |

|  | Azulay et al. 1994 (24)                       | Van den Berg et al. 1995 (25)                 | Federico et al. 2000 (26)   | Leger et al. 2001 (27)                                   | Hahn et al. 2013 (28)                                    |
|--|---|---|---|--|--|
|  |   |   | the incomplete follow-up data was that examining neurologists did not complete all measurements on a few occasions. |  |  |
| <b>Reporting Bias</b>  |   |   |   |  |  |
| <b>Selective reporting</b> – reporting bias due to selective outcome reporting | Low<br>Results for all outcomes were reported | Low<br>Results for all outcomes were reported | Low<br>Data for all outcomes were reported in the study.  | Low<br>Data for all outcomes were reported in the study. | Low<br>Data for all outcomes were reported in the study. |

Abbreviations: AEs = adverse events; NDS = neurologic disability scale

## APPENDIX D

## EXCLUDED STUDIES

**Table 54. List of excluded studies RCTs**

| Study                     | Title+citation  | Reason for exclusion                  |
|---------------------------|---|---------------------------------------|
| Cochrane et al. 2009      | Cochrane T, Lee D, Gauthier M, Schiff R. Current patients versus future patients: Ethical design of a placebo-controlled RCT. <i>European Journal of Neurology</i> . 2009;16(S3):329.   | Conference poster.                    |
| NA.                       | Euctr DK. A Randomized, Double-Blind, Placebo Controlled, Cross-over Study of the Effectiveness of Immune Globulin Intravenous (Human), 10% (IGIV, 10%) for the Treatment of Multifocal Motor Neuropathy - IGIV, 10% MMN Trial. <a href="http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2009-013841-27-DK">http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2009-013841-27-DK</a> . 2009. | Results unavailable from WHO website. |
| NA                        | Euctr ES. A European, randomised, double-blind, active comparator-controlled, cross-over, efficacy and safety study of a new 10% ready-to-use liquid human intravenous immunoglobulin (I10E) versus Kiovig® in patients with Multifocal Motor Neuropathy.   | No results reported.                  |
| Federico et al. 1999.     | Federico P, Zochodne DW, Feasby TE. Intravenous immunoglobulin treatment in multifocal motor neuropathy with conduction block: a double-blind, placebo-controlled, cross-over study. <i>Neurology</i> . 1999;52(Suppl 2):49, Abstract no: A127.   | Abstract only.                        |
| Hahn et al. 2012.         | Hahn AF, Beydoun SR, Lawson V, Oh M, Empson VG, Gelmont D. A phase III, randomized, placebo-controlled study of the efficacy and safety of 10% liquid intravenous immunoglobulin (intravenous Ig) for the treatment of multifocal motor neuropathy (MMN). <i>Journal of the peripheral nervous system: JPNS</i> . 2012; 17(2):243-4.  | Abstract only.                        |
| Koski et al. 2012.        | Koski C, Beydoun S, Schiff R, Oh M, Ngo L, Leibl H, et al. Efficacy, safety, and tolerability of intravenous gammaglobulin (IGIV, 10%) in a phase 3, randomized, placebo-controlled, cross-over trial for the treatment of multifocal motor neuropathy (MMN). <i>Neurology</i> . 2012;78(1 Meeting Abstract).   | Abstract only.                        |
| Koski et al. 2013.        | Koski CL, Beydoun SR, Lawson V, Oh M, Gelmont D, Empson VG. A phase iii, randomized, placebo-controlled study of the efficacy and safety of 10% liquid intravenous immunoglobulin (IGIV) for the treatment of multifocal motor neuropathy (MMN). <i>PM and R</i> . 2013;5(9 SUPPL. 1):S152.   | Abstract only.                        |
| Koski et al. 2011.        | Koski CL, Schiff R, Oh M, Lee D. A randomized placebo controlled phase III trial of intravenous immunoglobulin (Ig) for the treatment of multifocal motor neuropathy (MMN): Baseline patient characteristics. <i>Journal of the Peripheral Nervous System</i> . 2011;16(SUPPL. 3):S69.  | Abstract only.                        |
| NA                        | Nct. Study of the Effectiveness of Intravenous Immune Globulin (10%) for the Treatment of Multifocal Motor Neuropathy. <a href="https://clinicaltrials.gov/show/NCT00666263">https://clinicaltrials.gov/show/NCT00666263</a> . 2008.  | Duplicate                             |
| Van den Berg et al. 1995. | Van den Berg LH, Franssen H, Oey PL, Wokke JHJ. The effect of intravenous immunoglobulin treatment in patients with multifocal motor neuropathy or lower motor neurone disease. <i>Journal of neurology</i> . 1995;242:149, Abstract no: 806.   | Abstract only.                        |

