# *Immunoglobulin for chronic Inflammatory Demyelinating Polyneuropathy*

**April 2021**

**MSAC application no. 1564**

**Re-submission assessment report**

Electronic copies of the report can be obtained from the Medical Service Advisory Committee's Internet site at http://www.msac.gov.au/

Enquiries about the content of the report should be emailed to hta@health.gov.au.

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

> ### Main issues for MSAC consideration
>
> - That the requests made by MSAC in this *fit-for purpose* resubmission have been addressed.
>
> - Overall the evidence base for immunoglobulin (Ig) therapy in patients with Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) is very small, and of low quality. Similarly, there is only a small evidence base for plasma exchange (PE) and glucocorticoid therapy (GC). The lack of quality data limits the conclusions that can be made about effectiveness, impact of adverse events and long-term safety compared to PE or GC.
>
> Update of the systematic literature review
>
> - In the update of the systematic literature review of comparative safety and effectiveness of Ig for CIDP, there was no additional randomised control trial (RCT) evidence identified comparing Ig with steroids, PE, immunosuppressants, or combination therapies for CIDP.
>
> - In a RCT that evaluated two doses of subcutaneous Ig (SCIg) in stabilised patients, both SCIg doses (0.2 g/kg and 0.4 g/kg) performed better than placebo for improving relapse rate, time to relapse, and patient reported outcome scores in patients with CIDP. There were more adverse events associated with SCIg treatment (either dose), than placebo. There were few differences in effectiveness or safety between the two SCIg doses.
>
> - MSAC may want to consider whether it should be recommended to start treatment at the lower SCIg dose (0.2 g/kg) and increase if required, or start at the higher dose (0.4 g/kg) and reduce the dose when the patient is ready.
>
> - Two intravenous Ig (IVIg) dose and interval regimens (normal individualised dose and interval, and half the individualised dose at half the interval) showed similar safety and effectiveness when compared in a cross-over RCT. More flexible dosing regimens could be offered to patients with CIDP receiving IVIg.
>
> Extended assessment of harms
>
> - **Plasma Exchange:** Based on one systematic review (SR), the frequency of mild or moderate adverse events (AEs) was low (2.05%) in patients with neurological conditions receiving PE, and ranged from 5.31% to 40% per PE procedure in three other retrospective studies. The rate of serious AEs was reported in two studies as 0.12% and 1.68% of procedures. Common AEs were hypotension, and problems with venous access.

- **Glucocorticoids:** The frequency of AEs was high for patients taking steroids long-term, however the data is less certain due to widely varying populations considered, and because only the most frequent events were reported. The most frequent AEs recorded were serious infection (37% of patients) and hypertension (> 30% of patients). There was a dosage effect in the use of long-term steroids, with several AEs increasing in rate linearly with dosage.

- **IVIg**: AEs occurred in 2.9% of all infusions and 16.9% of patients with autoimmune neurological conditions receiving IVIg in an outpatient setting. In the sub-group with CIDP, AEs occurred in 1.9% of infusions and 12.2% of patients. The most frequent AEs were headache, hypertension, rash and nausea, but the rates of these were generally low. Serious AEs were rare.

Economic analysis

- Given the underlying uncertainty associated with the estimates of treatment effectiveness and safety for both intervention and comparators, the economic model is therefore also associated with uncertainty.

- The previous economic evaluation only presented a cost-utility study for Ig therapy versus corticosteroids in patients with CIDP (comparisons with PE or placebo were not presented in the last report).

- A *de novo* model has been structured in this revised DCAR to address ESC's concerns. The new model allows for treatment stopping and withdrawal and incorporates the additional safety evidence (long-term and short-term) for steroids and PE treatments.

- The resulting costs and outcomes associated with the Ig therapy in the current evaluation are reasonably similar to the previous report, despite the differences in the modelling approach, as average annual dose per patient used in the previous evaluation would have indirectly captured treatment stopping in the model. However, the base-case incremental cost-effectiveness ratio (ICER) in this report is significantly lower compared with the previous DCAR for Ig versus corticosteroids ($116,088 vs $197,472). This can be attributed to the incorporation of severe/long-term AEs associated with steroids driving the larger difference in quality-adjusted life years (QALYs) (1.184 in the present report vs 0.66 in the previous DCAR).

Financial analysis

- A market-based approach has been used to estimate the financial implications of Ig in CIDP, based on current utilisation of Ig products in patients with CIDP. As data available on utilisation were only available for use under the Criteria V2 or when patients were transitioning to the Criteria V3, the impact of transitioning to the Criteria V3 could not be captured in the analysis.

> *Main issues for MSAC consideration*
>
> There is also uncertainty as to whether the trends observed in the Criteria V2 period would continue under the Criteria V3.
>
> - The cost of Ig is the main driver in the financial analysis; higher cost per gram of Ig results in higher budget impact and the lower cost of Ig per gram reduces the estimated net cost to the Government.

### CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

This Contracted Assessment is a resubmission of the DCAR 1564 Review. It examines recent evidence on the safety and effectiveness of Ig for the management of CIDP, and examines new evidence on the safety of comparator treatments for CIDP. It also provides new economic modelling for the management of CIDP. This resubmission is a *fit-for-purpose* report, conducted as part of the Review of Immunoglobulin use in Australia.

### ALIGNMENT WITH AGREED PROTOCOL

A protocol was written a priori for this resubmission to address the specific requests of MSAC. Only these requests were covered in the Protocol (methodology for the update of the systematic literature review was based on the PICO Confirmation agreed to for DCAR 1564). This Contracted Assessment resubmission (DCAR 1564 Update) addresses all of the elements pre-specified in the Protocol. MSAC's requests were the objectives of this report:

- an update of the systematic literature review on the safety and effectiveness of Ig for CIDP (including IVIg and SCIg), especially with relation to the safety of comparators

- revised economic modelling and evaluation of Ig for the management of patients with CIDP, including the development of three distinct models using three different comparators, and addressing specific issues raised by MSAC.

### PROPOSED MEDICAL SERVICE

The proposed medical service is Ig therapy. Ig may be administered either intravenously or subcutaneously. At the commencement of the Review of Ig use for CIDP, only IVIg was funded for CIDP. SCIg was approved for the treatment of CIDP from 1 August 2019. Ig is a purified plasma product, sourced from the Australian Red Cross LifeBlood service and imported supplies; it is funded by the National Blood Authority (NBA).

## POPULATION

The eligible population in Australia are patients with CIDP who meet Version 3 of the *Criteria,* a list of requirements of Ig usage developed by the NBA and updated between 2014 and 2018. Version 3 of the Criteria for CIDP can be seen in **Appendix E**.

In a broader setting, the European Federation of Neurological Societies and Peripheral Nerve Society (EFNS/PNS) guidelines are applied to establish the diagnosis of CIDP. These criteria are widely used in the published literature on CIDP (**Appendix E**).

## COMPARATOR DETAILS

Comparators required in the resubmission as identified by MSAC are:

- Steroids/GC (oral and IV)
- Plasma exchange

GCs and PE have been re-examined in the extended assessment of harms section (B.7.) of this document. In the systematic literature review (Section B.6.), all comparators agreed to in the PICO Confirmation for DCAR 1564 were considered if data were identified. Ig dose comparisons and Ig dosing regimen comparisons were also considered for Section B.6.

## CLINICAL MANAGEMENT ALGORITHM(S)

The current and proposed clinical management algorithms can be found in Appendix F.

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

As reported in DCAR 1564, treatments for CIDP differ in their mode of action, speed of control, degree of invasiveness, side effect profile and costs (Duncan J et al. 2019). Ig may be administered intravenously, usually in a hospital day-care setting, or may be subcutaneously self-administered at home following appropriate training. PE is administered in a similar setting to IVIg, although its availability is restricted to major hospitals in Australia. GC can be taken orally and are the least invasive treatment; they can be self-administered at home.

## CLINICAL CLAIM

The Clinical claim in the original DCAR 1564 was:

> Ig has at least non-inferior effectiveness and superior safety than the comparator interventions of GC (oral and IV), and PE, in the management of CIDP.

No change has been made to the clinical claim in this update report.

## Approach Taken to the Evidence Assessment

The medical literature was searched on 7 October 2020 to update the systematic literature review on the treatment of CIDP with Ig. Evidence was limited to RCTs comparing Ig therapy with an appropriate comparator.

For the extended assessment of harms related to Ig comparators, an additional literature search was conducted on the 26 October 2020, in a broader population base than CIDP alone. Large cohort studies were considered for inclusion, and for GC therapy studies with long-term follow-up were sought. Systematic reviews (SRs) of RCTs or cohort studies were also considered. Studies were selected on the basis of the quality and relevance of the evidence they reported.

## Characteristics of the Evidence Base

The evidence base for the use of Ig, PE or GC in patients with CIDP was very small. No additional RCTs were identified for Ig therapy compared to PE or GC therapy in CIDP patients in the updated literature search. Study populations of CIDP patients receiving Ig were too small to provide accurate safety data in particular, or to accurately determine the effectiveness of Ig in sub-populations such as those receiving multiple medications or in specific age groups. Evidence sought from populations receiving PE or corticosteroids at similar doses to what CIDP patients might receive, filled some gaps in the safety evidence base, albeit with lower applicability than direct evidence. Confounding due to patients receiving multiple medications could not be ruled out in the low-level observational studies included for evidence on safety.

Evidence from two RCTs reported in three articles, was included to update the review on the safety and effectiveness of Ig for CIDP. Both trials were conducted in patients with CIDP who had been stabilised on IVIg, and were assessing Ig as maintenance therapy. One of the RCTs (rated low for risk of bias) compared two doses of SCIg with each other and with placebo (the Polyneuropathy and Treatment with Hizentra trial; PATH) (Hartung et al. 2019). The second RCT was a cross-over design (rated moderate for risk of bias) and compared two IVIg dosing regimens in patients on individualised doses and schedules (IVIg DOSE)[1] (Kuitwaard et al. 2020b).

For the extended assessment of harms, evidence from nine articles was included. To assess the harms of PE, one SR and three retrospective observational studies provided evidence. To assess the harms of GC included studies were limited to those with long-term follow-up. One further SR and three retrospective observational studies were included for GC. All were rated as moderate for risk of bias,

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[1] Note that the name 'IVIg DOSE' has been given for the purposes of writing this assessment only, and was not applied by the authors of the study.

and the follow-up periods ranged from six months to five years. One additional retrospective study was included that assessed the safety of IVIg over a median follow-up period of 21 weeks.

**RESULTS**

**Comparative Safety and Effectiveness of Ig therapy for CIDP**

***0.2 g/kg SCIg compared to 0.4 g/kg of SCIg or placebo***

Safety

The frequency of AEs was higher in patients receiving either 0.2 g/kg or 0.4 g/kg of SCIg when compared to placebo, however there was only a small difference between the two SCIg treated groups. Treatment related AEs occurred in 18% of patients receiving placebo, 30% of patients given low-dose SCIg and 35% of patients given high-dose SCIg. There were 11 serious AEs, 10 of which occurred in patients given SCIg, but only one was considered related to treatment (van Schaik, Ivo N. et al. 2018).

Effectiveness

There were few differences in effectiveness found between the two SCIg treated groups, but significantly better effectiveness was found when either 0.2 g/kg and 0.4 g/kg was compared to placebo. There was a statistically significant greater proportion of patients who relapsed or withdrew in the placebo group compared to either SCIg treated group. The relapse rate was 58% in the placebo group, 35% in the low-dose group, and 22.4% in the high-dose group, showing an inverse trend of dose dependent reduction for relapse rate. In addition, time to relapse or withdrawal was significantly shorter for the placebo group compared to either SCIg treated group (Hartung et al. 2019).

Patient reported outcomes (PROs) were reported for the trial. There were differences favouring SCIg treatment (either dose) over placebo for Health-related quality of life (EQ-5D), health status (EQ-VAS), treatment satisfaction (TSQM), and work productivity (WPAI-GH) (Hartung et al. 2019).

***Normal individualised IVIg dose and interval compared to half individualised IVIg dose at half the interval***

Safety

There was a similar frequency in AEs for patients receiving their individualised normal dose and interval versus half their individualised dose at half the interval IVIg. The most common events were fatigue, muscle and joint ache, headache, and warm feeling. These occurred at rates of 50% to 91% of patients. There were no serious AEs reported (Kuitwaard et al. 2020b).

Effectiveness

Effectiveness was measured by change from baseline measures of hand-grip strength, overall disability (IRODS), fatigue severity (RFSS), and overall health (SF-36) in patients receiving either their normal dose and interval regime, or half dose at half the interval regime. Hand-grip strength favoured the normal dose and interval regime but the difference when compared to the half dose at half the interval regime did not reach statistical significance (p = 0.07). There was very little difference in results when effectiveness was measured with the other tools (Kuitwaard et al. 2020b).

**Extended assessment of harms**

*Adverse events associated with plasma exchange*

AE rates were considered from four studies:, one SR and meta-analysis (Ortiz-Salas et al. 2016), and three retrospective studies (Basic-Jukic et al. 2005; Mörtzell Henriksson et al. 2016; Nieto-Aristizábal, Vivas, et al. 2020). The studies were conducted in mixed populations with neurological diseases, with two studies including a proportion of patients with CIDP. Mild or moderate AE rates were 2.05% of patients (reported in one SR), and 4.75% to 40% of procedures (reported in three retrospective studies). The study reporting a 40% AE rate per procedure, also reported an AE rate of 38.2% per procedure in CIDP patients. Both of these rates were considerably higher than those reported in other studies. This may be explained by a more severely affected population in the study than in others, but cannot be confirmed. In the two other studies which reported a per procedure rate, the mild and moderate AE rates were 4.75% and 5.31%.

Serious AE rates were 0.1% and 1.68% of procedures in two retrospective studies.

The most common mild or moderate AEs associated with PE were poor venous access, tingling or paresthesia, hypotension and urticaria. Serious cases of hypotension and anaphylactic reaction were the most commonly reported serious AEs. Three deaths in one study were reportedly the result of "patients' neurological disease and septic shock". One large retrospective database analysis found that procedures performed by central access were associated with more severe AEs, but more access problems were associated with peripheral access.

*Adverse events associated with glucocorticoids*

One SR reported AEs in patients on long-term GCs (Rice et al. 2017). Large retrospective studies reporting AEs associated with long-term GC treatment were identified in populations of rheumatoid arthritis (RA) (Huscher et al. 2009), and giant-cell arteritis (GCA) (Wilson, J. C. et al. 2017a), and one smaller retrospective study of CIDP patients (van Lieverloo et al. 2018). The studies consistently reported only the most common AEs, so it is not possible to determine overall AE rates. One study reported incidence rates of specific AEs in patients with GCA who had a median prednisolone duration of 0.8 (IQR 1.9) years. The incidence rates were 37.9% for serious infection, 22.9% for osteoporosis, and 16.5% for fractures (Wilson, J. C. et al. 2017b).