**Table 55. List of single arm studies excluded studies**

| Study               | Title+citation   | Reason for exclusion   |
|---------------------|--|--|
| Boerio et al. 2010. | Boerio D, Creange A, Hogrel JY, Gueguen A, Bertrand D, Lefaucheur JP. Nerve excitability changes after intravenous immunoglobulin infusions in multifocal motor neuropathy and chronic inflammatory demyelinating neuropathy. <i>J Neurol Sci</i> . 2010;292(1-2):63-71. | Aim was at looking diagnostic features of patients with CIDP and MMN (10 MMN and 10 CIDP patients) |

| Study                       | Title+citation   | Reason for exclusion  |
|-----------------------------|--|---|
| Cammarota et al. 2001       | Cammarota A, Nogues M, Rivero A, Garcia H. [Multifocal motor neuropathy. Immediate response to intravenous immunoglobulin]. <i>Medicina (BAires)</i> . 2001;61(4):441-4.   | Article in Spanish.   |
| Chaudhry et al. 2002        | Chaudhry V, Escolar DM, Comblath DR. Worsening of multifocal motor neuropathy during pregnancy. <i>Neurology</i> . 2002;59(1):139-41.  | Case series of three pregnant women with MMN.   |
| Cros et al. 2006            | Cros D, Drake K. Multifocal motor neuropathies with conduction block: Long-term follow-up of ten patients treated with intravenous Ig. <i>Revue Neurologique</i> . 2006;162(HS1):3S46-3S50.  | Article in French.  |
| Dalakas et al. 1994.        | Dalakas MC, Stein DP, Otero C, Sekul E, Cupler EJ, McCrosky S. Effect of high-dose intravenous immunoglobulin on amyotrophic lateral sclerosis and multifocal motor neuropathy. <i>Archives of Neurology</i> . 1994;51(9):861-4.   | Mainly patients with ALS and only 1 patient with suspected MMN (likely to have been LMs)                    |
| Elliott et al. 1994.        | Elliott JL, Pestronk A. Progression of multifocal motor neuropathy during apparently successful treatment with human immunoglobulin. <i>Neurology</i> . 1994;44(5):967-8.  | Case report of 1 MMN patient who experienced an unusual presentation of the disease.                        |
| Ellis et al. 1999           | Ellis CM, Leary S, Payan J, Shaw C, Hu M, O'Brien M, et al. Use of human intravenous immunoglobulin in lower motor neuron syndromes. <i>Journal of Neurology Neurosurgery and Psychiatry</i> . 1999;67(1):15-9.  | 10 patients presumably with MMN (clinical phenotype) without conduction block. Patients also had, ALS, SMA. |
| Galassi et al. 2014         | Galassi G, Ariatti A, Tondelli M, Benuzzi F, Stefani M, Miceli P, et al. Long-term prognosis and health-related quality of life (HRQoL) in multifocal motor neuropathy (MMN). <i>Journal of Neurology</i> . 2014;261(SUPPL. 1):S96   | Conference paper.   |
| Galassi et al. 2012         | Galassi G, Girolami F. Acute-onset multifocal motor neuropathy (AMMN): how we meet the diagnosis. <i>Int J Neurosci</i> . 2012;122(8):413-22.  | Case study of an unusual presentation of the disease.   |
| Galassi et al. 2012         | Galassi G, Girolami F, Ariatti A, Monelli M, Sola P. Fulminant multifocal motor neuropathy: a report of two cases. <i>Int J Neurosci</i> . 2012;122(7):395-400.  | Case study of an unusual presentation of the disease.   |
| Gallia et al. 2016          | Gallia F, Balducci C, Nobile-Orazio E. Efficacy and tolerability of different brands of intravenous immunoglobulin in the maintenance treatment of chronic immune-mediated neuropathies. <i>Journal of the Peripheral Nervous System</i> . 2016;21(2):82-4.  | Aim was to test response to different brands.   |
| Garg et al. 2016            | Garg N, Park SB, Howells J, Yiannikas C, Huynh W, Vucic S, et al. Differences in response to intravenous immunoglobulin in immune-mediated neuropathy: The importance of conduction block. <i>Journal of the Peripheral Nervous System</i> . 2016;21(3):175.   | Aim of study was to assess conduction block after use of IVIg.  |
| Ghosh et al. 2005.          | Ghosh A, Busby M, Kennett R, Mills K, Donaghy M. A practical definition of conduction block in intravenous Ig responsive multifocal motor neuropathy. <i>Journal of Neurology, Neurosurgery and Psychiatry</i> . 2005;76(9):1264-8.  | Aim was to establish meaning of CB, not establish effectiveness of intravenous Ig.                          |
| Guimaraes-Costa et al. 2017 | Guimaraes-Costa R, Muntean C, Iancu Ferfoglia R, Viala K, Maisonobe T, Musset L, et al. Multifocal motor neuropathy >= 7 years off treatment: 8 Patients. <i>Journal of the Peripheral Nervous System</i> . 2017;22(Supplement 1):S21-S2.  | Conference paper  |
| Herraets et al. 2018.       | Herraets I, Goedee S, Telleman J, Van Asseldonk T, Van Der Pol L, Visser L, et al. Platform Session - Electromyography: Nerve ultrasound for the identification of treatment-responsive chronic neuropathies without nerve conduction abnormalities. <i>Clinical Neurophysiology</i> . 2018;129(Supplement 1):e223-e4. | Full text not found.  |