One retrospective study in CIDP patients reported a moderate AE rate of 8% of patients, and a severe AE rate of 1.6% of patients. Moderate AEs included hypertension, diabetes mellitus *de novo*,

glaucoma, and depression. Of the two severe adverse events, one was severe hypertension, and the other was an acute myocardial infarction (van Lieverloo et al. 2018).

In a large retrospective database analysis of dose effects of GC in RA patients, Huscher et al (Huscher et al. 2009) found that some AEs increased in a linear pattern with increasing doses from < 5 mg/day to 5 – 7.5 mg/day, and > 7.5 mg/day. The AEs were Cushingoid phenotype, ecchymosis, leg oedema, mycosis, and sleep disturbance. Other AEs occurred at dose thresholds, including cataracts (threshold of < 5 mg/day), epistaxis and weight gain (threshold of 5 – 7.5 mg/day), and increased blood pressure, depression or listlessness, and glaucoma (threshold of > 7.5 mg/day).

### *Adverse events associated with IVIg*

One retrospective study (Waheed et al. 2019) analysed AEs in patients with neuromuscular diseases, 50.5% of whom had CIDP. The median follow-up period was 21 weeks. AEs were found to occur in 16.9% of patients and 2.9% of infusions. The most common AE was headache (7.2% of patients), followed by hypertension (4.1% of patients), rash (2.7% of patients), and flu-like symptoms (2.7% of patients).

There were four serious AEs recorded. Four serious cases of aseptic meningitis occurred (0.9% of patients), one in a patient with CIDP (0.5%).

### TRANSLATION ISSUES

The economic model presented is a cost-utility analysis, where Ig therapy is associated with non-inferior effectiveness and better safety profile compared with corticosteroids and PE therapy. Ig therapy is already in use in Australia and eight translation studies were conducted to address issues regarding the applicability, extrapolation and transformation of the evidence to the proposed setting. These are summarised in Table 1

**Table 1        Summary of results of pre-modelling studies and their uses in the economic evaluation**

| Pre-modelling study | Results used in Section D | Results used in sensitivity analyses |
|---|---|---|
| **Applicability issues** | | |
| Does the patient profile in the clinical evidence match the demographic characteristics of patients with CIDP in Australia? | Patient weight: 78 kgs<br>Patient age: 65 years | - |
| Is the Ig dosing and frequency of administration schedule in the clinical trials consistent with the current recommendation in Australia (Criteria V3)? | Treatment doses and frequency vary across trial and clinical practice. The base case uses doses based on the Australian BloodStar Criteria V3 and NBA data rather than clinical trial doses. Table 28 summarises the values used in the analyses. | Alternative estimates of IVIg dosing (higher and lower per infusion doses and higher and lower infusion frequency) are tested in sensitivity analyses. |

| Is the duration of Ig treatment in the clinical evidence consistent with use in the current Australian population? | There is little information on duration of treatment, therefore the modelled duration of treatment is driven by response, relapse and remission data synthesised from RCTs, observational studies and BloodStar data. | - |
|---|---|---|
| What is the optimum period of disease stability that would trigger a decision to reduce the maintenance dose, in order to inform the Criteria? | The base case dosing is based on Criteria V3. | An Ig dose reduction by 20% per treatment course for 6 cycles for Ig maintenance treatment is presented. |
| **Extrapolation issues** | | |
| What is the appropriate time horizon for the economic analysis of maintenance IVIg? | Follow-up in key trials and 10 year | Results across variable time horizons |
| What is the duration of the treatment effect (Ig and comparators) in patients with CIDP and was the duration of effect expected in the Australian setting captured in the available clinical evidence? | On and off-treatment transition probabilities estimated from RCTs, observational studies and BloodStar data (Table 31) and are extrapolated over the modelled time horizon. | A range of alternative transition values (summarised in Table 31) are tested. |
| What safety implications and adverse events are associated with the intervention and comparator drugs treatments when used for longer durations? | Adverse events associated with long-term corticosteroids and ongoing PE are included in the base case economic models. A summary is presented in Table 32 | Alternative estimates of long-term adverse event rates are tested. |
| **Transformation issues** | | |
| What are the utility/disutility values associated with various treatments and health states for patients with CIDP? | External literature identified estimates of utility and utility decrements associated with modelled health states and adverse events. A summary presented in Table 33 and Table 34 | Alternative health state utility values and decrements are tested A summary is presented in Table 33 and Table 34. |

CIDP = chronic inflammatory demyelinating polyneuropathy; IVIg = intravenous immunoglobulin; PE = plasma exchange; RCT = randomised controlled trials

## ECONOMIC EVALUATION

A number of the revisions that the MSAC requested for the economic model in the original DCAR 1564 required significant changes to the model structure and application of inputs. Three distinct models were developed; one for each of the three different comparators – Ig versus steroids; Ig versus therapeutic PE; and second line use of Ig in a steroid-resistant population versus placebo. The first two models are based on assumptions of non-inferior efficacy of Ig, but incorporating further investigation of the comparative safety of the therapies. The third model assumes superior effectiveness and likely inferior or non-inferior safety for Ig use.

A stepped approach is used, moving from a trial-based analysis (Step 1) to the modelled Australian setting (based on BloodStar data and clinical opinion (Department of Health 2021c)), and incorporating important long-term structural assumptions.

A summary of the key characteristics of the economic evaluation is provided in Table 2.

**Table 2        Summary of the economic evaluation**

| | |
|---|---|
| Perspective | Australian healthcare system |
| Comparator(s) | i)  Steroids<br>ii)  Therapeutic plasma exchange<br>iii)  Placebo (in steroids resistant subgroup) |
| Type of economic evaluation | Stepped cost-utility analysis |
| Sources of evidence | Systematic review, expert opinion (Ig review reference group) and data provided by NBA and Department of Health |
| Time horizon | 10 years |
| Outcomes | Cost per QALYs gained |
| Methods used to generate results | Decision analytic Markov model |
| Health states | A.  Active disease: treatment induction or a relapse after more than 6 months off treatment<br>B.  Active but stable disease: maintenance phase (on treatment more than 4 months)<br>C.  No active disease: in remission (off treatment)<br>D.  Treatment resistant/intolerant disease: best supportive care<br>E.  Dead |
| Cycle length | Four weeks |
| Discount rate | 5% |
| Software packages used | Microsoft Excel and TreeAge Pro |

AE = adverse event; Ig = immunoglobulin; NBA = National Blood Authority; QALY = quality-adjusted life year.

Key structural assumptions of the model are:

- Treatment effects are assumed to be constant throughout the model.

- Transient (mild) AEs are not included in the model as these are considered to have no or very low cost or health consequences.

- Moderate AEs associated with chronic steroids use (diabetes, glaucoma, fractures, osteoporosis and serious infections) are assumed to have a health impact for one year after stopping the treatment. It is assumed that patients with these AEs will revert back to their original health one year after ceasing steroids therapy.

- No clinical evidence was identified regarding long-term treatment effect of PE. Utility gain with PE treatment is considered similar to IVIg and the transition probabilities for relapse are from Ig studies.

The results of the modelled base-case economic analyses for three comparisons are presented in Table 3.

**Table 3      Results of the modelled base-case economic analysis**

| Modelled base case economic evaluation | Inc. cost | Inc. QALYs | ICER |
|---|---|---|---|
| **Ig versus corticosteroids**<br>Applies the dose and frequency based on the Criteria version 3 (2g/kg loading dose and 0.7g/kg maintenance dose for Ig), the best estimates of transitions for remission, relapse and adverse events as described in section C.3.2 and Table 39, with the model time horizon of 10 years. | $137,443 | 1.1840 | $116,088 |
| **Ig versus plasma exchange**<br>Applies the dose and frequency based on the Criteria version 3 for Ig and for PE from Gwathmey et al (2020) (Table 28), the best estimates of transitions for remission, relapse and adverse events as described in section C.3.2 and Table 39 with the model time horizon of 10 years. | $49,991 | 0.5316 | $94,038 |
| **Second line Ig versus placebo**<br>Applies the dose and frequency based on the Criteria version 3 for Ig and no treatment for placebo, the best estimates of transitions for remission, relapse and adverse events as described in section C.3.2 and Table 39 with the model time horizon of 10 years. | $159,573 | 1.7162 | $92,983 |

ICER = incremental cost-effectiveness ratio; Inc = incremental; Ig = immunoglobulin; PE = plasma exchange; QALY = quality-adjusted life years.

In all analyses, the cost of Ig was the main driver of the incremental cost, with offsets related to a reduction in the number of adverse events and costs associated with it. The incremental QALYs were primarily accrued in the 'on treatment (induction phase or maintenance phase)' health states due to improved QALYs with Ig treatment. As Ig was associated with higher response rate and fewer AEs, less time was spent in the 'Treatment resistant/intolerant: best supportive care' health state with Ig.

A number of univariate sensitivity analyses were performed to address the uncertainty associated with the model inputs. The cost of Ig per gram is a key cost driver in the model. Any reduction in the Ig doses either by increasing the interval length between doses or decreasing the maintenance dose (such as with weaning off trial or using lower maintenance dose of 0.4g/kg) favours Ig and reduces the ICERs substantially. The base case modelled time horizon is ten years. Decreasing the time horizon below five years increases the ICERs substantially. Varying transition probabilities for treatment response, treatment effect and treatment associated severe adverse effects for intervention and comparators have variable effects across the three models.

The administration cost per PE procedure ($1,477) is the key cost driver in the Ig versus PE comparison, reducing the administration cost of PE by 50% increases the ICER by 67%.

Table 4 presents key sensitivity analyses.

**Table 4      Key sensitivity analyses**

| | Inc. cost | Inc. QALYs | ICER | % change |
|---|---|---|---|---|
| **Ig versus corticosteroids** | | | | |

|  | Inc. cost | Inc. QALYs | ICER | % change |
|---|---|---|---|---|
| Base case analysis | $137,443 | 1.1840 | $116,088 | - |
| *Cost per gram of Ig (base case: $60.41/g of Ig )* | | | | |
| High cost (domestic IVIg, including cost of plasma), $140.18/g | $310,795 | 1.1840 | $262,505 | 126% |
| Weighted average across all indications, $94.51/g | $211,540 | 1.1840 | $178,672 | 54% |
| *Maintenance IVIg dose per treatment course (base case: 0.7 g/kg)* | | | | |
| 0.4 g/kg | $87,628 | 1.1840 | $74,013 | -36% |
| 1.0 g/kg | $187,259 | 1.1840 | $158,163 | 36% |
| *Transition from 'in remission' health state to treatment health states in Ig arm (base case: 3.8%)* | | | | |
| 1.50% | $91,384 | 1.3294 | $68,740 | -41% |
| *Transition from treatment health states to 'in remission' health state (base case: 5.3%)* | | | | |
| 0.57% | $276,595 | 1.0566 | $261,775 | 125% |
| Weaning off trial for Ig | | | | |
| Starting dose in maintenance phase- 1g/kg, then applying 20% dose reduction for 5 cycles | $100,559 | 1.1840 | $84,934 | -27% |
| **Ig versus plasma exchange** | | | | |
| Base case analysis | $49,991 | 0.5316 | $94,038 | - |
| *Cost per gram of Ig (base case: $60.41 per gram of Ig )* | | | | |
| High cost (domestic IVIg, including cost of plasma), $140.18/g | $223,343 | 0.5316 | $420,129 | 347% |
| Weighted average across all indications, $94.51/g | $124,088 | 0.5316 | $233,422 | 148% |
| *Maintenance IVIg dose per treatment course (base case: 0.7 g/kg)* | | | | |
| 0.4 g/kg | $176 | 0.5316 | $331 | -100% |
| 1.0 g/kg | $99,807 | 0.5316 | $187,745 | 100% |
| *Weaning off trial for Ig* | | | | |
| Starting dose in maintenance phase- 1g/kg, then applying 20% dose reduction for 5 cycles | $13,107 | 0.5316 | $24,656 | -74% |

ICER = incremental cost-effectiveness ratio; g = grams; Ig = immunoglobulin; Inc = incremental; IV = intravenous; QALY = quality-adjusted life year.

## ESTIMATED EXTENT OF USE AND FINANCIAL IMPLICATIONS

A market-based approach has been used to estimate the financial implications of Ig in CIDP, based on current utilisation data available for Ig products in patients with CIDP. As most data available was collected under the Criteria V2, or when patients were transitioning to the Criteria V3, the impact of Criteria V3 is not properly captured in the analysis. There is also uncertainty as to whether the trends observed in the past would continue in the future.

The primary sources of data used in the estimates of the financial impact of Ig in CIDP are: NBA (2021a) National reports on the issue and use of immunoglobulin (Ig), and the 'HTA Data 31 Dec 2020.xlsx' workbook provided by the Department (NBA 2021b).

The financial implications associated with funding Ig for CIDP are presented in Table 5.

**Table 5**        Net financial implications to government associated with Ig for CIDP

| | 2021–22 | 2022–23 | 2023–24 | 2024–25 | 2025–26 |
|---|---|---|---|---|---|
| Total cost of Ig | $100,373,758 | $106,243,380 | $112,113,002 | $117,982,625 | $123,852,247 |
| Cost of Ig to the Commonwealth | $63,235,467 | $66,933,329 | $70,631,191 | $74,329,054 | $78,026,916 |
| Cost of Ig to the States | $37,138,290 | $39,310,051 | $41,481,811 | $43,653,571 | $45,825,331 |
| Cost of Ig administration to the States | $27,807,744 | $28,241,137 | $28,544,731 | $28,721,337 | $28,773,765 |
| **Net cost** | **$128,181,501** | **$134,484,517** | **$140,657,733** | **$146,703,962** | **$152,626,012** |
| Net cost to the Commonwealth | $63,235,467 | $66,933,329 | $70,631,191 | $74,329,054 | $78,026,916 |
| Net cost to States | $64,946,034 | $67,551,187 | $70,026,542 | $72,374,908 | $74,599,096 |
| Sensitivity analyses for the cost per gram of Ig (base case: $60.41) | | | | | |
| High cost of Ig $140.18 | $260,722,714 | $274,776,429 | $288,700,345 | $302,497,273 | $316,170,024 |
| Low cost of Ig, $44.94 | $102,477,445 | $107,277,348 | $111,947,451 | $116,490,566 | $120,909,504 |
| Weighted average cost of Ig, $94.51 | $184,834,531 | $194,450,483 | $203,936,636 | $213,295,801 | $222,530,788 |

CIDP = chronic inflammatory demyelinating polyneuropathy; Ig = immunoglobulin

**CONSUMER IMPACT SUMMARY**

There was no additional feedback from consumers to report.