| Study                        | Title+citation  | Reason for exclusion   |
|------------------------------|---|--|
| Higgoda et al. 2018.         | Higgoda R, Perera D, Thirumavalavan K. Multifocal motor neuropathy presenting as a post-infectious complication of dengue: a CASE report. <i>BMC Infect Dis.</i> 2018;18(1):415.  | Outcomes reported in general terms in a case report where patient had suffered dengue infection. |
| Hoang-Xuan et al. 1993.      | Hoang-Xuan K, Leger JM, Younes-Chennoufi AB, Saidi H, Bouche P, Baumann N, et al. Treatment of immune-mediated neuropathies with intravenous human immune globulin. Open study in 16 cases. <i>Revue Neurologique.</i> 1993;149(6-7):385-92.  | Full text not found.   |
| Jusufovic et al. 2018.       | Jusufovic E, Sinanovic O, Zukic S, Burina A, Dzinic Jusufovic Z, Sakic A. Multifocal Motor Neuropathy: Case Reports. <i>Acta Clin Croat.</i> 2018;57(3):581-7.  | Outcomes reported in general terms.  |
| Kapoor et al. 2018           | Kapoor M, Carr A, Lunn M, Reilly MM. Comparison of clinical factors that impact disease activity in patients with inflammatory neuropathies. <i>Neuromuscular Disorders.</i> 2018;28(Supplement 1):S21-S2.  | Full text not found.   |
| Kazuki et al. 2017.          | Kazuki W, Uchiyama T, Myojin H, Suzuki S, Wakatsuki R, Yamamoto D, et al. Clinical presentation of and maintenance treatment for chronic immune-mediated demyelinating neuropathy. <i>Journal of the Neurological Sciences.</i> 2017;381(Supplement 1):645-6.   | Full text not found.   |
| Larrode-Pellicer et al. 2005 | Larrode-Pellicer P, Salgado-Alvarez de Sotomayor F, Iniguez-Martinez C, Santos S, Tejero-Juste C, Pascual-Millan LF. [Clinical, electrophysiological and immunological evaluation of the response to treatment with intravenous immunoglobulins in several immune-mediated neuropathies]. <i>Rev Neurol.</i> 2005;40(6):345-50. | Article in French.   |
| Lefaucheur et al. 2003.      | Lefaucheur JP, Gregson NA, Gray I, von Raison F, Bertocchi M, Creange A. A variant of multifocal motor neuropathy with acute, generalised presentation and persistent conduction blocks. <i>J Neurol Neurosurg Psychiatry.</i> 2003;74(11):1555-61.   | Outcomes reported in general terms.  |
| Lievens et al. 2009.         | Lievens I, Fournier E, Viala K, Maisonobe T, Bouche P, Leger JM. Multifocal motor neuropathy: A retrospective study of sensory nerve conduction velocities in long-term follow-up of 21 patients. <i>Revue Neurologique.</i> 2009;165(3):243-8.   | Article in French.   |
| Lin et al. 1995              | Lin YY, Tsai CP, Ting YC, Lin KP, Liao KK, Kao KP, et al. Intravenous immunoglobulin infusion in multifocal demyelinating motor neuropathy: a case report. <i>Zhonghua Yi Xue Za Zhi (Taipei).</i> 1995;56(1):66-9.   | Full text not available, conference Abstract only.   |
| Mezaki et al. 1994           | Mezaki T, Kaji R, Akiguchi I, Kimura J. Intravenous immunoglobulin therapy in multifocal motor neuropathy. <i>Clinical Neurology.</i> 1994;34(1):22-6.  | Article in Japanese  |
| Muntean et al. 2015          | Muntean C, Guimaraes-Costa R, Iancu Ferfoglia R, Viala K, Maisonobe T, Musset L, et al. Multifocal motor neuropathy >= 5 years off treatment: 8 patients. <i>Journal of the Peripheral Nervous System.</i> 2015;20(2):196.  | Full text not available, conference Abstract only.   |
| Murata et al. 2010.          | Murata Y, Okamoto T, Kondo Y, Chihara N, Furusawa Y, Murata M. [Monthly low-dose immunoglobulin infusion as a maintenance therapy for multifocal motor neuropathy may reduce allergic adverse effects: a case report]. <i>Rinsho Shinkeigaku.</i> 2010;50(8):561-5.   | Article in Japanese.   |
| Pruppers et al. 2015         | Pruppers MH, Draak TH, Vanhoutte EK, Van der Pol WL, Gorson KC, Léger JM, et al. Outcome measures in MMN revisited: further improvement needed. <i>Journal of the peripheral nervous system : JPNS.</i> 2015;20(3):306-18   | Outcomes reported in general terms   |
| Seror et al 2002.            | Seror P, Leger JM, Maisonobe T. Anterior interosseous nerve and multifocal motor neuropathy. <i>Muscle and Nerve.</i> 2002;26(6):841-4.   | Aim was purely diagnostic: evaluates association between nerve dysfunction and MMN               |

| Study                    | Title+citation  | Reason for exclusion   |
|--------------------------|---|--|
| Shiratori et al. 1996.   | Shiratori M, Saitou K, Inukai A, Aoki S, Sobue G. [Long-term maintenance therapy of multifocal motor neuropathy by weekly administration of human immunoglobulin]. Rinsho Shinkeigaku. 1996;36(6):793-6.  | Article in Japanese.   |
| Sinkunaite et al 2018.   | Sinkunaite L, Burbaud P, Soulages A, Vergnet S, Duval F, Sole G, et al. Focal neurogenic muscle hypertrophy and fasciculations in multifocal motor neuropathy. Muscle Nerve. 2018;58(5):E36-E9.   | Unusual MMN presentation   |
| Stangel et al 2016 (a)   | Stangel, Gold, Baumann, Borte, Fashauer, Hensel, et al. Real-world data on the management of patients with multifocal motor neuropathy (MMN) or chronic inflammatory demyelinating polyneuropathy (CIDP) with immunoglobulins: Long-term data of the SIGNS study. Swiss Medical Weekly. 2016;146(Supplement 219):95S. | Irrelevant outcomes reported.  |
| Stangel et al 2016 (b)   | Stangel M, Gold R, Pittrow D, Baumann U, Borte M, Fasshauer M, et al. Treatment of patients with multifocal motor neuropathy with immunoglobulins in clinical practice: The SIGNS registry. Therapeutic Advances in Neurological Disorders. 2016;9(3):165-79.   | Outdated version of Stangel et al 2016 (a).  |
| Stern et al. 2006.       | Stern BV, Baehring JM, Kleopa KA, Hochberg FH. Multifocal motor neuropathy with conduction block associated with metastatic lymphoma of the nervous system. J Neurooncol. 2006;78(1):81-4.  | Unusual MMN presentation   |
| Toscano et al. 2002      | Toscano A, Rodolico C, Benvenga S, Giralda P, Laura M, Mazzeo A, et al. Multifocal motor neuropathy and asymptomatic Hashimoto's thyroiditis: first report of an association. Neuromuscul Disord. 2002;12(6):566-8.   | Based on one patients with unusual symptoms and disease profile for MMN.   |
| Van den Berg et al. 1997 | Van den Berg LH, Lokhorst H, Wokke JH. Pulsed high-dose dexamethasone is not effective in patients with multifocal motor neuropathy. Neurology. 1997;48(4):1135.  | Wrong intervention (dexamethasone).  |
| Veltkamp et al. 2003.    | Veltkamp R, Krause M, Schranz C, Meinck HM. Progressive arm weakness and tonic hand spasm from multifocal motor neuropathy in the brachial plexus. Muscle Nerve. 2003;28(2):242-5.  | Unusual MMN presentation   |
| Vucic et al. 2004.       | Vucic S, Dawson K, Sun D, Cros D. Pure motor mononeuropathy with distal conduction block: an unusual presentation of multifocal motor neuropathy with conduction blocks. Clin Neurophysiol. 2004;115(10):2323-8.  | Outcomes reported in general terms, and not relevant.  |
| Wang et al. 2017.        | Wang HF, Yang F, Cui F, Chen ZH, Ling L, Huang XS. [Analysis of the clinical and electrophysiological characteristics of multifocal motor neuropathy]. Zhonghua Nei Ke Za Zhi. 2017;56(11):842-5.   | Language not English   |
| White et al. 1996.       | White JR, Sachs GM, Gilchrist JM. Multifocal motor neuropathy with conduction block and Campylobacter jejuni. Neurology. 1996;46(2):562-3.  | Based on 1 patient with unusual course of MMN. Assessment of outcomes reported as overall change without quantitative assessment; no definition of response vs. no response. Quantitative assessment provided only as diagnostic measures. |
| Wittstock et al. 2003.   | Wittstock M, Benecke R, Zettl UK. Therapy with intravenous immunoglobulins: Complications and side-effects. European Neurology. 2003;50(3):172-5.   | Outcomes reported in general terms, and not relevant.  |