# ACRONYMS AND ABBREVIATIONS

| Acronym/abbreviation | Meaning |
|---|---|
| AE | Adverse event |
| CI | Confidence interval |
| CIDP | Chronic Inflammatory Demyelinating Polyneuropathy |
| CPRD | Clinical Practice Research Datalink |
| EFNS/PNS | The European Federation of Neurological Societies/Peripheral Nerve Society |
| EQ-5D | EuroQol 5-dimension health profile |
| EQ-VAS | EuroQoL health status visual analogue scale |
| GC | Glucocorticoid therapy |
| HR | Hazard ratio |
| HRQoL | Health-related quality of life |
| HTA | Health technology assessment |
| ICER | Incremental cost-effectiveness ratio |
| Ig | Immunoglobulin therapy |
| INCAT | Inflammatory Neuropathy Cause and Treatment |
| IRODS | Rasch-built Overall Disability Scale |
| IV | Intravenous |
| LY | Life-years |
| MBS | Medicare Benefits Schedule |
| MD | Mean difference |
| MRC | Medical Research Council |
| MRS | Modified Rankin Scale |
| MSAC | Medical Services Advisory Committee |
| NBA | National Blood Authority |
| ONLS | Overall Neuropathy Limitations Scale |

| PASC | PICO Confirmation Advisory Sub-Committee of the MSAC |
| --- | --- |
| PBS | Pharmaceutical Benefits Schedule |
| PE | Plasma exchange therapy |
| PICO | Population, Intervention, Comparator and Outcomes |
| PROs | Patient reported outcomes |
| RFSS | Rasch-built Fatigue Severity Scale |
| QALY | Quality-adjusted life year |
| QoL | Quality of life |
| SAE | Serious adverse event |
| SCIg | Subcutaneous Immunoglobulin |
| SD | Standard deviation |
| TGA | Therapeutic Goods Administration |
| TQSM | Treatment Satisfaction Questionnaire for Medicine |
| WPAI-GH | Work Productivity and Activity Impairment Questionnaire for General Health |

# SECTION A      CONTEXT

This Contracted Assessment of Ig for the management of patients with CIDP is intended for the Medical Services Advisory Committee (MSAC). MSAC evaluates new and existing health technologies and procedures for which funding is being sought under the Medicare Benefits Schedule (MBS) in terms of their safety, effectiveness and cost-effectiveness, while taking into account issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, utilising reviews of the scientific literature and other information sources, including clinical expertise.

Adelaide Health Technology Assessment (AHTA), from the University of Adelaide, has been commissioned by the Australian Government Department of Health to conduct a *fit-for-purpose* resubmission of the DCAR 1564 Review of immunoglobulin therapy (Ig) for chronic inflammatory demyelinating polyneuropathy (CIDP). This resubmission (DCAR 1564 Update) has been undertaken as part of the review of Ig use in Australia.

A Protocol was written to guide the DCAR 1564 update report to meet the specific requests of MSAC. The Protocol was agreed with the Department, with input invited from the Ig Review Reference Group. The PICO Confirmation that was ratified by the Ig Review Reference Group for the original DCAR 1564 Review, was used to guide the update of the systematic literature review.

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

## A.1.      ITEMS IN THE AGREED PROTOCOL

The MSAC deferred providing advice on the review of Ig for CIDP, requesting changes to be addressed in a revised DCAR. As this is a resubmission, in which the MSAC has requested specific issues be addressed, only these issues were covered in the Protocol. This Contracted Assessment resubmission (DCAR 1564 Update) addresses all of the specific issues requested by MSAC. They were:

- an update of the systematic literature review on the safety and effectiveness of Ig for CIDP (including IVIg and SCIg), especially with relation to the safety of comparators
- revised economic modelling and evaluation of Ig for the management of patients with CIDP, including the development of three distinct models using three different comparators, and addressing specific issues raised by MSAC.

The specific issues raised by MSAC at its April 2020 meeting in its consideration of the DCAR 1564 (MSAC 2020) are summarised as follows:

*Comparator(s) for new economic analyses*
- *Main comparison - Ig versus steroids.*
- *Secondary comparison Ig versus PE.*

- *Tertiary comparison Ig versus Placebo in steroid resistant population (possibly a scenario analysis of the main comparison).*

*Safety*
- *Review evidence for safety of steroid use over the modelled lifetime of the disease and the appropriate utility decrements.*
- *The DCAR reported insufficient evidence to make an assessment of the comparative safety between Ig and PE and this could be problematic for an economic comparison. Also review safety concerns resulting from vascular access for PE.*

*Efficacy*
- *For Ig versus steroids, the claim is non-inferiority based on Nobile-Orazio et al (2012b) and Hughes (2002) to be used in the base case, but include a sensitivity analysis to model superior efficacy as per Reference Group clinical opinion.*
- *For Ig versus PE a claim of non-inferiority based on Dyck et al (1994).*
- *For Ig versus steroid resistant - a claim of superiority over placebo – based on trial evidence in steroid resistant trial populations.*

*Structure of the economic model*
- *Consider health states where patients cease Ig or the comparator due to remission as well as treatment failure.*
- *Base case should start with trial-based inputs for efficacy, safety, cessation rates and doses over trial time horizon.*
- *Add inputs on dose and time on treatment reflective of clinical practice in Australia. This may come from BloodSTAR data and / or clinician input.*

## A.2.        TO A.8.

There are no changes to the following background sections in the DCAR 1564 Update:

**A.2.   Medical Service;**

**A.3.   Proposal for Public Funding;**

**A.4    Population;**

**A.5.   Comparator Details;**

**A.6    Clinical Management Algorithms;**

**A.7.   Key differences in the delivery of the Medical Service and the Main Comparator;**

**A.8.   Clinical Claim.**

Please refer to the original DCAR 1564 Review for these sections.

## 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 likely future practice with the medical service.

The Population, Intervention, Comparator and Outcomes (PICO) that were pre-specified to guide the systematic literature review in the original DCAR 1564 Review, and for the 1564 Update are presented in Box 1 and Box 2.

**Box 1   Criteria for identifying and selecting studies to determine the safety of Ig in patients with CIDP**

| Selection criteria | Description |
|---|---|
| Population | Patients with chronic inflammatory demyelinating polyneuropathy (CIDP) |
| Intervention | Intravenous and subcutaneous immunoglobulin (IVIg and SCIg) |
| Comparators | • Steroids (oral and intravenous)<br>• Plasma exchange<br>• Immunosuppressant and/or immunomodulatory drugs and therapies (not including steroids)<br>• A combination of two or more of the above therapies<br>• No active treatment |
| Outcomes | Critical for decision making:<br>Any adverse events including the development of disease or side effects (e.g. infections, diabetes, hypertension, cardiovascular disease, prolonged ventilation in ICU). |
| **Systematic review question** | What is the relative safety of Ig (IVIg and SCIg) for the management of CIDP? |

Abbreviations: CIDP = chronic inflammatory demyelinating neuropathy; ICU = intensive care unit; IVIg = intravenous immunoglobulin; SCIg = subcutaneous immunoglobulin

**Box 2   Criteria for identifying and selecting studies to determine the efficacy of Ig in patients with CIDP**

| Selection criteria | Description |
|---|---|
| Population | Patients with chronic inflammatory demyelinating polyneuropathy (CIDP) |
| Intervention | Intravenous and subcutaneous immunoglobulin (IVIg and SCIg) |
| Comparators | • Steroids (oral and intravenous)<br>• Plasma exchange<br>• Immunosuppressant and/or immunomodulatory drugs and therapies (not including steroids)<br>• A combination of two or more of the above therapies<br>• No active treatment |
| Outcomes | Critical for decision making:<br>• Change in disability (e.g. Overall Neuropathy Limitations Scale (ONLS) score, Six-Minute Walk Test (6MWT) in children only)<br>• Change in muscle strength (e.g. Medical Research Council (MRC) Sum (12) in adults, Modified Rankin Scale (MRS) in children)<br>• Change in quality of life<br>• Mortality |
| **Systematic review question** | What is the relative efficacy of Ig (IVIg and SCIg) for the management of CIDP? |

## A.10. CONSUMER IMPACT STATEMENT

There were no changes to the consumer impact statement. Please refer to the original DCAR 1564.