Abbreviations: ALS = Amyotrophic Lateral Sclerosis; LMS = lower motor neuron syndrome; SMA=spinal muscular atrophy.

## FIXED EFFECT MODELS

Figure 17. Improvement in disability using the fixed effect model

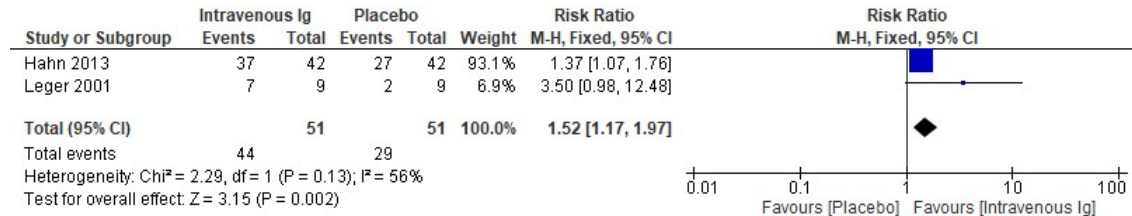


Figure 18. Mean change in disability using the fixed effect model

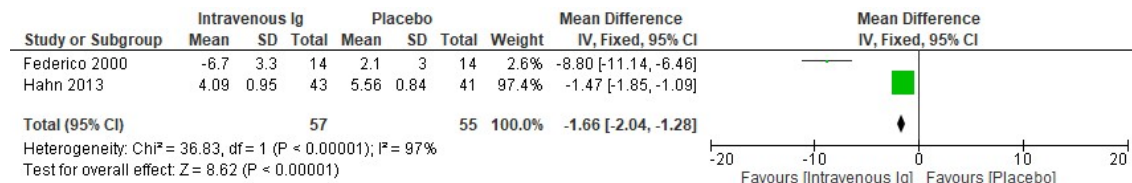
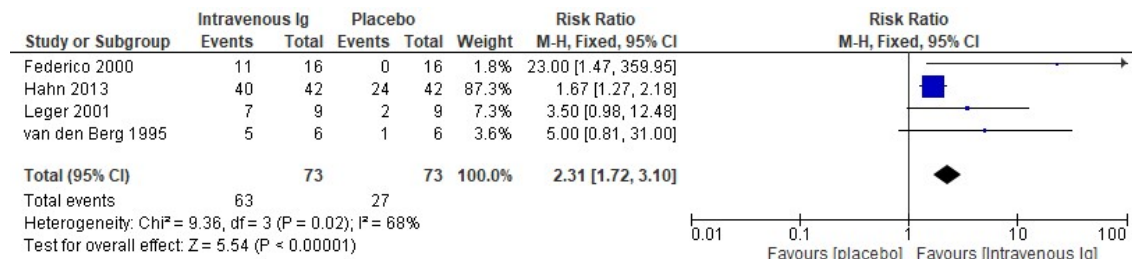


Figure 19. Improvement in muscle strength/grip using the fixed effect model.