# SECTION B            CLINICAL EVALUATION

## B.1.        LITERATURE SOURCES AND SEARCH STRATEGIES

### *Comparative safety and effectiveness of Ig for CIDP*

The search terms and databases used in the DCAR 1564 Review were used in the DCAR 1564 Update for consistency. The medical literature search was updated on 7 October 2020 to identify all relevant studies published from the beginning of 2019 to the search date on the treatment of CIDP with IVIg or SCIg. There was an overlap of approximately three months with the search of the original review, to identify any articles that may have been in the pre-publication phase previously. Searches were conducted of the databases and sources described in **Appendix B**. Search terms are described in Table 6.

To ensure all relevant data on treatment of CIDP were identified, a broad search strategy was employed, including only terms for the population of interest.

**Table 6      Search terms used in PubMed (adapted for Embase)**

| Element of clinical question | Search terms |
|---|---|
| Population | CIDP, Chronic inflammatory demyelinating polyneuropathy, chronic inflammatory demyelinating polyradiculoneuropathy [MeSH Terms] |
| Limits | Randomised controlled trials, or systematic reviews of randomised controlled trials only |

CIDP = chronic inflammatory demyelinating polyneuropathy; MeSH = Medical Subject Headings

### *Extended assessment of harms*

To broaden the evidence base for the assessment of harms related to Ig comparators, an additional literature search was performed using the terms described in Table 7. The search was performed of the literature databases listed in **Appendix B**, on the 26 October 2020.

Limits applied to the expanded search for comparator safety were systematic reviews (SRs), and cohort studies, implemented using the appropriate filters in each database. A simple search string based on safety outcomes, using terms such as 'safety', 'adverse event', 'side effect' and 'adverse effect', was applied to further focus the search.

**Table 7    Search terms used for evidence on safety of comparator therapies**

| Component | MeSH terms | Text terms |
|---|---|---|
| Autoimmune diseases | Autoimmune diseases | 'autoimmune disease' |
| Steroids | glucocorticoids<br>Prednisone<br>Prednisolone<br>Methylprednisolone<br>Dexamethasone | Corticosteroid*<br>Glucocorticoid*<br>Prednisone<br>Prednisolone<br>Dexamethasone<br>methylprednisolone |
| Plasma exchange | Plasma exchange | 'plasma exchange'<br>'therapeutic plasma exchange'<br>TPE<br>PLEX |
| Immunosuppressants<br>Immunomodulating agents | Immunosuppressive agents<br>Immunosuppression | Immunosuppress*<br>Immunomodulat*<br>Azathioprine<br>Ciclosporin<br>Cyclophosphamide<br>Fingolimod<br>Methotrexate<br>Mycophenolate mofetil<br>Rituximab<br>Tacrolimus |

## B.2.    RESULTS OF LITERATURE SEARCH

The PRISMA flowchart (Figure 1) graphically describes the literature searches and the application of selection criteria (Liberati et al. 2009). For the update of safety and effectiveness (Section B.6) the study selection criteria (**Appendix B**) were identical to those of the earlier report. Evidence was restricted to RCTs. Articles with a study design other than RCT were considered for the extended assessment of harm (Section B.7).

The evidence base was small overall and very few higher level studies (RCTs or prospective comparative cohorts) were identified.

For the safety and effectiveness search, studies were screened by title, abstract, and full-text by a single reviewer, with final selections made in consultation with a second reviewer when there was doubt over inclusion. Any RCT comparing IVIg or SCIg with one of the specified comparators (GC, PE, immunosuppressants, no treatment, or placebo) was considered for inclusion. In addition, studies comparing two or more doses of IVIg or SCIg, or comparing two or more treatment regimens were considered for inclusion, as these had the potential to inform the management of patients with CIDP. Two RCTs were identified in the updated search.

For the extended assessment of harms search, studies were screened by title, abstract, and full-text by a single reviewer. Reference lists of relevant articles were pearled, and articles were considered

from other sources, such as those referenced by the Ig Reference Group, or identified in the safety and effectiveness search. After extensive screening articles were selected based on the applicability of the patient population, follow-up period, and steroid and PE dose and treatment regimens. Further considerations for selection were the size of the study population, date of publication, and risk of bias of the study[2], as these factors contribute to the reliability of the data. Eight studies were included in the extended assessment of harms, including two SRs and seven retrospective cohort studies.

A profile of each included study is provided in **Appendix C**, describing the authors, study ID, publication year, study design and quality (risk of bias), study location, setting, length of follow-up of patients, study population characteristics, description of the intervention, description of the comparator, and relevant outcomes assessed. Study characteristics are also summarised in a shorter format in Section B.4.

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[2] Systematic reviews were appraised using the AMSTAR 2 checklist, and retrospective studies were appraised for using the SIGN 3 checklist for cohort studies.
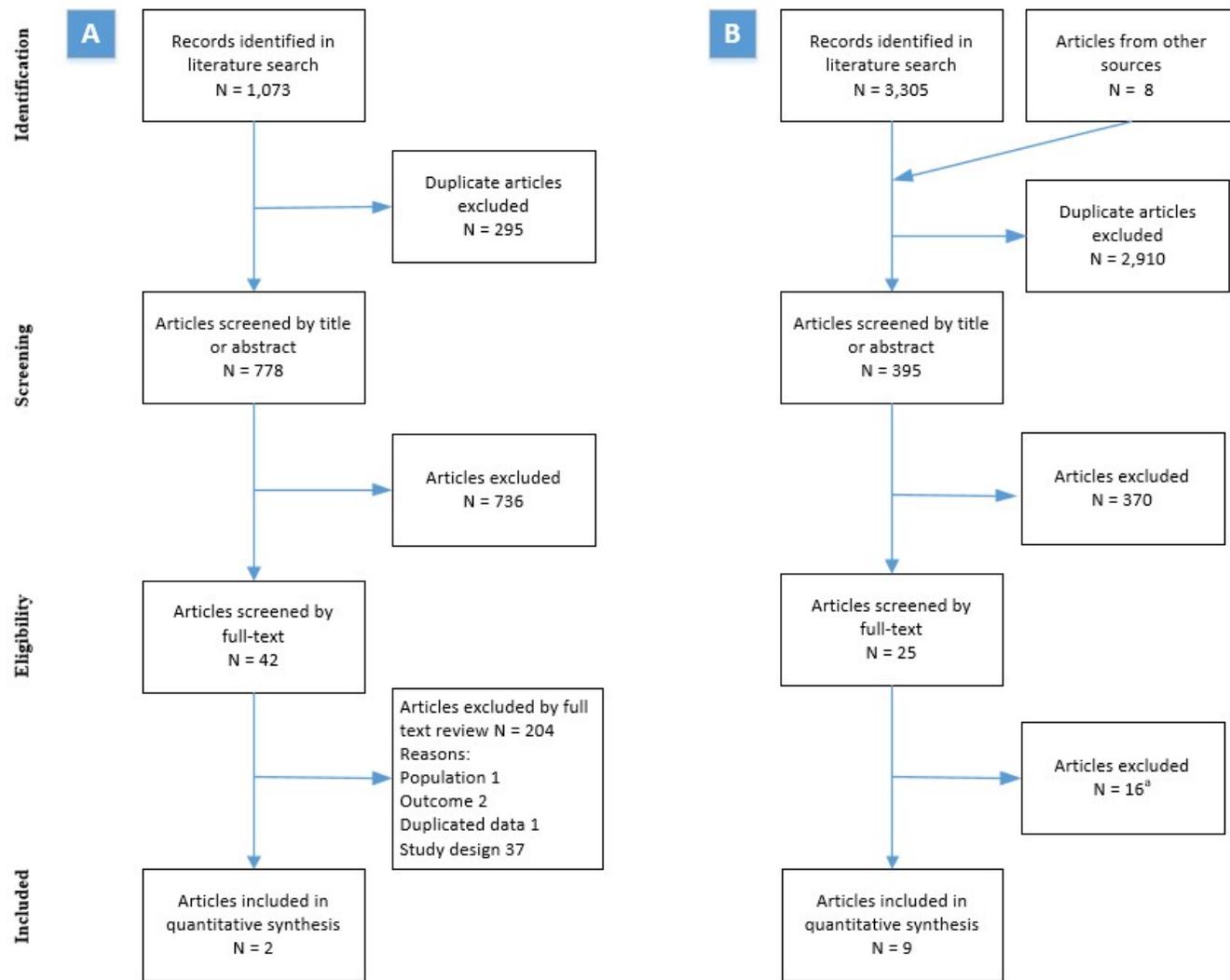
**Figure 1** **Summary of the process used to identify and select studies for A – Update of safety and effectiveness of Ig for CIDP, and B – Extended assessment of harms**