## APPENDIX G ECONOMIC ANALYSIS

### INPUTS TO THE ECONOMIC EVALUATION (BASE CASE ANALYSIS)

Table 56. Estimated cost per health state

| Health states   | Frequency (%) | Quantity (n) per cycle (6 m) | Unit price (\$) | Total cost (\$) | Source   |
|---|---------------|------------------------------|-----------------|-----------------|--|
| <b>Initial treatment</b>  |               |                              |                 |                 |  |
| Specialist consultation   | 100           | 1                            | \$124.93        | \$124.93        | Average of MBS item: 6013, 6007, 6015, 6011          |
| Pathology   | 100           | 1                            | \$208.90        | \$208.90        | Average of MBS item: 65070, 71059, 701, 12527, 66500 |
| Diagnostics   | 100           | 0.5                          | \$227.55        | \$113.78        | MBS item 11018                                       |
| Intravenous Ig  | 100           | 5                            | \$2,306.72      | \$11,533.62     | Calculated based on HTA Condition Report 1           |
| <b>Intravenous Ig administration</b>                            |               |                              |                 |                 |  |
| Public hospital (outpatient)                                    | 67            | 5                            | \$461.00        | \$1,544.35      | MSAC 1566, Table 73, p148                            |
| Private hospital (outpatient)                                   | 33            | 5                            | \$500.00        | \$825           | Assumption   |
| Port-a-cath   | 50            | 0.1                          | \$276.75        | \$27.68         | MBS item 34528                                       |
| Pre-medications (antihistamine for infusion reactions)          | 100           | 5                            | \$35.07         | \$175.35        | PBS item 1948M                                       |
| Pathology during Ig infusion                                    | 100           | 5                            | \$208.90        | \$1,044.50      | Average of MBS item: 65070, 71059, 701, 12527, 66500 |
| Physiotherapy   | 100           | 4                            | \$63.25         | \$253.00        | MBS item 10960                                       |
| Rehabilitation  | 100           | 4                            | \$78.84         | \$315.36        | Average of MBS item: 385, 386, 387, 388              |
| <b>Responder</b>  |               |                              |                 |                 |  |
| Consultation (specialist visit)                                 | 100           | 1                            | \$124.93        | \$124.93        | Average of MBS item: 6013, 6007, 6015, 6011          |
| Pathology   | 100           | 1                            | \$208.90        | \$208.90        | Average of MBS item: 65070, 71059, 701, 12527, 66500 |
| Diagnostic  | 100           | 0.5                          | \$227.55        | \$113.78        | MBS item 11018                                       |
| Intravenous Ig  | 100           | 7                            | \$2,306.72      | \$16,147.07     | Calculated based on HTA Condition Report 1           |
| <b>Intravenous Ig administration</b>                            |               |                              |                 |                 |  |
| Public hospital (outpatient)                                    | 67            | 7                            | \$461.00        | \$2,162.09      | MSAC 1566, Table 73, p148                            |
| Private hospital (outpatient)                                   | 33            | 7                            | \$500.00        | \$1,155.00      | Assumption   |
| Port-a-cath   | 50            | 0.1                          | \$276.75        | \$27.68         | MBS item 34528                                       |
| Prophylactic-medications (antihistamine for infusion reactions) | 100           | 7                            | \$35.07         | \$245.49        | PBS item 1948M                                       |
| Pathology during Ig infusion                                    | 100           | 7                            | \$208.90        | \$1,462.30      | Average of MBS item: 65070, 71059, 701, 12527, 66500 |
| Physiotherapy   | 100           | 6                            | \$63.25         | \$379.50        | MBS item 10960                                       |
| Rehabilitation  | 100           | 6                            | \$78.84         | \$473.04        | Average of MBS item: 385, 386, 387, 388              |