[a] Final articles were selected based on best available evidence (see Section B.7 for more detail).

Appraisal of the evidence was conducted in three stages:

Stage 1: Appraisal of the risk of bias within individual RCTs included in the review (Section B.3).

Stage 2: Extraction of the pre-specified outcomes for this Assessment, synthesising to determine an estimate of effect per outcome.

Stage 3: Integration of this evidence for conclusions about the net clinical benefit of the intervention in the context of Australian clinical practice (Sections B.6-8).

A GRADE assessment (rating of overall quality per outcome across studies) was not performed due to the limited evidence presented in the update report.

## B.3. RISK OF BIAS ASSESSMENT

### RISK OF BIAS IN THE RANDOMISED CONTROLLED TRIALS

The risk of bias in the two included RCTs (level II evidence) (Hartung et al. 2019; Kuitwaard et al. 2020b) was assessed using the SIGN Methodology Checklist 2 for Randomised Controlled Trials(SIGN 2014). Studies were assessed by a single reviewer.

The overall risk of bias was found to be moderate in one RCT (IVIg DOSE) (Kuitwaard et al. 2020b) and low in the second (PATH) (Hartung et al. 2019). The randomisation and concealment processes were satisfactory in both studies. The difference in characteristics of those who dropped out and those remaining in one study was not well addressed, and differences between study sites was not addressed when applicable. The study with moderate risk of bias was a cross-over design with relatively small numbers (n = 25). The possibility of carry-over effect from the early to the later phase of the trial could not be ruled out, and patients were enrolled over variable periods. Despite some shortfalls, there was moderate to high confidence that the results reported in the studies were reliable and applicable to the population of interest.

### STUDIES INCLUDED FOR THE EXTENDED ASSESSMENT OF HARMS

The studies included for the extended assessment of harms were appraised for risk of bias using appropriate tools. The SRs were assessed using the AMSTAR 2 checklist (Shea et al. 2007), and the cohort studies were assessed using the SIGN Checklist 3 for Cohort Studies (SIGN 2014). Appraisal was performed by one reviewer.

The two SRs (level I evidence) were assessed as moderate for risk of bias (Ortiz-Salas et al. 2016; Rice et al. 2017). The SRs performed well in describing the search and eligibility criteria, but did not include a list of excluded studies and only partially satisfied risk of bias reporting guidelines or did not perform

risk of bias assessments for individual studies at all. One SR did not report funding sources or competing interests. Pooling of results was performed through meta-analysis in one SR, and heterogeneity was discussed. The second SR provided ranges in outcomes without meta-analysis. There was very little description of the methodology and heterogeneity across studies. Both SRs included broader populations than that of interest, therefore the applicability of the results may be limited.

Seven retrospective cohort studies (level III-3 to IV evidence) were assessed using the SIGN 3 checklist. They were all assessed as moderate for risk of bias. The studies were retrospective and observational in design, in some cases including a control population for comparison. Despite limitations of design, observational studies can have longer follow-up periods than RCTs, and have the potential to provide long-term data on adverse events for the extended use of therapies. Due to the retrospective design, selection bias cannot be ruled out, and it was not possible to give any of the studies a low risk of bias ranking. In addition, applicability is reduced due to the populations in the studies being broader than the population of interest.

The following limitations that were identified in the DCAR 1564 Review, also apply to the DCAR 1564 Update report:

- Level IV and III-3 studies do not exclude patients receiving multiple interventions and therefore the attribution of a particular adverse event to the intervention under study may be questionable.
- Studies were retrospective in design and therefore AE reporting was typically limited to the availability and accuracy of case notes or records.
- The risk of any particular outcomes is difficult to estimate as the reported rates of adverse events exhibit significant heterogeneity across studies.
- Whether there was consecutive enrolment in studies was sometimes unclear and the inclusion and exclusion criteria were at times poorly defined. Consequently, selection bias may be significant within this evidence base.
- Adverse events were under-reported in the included evidence as revealed by statements from authors such as: "the most frequent minor side effect was headache, which was easily controlled with symptomatic medications", wherein the actual number of patients or events was not reported (Jann, Beretta & Bramerio 2005). Typically, only the most common adverse events were reported.

## B.4. CHARACTERISTICS OF THE EVIDENCE BASE

See **Appendix C** for details on the individual studies included in the evidence base. A summary of key features is provided in Table 8. Overall, the evidence base was very small and no additional RCTs were identified that compared IVIg or SCIg with PE or GC in CIDP patients. Two RCTs were identified that compared doses or regimens for the maintenance of Ig treatment for CIDP.

**Table 8    Key features of the included evidence assessing Ig maintenance of CIDP**

| Trial | I vs C<br>N | Design/ duration<br>Risk of bias | Key Inclusion criteria | Key outcome(s) |
|---|---|---|---|---|
| **RCT comparing two SCIg doses and placebo** | | | | |
| PATH trial (Hartung et al. 2019) (van Schaik, Ivo N. et al. 2018) | 1. SCIg 0.2 g/kg<br>2. SCIg 0.4 g/kg<br>3. placebo<br>172 | MC DB RCT (no CO)<br>25 weeks<br>Low | PATH subjects with CIDP; relapse during the Ig dependency period; successful stabilisation using 10% IVIg solution (2 g/kg followed by 1g/kg every 3 weeks) | QoL (EQ-5D, EQ-VAS)<br>Treatment satisfaction (TQSM)<br>Work impact (WPAI-GH)<br>Relapse rate<br>Withdrawal rate<br>INCAT score<br>Mean grip strength<br>MRC sum score<br>IRODS<br>AEs |
| **RCT comparing two IVIg dosing regimens** | | | | |
| IVIg DOSE (Kuitwaard et al. 2020b) | I. IVIg full dose & interval (individualised to patient)<br>C. IVIg half dose & interval<br>25 | CO DB RCT<br>Duration variable: 1 baseline infusion, 2x 4 blind infusions separated by 2 wash-out infusions<br>Moderate | CIDP based on FNS/PNS criteria; stable dose and interval of 10% liquid IVIg maintenance therapy; deterioration based on Martin Vigorimeter following dose reduction or interval lengthening within 9 mo prior to randomisation | Hand grip strength (Martin Vigorimeter)<br>Health related QoL (SF-36)<br>Disability (IRODS)<br>Fatigue (RFSS)<br>Serious AEs |