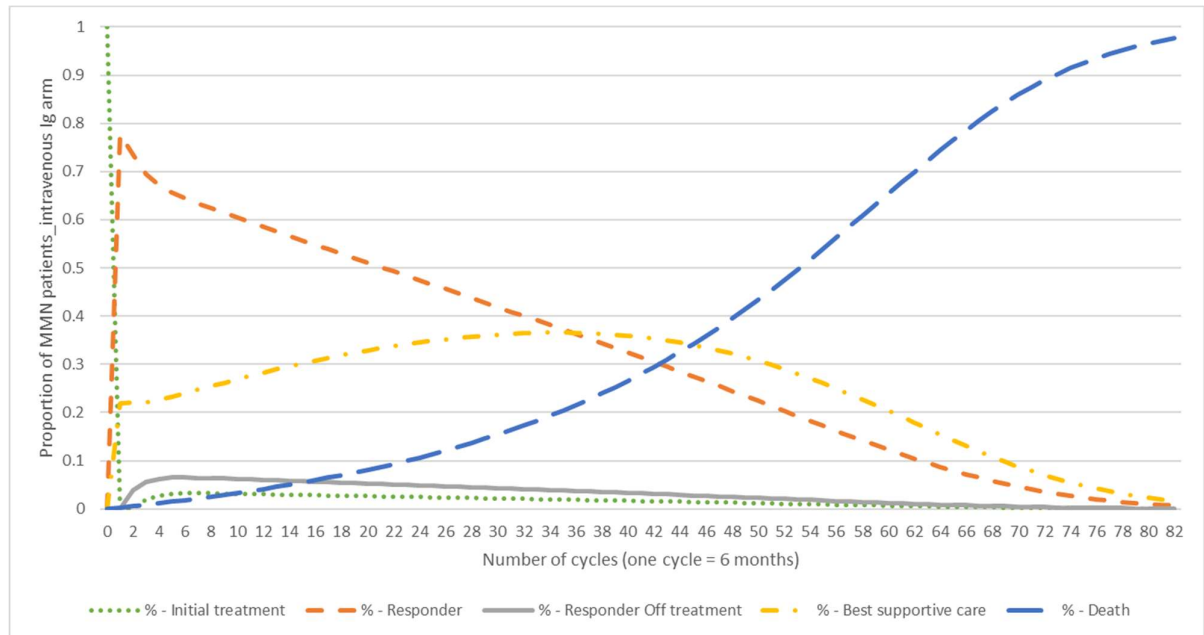
| Health states   | Frequency (%) | Quantity (n) per cycle (6 m) | Unit price (\$) | Total cost (\$) | Source   |
|---|---------------|------------------------------|-----------------|-----------------|--|
| <b>Responder off treatment state (50% of patient with end of dose effect weaning)</b> |               |                              |                 |                 |  |
| Specialist consultation   | 100           | 1                            | \$124.93        | \$124.93        | Average of MBS item: 6013, 6007, 6015, 6011          |
| Pathology   | 100           | 1                            | \$208.90        | \$208.90        | Average of MBS item: 65070, 71059, 701, 12527, 66500 |
| Diagnostic  | 100           | 0.5                          | \$227.55        | \$113.78        | MBS item 11018                                       |
| Intravenous Ig  | 100           | 3.5                          | \$2,306.72      | \$8,073.54      | Calculated based on HTA Condition Report 1           |
| <b>Intravenous Ig administration</b>  |               |                              |                 |                 |  |
| Public hospital (outpatient)  | 67            | 3.5                          | \$461.00        | \$1,081.05      | MSAC 1566, Table 73, p148                            |
| Private hospital (outpatient)   | 33            | 3.5                          | \$500.00        | \$577.50        | Assumption   |
| Port-a-cath   | 50            | 0.1                          | \$276.75        | \$27.68         | MBS item 34528                                       |
| Pre-medications (antihistamine for infusion reactions)                                | 100           | 3.5                          | \$35.07         | \$122.75        | PBS item 1948M                                       |
| Pathology during Ig infusion  | 100           | 3.5                          | \$208.90        | \$731.15        | Average of MBS item: 65070, 71059, 701, 12527, 66500 |
| Physiotherapy   | 100           | 6                            | \$63.25         | \$379.50        | MBS item 10960                                       |
| Rehabilitation  | 100           | 6                            | \$78.84         | \$473.04        | Average of MBS item: 385, 386, 387, 388              |
| <b>Patients who cease Ig treatment after initiation of weaning (50%)</b>              |               |                              |                 |                 |  |
| Consultation (specialist)   | 100           | 1                            | \$124.93        | \$124.93        | Average of MBS item: 6013, 6007, 6015, 6011          |
| Physiotherapy   | 100           | 6                            | \$63.25         | \$379.50        | MBS item 10960                                       |
| Pathology   | 100           | 1                            | \$208.90        | \$209.90        | Average of MBS item: 65070, 71059, 701, 12527, 66500 |
| Rehabilitation  | 100           | 6                            | \$78.84         | \$473.04        | Average of MBS item: 385, 386, 387, 388              |
| Diagnostic  | 100           | 0.5                          | \$227.55        | \$113.78        | MBS item 11018                                       |
| <b>Best supportive care</b>   |               |                              |                 |                 |  |
| Specialist consultation   | 100           | 1                            | \$124.93        | \$123.93        | Average of MBS item: 6013, 6007, 6015, 6011          |
| Physiotherapy   | 100           | 6                            | \$63.25         | \$379.50        | MBS item 10960                                       |
| Pathology   | 100           | 1                            | \$208.90        | \$208.90        | Average of MBS item: 65070, 71059, 701, 12527, 66500 |
| Rehabilitation  | 100           | 6                            | \$78.84         | \$473.04        | Average of MBS item: 385, 386, 387, 388              |
| Diagnostic  | 100           | 0.5                          | \$227.55        | \$113.78        | MBS item 11018                                       |
| <b>Adverse events: Pulmonary embolism (probability of incidence 4.5%)</b>             |               |                              |                 |                 |  |
| Treatment including hospitalisation   | 4.5           | 1                            | \$7,542.00      | \$7,542.00      | Average of AR DRG E61 A and E61 B                    |
| Follow-up outpatient attendance   | 100           | 1                            | \$77.90         | \$77.90         | MBS item 116; MSAC 1565, Table 48, p120              |

Abbreviations: AR DRG= Australian refined diagnosis related group; HTA= health technology assessment; immunoglobulin; Ig= immunoglobulin; MBS = Medicare Benefit Schedule; PBS= Pharmaceutical Benefits Scheme; MSAC= Medical Services Advisory Committee.

Note:<sup>a</sup> In hospital use of promethazine hydrochloride 50 mg/2 mL injection

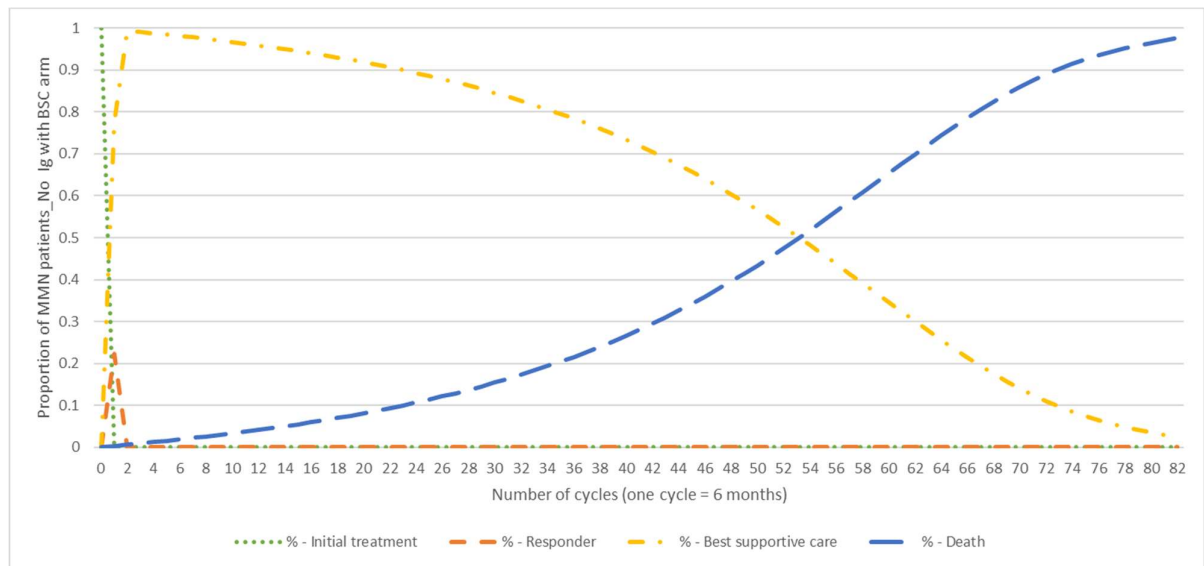
## MARKOV TRACES: LIFETIME TIME HORIZON

Figure 20. Markov traces for life time horizon: intravenous Ig arm.



Abbreviations: Ig = immunoglobulin; MMN = multifocal motor neuropathy

Figure 21. Markov traces for life time horizon: No Ig with BSC arm.



Abbreviations: Ig = immunoglobulin; MMN = multifocal motor neuropathy

**Table 57. Summary of all sensitivity analysis.**

| Variable Description  | SA        |          | ICER (\$/QALY) |         | Impact    |
|---|-----------|----------|----------------|---------|-----------|
|   | Low       | High     | Low            | High    |           |
| <b>Base case</b>  | <b>NA</b> |          | <b>158,776</b> |         | <b>NA</b> |
| 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    |
| Transition probability from 'Initial treatment' to 'Responder'.   | 0.389     | 0.929    | 331,544        | 315,361 | Low       |
| Transition probability from 'Responder' to 'BSC (probability of discontinuation due to AEs).                          | 0.095     | 0.113    | 329,662        | 332,372 | Low       |
| Utility of 'Initial treatment'  | 0.27      | 0.33     | 313,847        | 321,346 | Low       |
| Transition probability from 'Initial treatment to 'Responder' in the no intravenous Ig with BSC arm.                  | 0.111     | 0.69     | 317,552        | 317,552 | Null      |

Abbreviations: AEs = adverse events; BSC = best supportive care; ICER = incremental cost effectiveness ratio; Ig = immunoglobulin; NA = not applicable; QALY = quality adjusted life year.

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