Abbreviations: AE = adverse event; C = comparator; CIDP = chronic inflammatory demyelinating polyneuropathy; CO = crossover; DB = double-blind; I = intervention; EQ-5D = EuroQol 5-dimension health profile; EQ-VAS = EuroQoL health status visual analogue scale; INCAT = Inflammatory Neuropathy Cause and Treatment; IRODS = Rasch-built Overall Disability Scale; IVIg = intravenous immunoglobulin; MC = multicentre; MRC = Medical Research Council Sum Score; QoL = quality of life; RCT = randomised controlled trial; RFSS = Rasch-built Fatigue Severity Scale; SCIg = subcutaneous immunoglobulin; SF-36 = 36-item short form health survey; TQSM = Treatment Satisfaction Questionnaire for Medicine; WPAI-GH = Work Productivity and Activity Impairment Questionnaire for General Health

The study by Hartung et al (2019) provided patient reported outcomes (PROs) for randomised subjects of the PATH trial. The PATH trial randomised patients with CIDP to one of two doses of SCIg (0.2 g/kg or 0.4 g/kg) or placebo. If patients relapsed, they were stabilised with IVIg. Other outcomes measured in this trial, including the primary effectiveness outcomes (relapse rate and withdrawal rate during the SCIg treatment phase) and secondary outcomes (time to primary endpoint, INCAT score, mean grip strength, MRC sum score, and IRODS) were reported in an earlier article (van Schaik, Ivo N. et al. 2018). This paper by Van Schaik et al did not meet the eligibility criteria for the DCAR 1564 Update report because it fell outside the date range used in the search. However, as the effectiveness outcomes of the PATH trial were not included in the initial DCAR 1564 Review, and MSAC has specifically requested data for SCIg maintenance, therefore they have been added to Section B.6. Safety data from the article by van Schaik et al. (2018) have also been included in Section B.6.

The PATH trial included adults meeting the EFNS/PNS 2010 criteria, if they received their last IVIg treatment at least 8 weeks prior to enrolment. Randomisation was performed by a central facility and everyone involved in the trial was masked from treatment. There were 172 patients from 69 neuromuscular centres in North America, Europe, Israel, Australia and Japan included and randomised to the three arms of the trial. Observations went to 25 weeks post randomisation.

Kuitwaard et al (2020) reported on a randomised cross-over design trial (IVIg DOSE) which included 25 patients stabilised on individualised doses of IVIg therapy. The aim was to determine whether high-frequency low-dose IVIg was more effective and safer than a low-frequency high-dose regime. Eligible subjects were over 18 years and fulfilled the EFNS/PNS criteria. Patients transitioned through three phases consisting of a treatment phase in which they received their own full individualised dose at normal intervals, a flush-out phase, and a treatment phase in which they received half their individualised dose at half the normal interval. Because of varying doses and intervals in the trial, patients completed the three phases at different times. Both the patients and infusion nurses were blinded to treatment, which was given at home or in a hospital day-care setting.

**Studies included for the extended assessment of harms**

A summary of studies included for the extended assessment of harms is found in Table 9. Further details are given in Section B.7., and in Appendix C. The evidence base for patients with CIDP receiving PE or GC was very small. Data on the long-term effects of therapy were particularly limited, even when the population under investigation was broadened to include patients with other autoimmune disorders receiving PE or GC therapy.

**Table 9         Key features of studies included for safety outcomes**

| Study ID Country Study design ROB | Population/inclusion criteria n | Intervention Comparator (if applicable) | Outcome of interest |
|---|---|---|---|
| **Plasma exchange** | | | |
| (Ortiz-Salas et al. 2016) Multinational SR Moderate | RCTs or analytical OS in patients with neurological disease (GBS or MG); Studies reporting AEs: k = 15 Patients: n = 2,388 in studies reporting AEs | PE Cycles: typical strategy of 200-250 ml/kg over 10-14 days (5-6 cycles with 5% albumin) IVIg Dosage: 0.4 g/kg/day or a total of 2 g/kg | Mild to moderate AEs |
| (Mörtzell Henriksson et al. 2016) Multinational R O MC Moderate | Patient data from the WAA apheresis registry (www.waa-registry.org ) between 2004 and 2014 Procedures: n = 50,846 Patients: n = 7,142 | PE by either filtration or centrifugation methods | Mild, moderate and severe AEs |
| (Nieto-Aristizábal, Vivas Á, et al. 2020) | Patients receiving PE between 2011 and 2018, as prescribed by a neurologist | PE by centrifugation method | AEs |

| Study ID<br>Country<br>Study design<br>ROB | Population/inclusion criteria<br>n | Intervention<br>Comparator (if applicable) | Outcome of interest |
|---|---|---|---|
| Columbia<br>R O SC<br>Moderate | Patients: n = 187 | Average PE cycles per patient n = 5 (approx. 935) | |
| (Basic-Jukic et al. 2005)<br>Croatia<br>R O SC<br>Moderate | Data on PE procedures collected between 1982 and 2003 in a single dialysis centre<br>Patients: n = 507 | PE by membrane/filtration method<br>Sessions n = 4857 | AEs |
| **Long-term steroids** | | | |
| (Huscher et al. 2009)<br>Germany<br>R O SC<br>Moderate | Patient data from a RA patient database, Patients taking ongoing GC > 6 months n = 472 | GC<br>Dose categorisations: < 5mg/day; 5-7.5 mg/day; >7.5 mg/day | Dose comparison for individual AEs |
| (Rice et al. 2017)<br>Multinational<br>SR<br>Moderate | Articles published between 2007 and 2016 reporting economic or utilisation data on GC<br>Included studies: k = 32<br>Total patients: NR | GC | Individual AE prevalence rates |
| (van Lieverloo et al. 2018)<br>Serbia; The Netherlands; Italy<br>R MC<br>Moderate | Patient data on from 3 large CIDP centres; Patients with treatment naïve CIDP; patients who underwent first-line treatment with corticosteroids<br>Patients: n = 125 | Prednisone or prednisolone n = 67 (54%)<br>Pulsed dexamethasone n = 37 (30%)<br>Pulsed IV MP 21 (17%) | Moderate and severe AEs |
| (Wilson, J. C. et al. 2017b)<br>UK<br>R MC Co<br>Moderate | Patient data from a UK database CPRD on all patients 50 y and older who had a GCA diagnosis, at least one prednisolone prescription<br>Patients: n = 5011 | Prednisolone | AEs n (% patients)<br>All 2190 (43.7%)[a] |
| **Long-term IVIg** | | | |
| (Waheed et al. 2019)<br>US<br>R O MC<br>Moderate | Database provided by a infusion provider company; infusions provided in homes or pharmaceutical centres (outpatient setting); patients with neuromuscular disorders<br>All patients : n = 438<br>CIDP = 221 | IVIg<br>Infusions all: 5867<br>Infusions CIDP: 3256 | AEs<br>SAEs<br>Dose analysis<br>Number of treatments analysis |

Abbreviations: AE = adverse event; C = comparator; CIDP = chronic inflammatory demyelinating polyneuropathy; Co = Cohort; CPRD = Clinical Practice Research Datalink; GBS = Guillain Barre Syndrome; GC = glucocorticoids; GCA = giant cell arteritis; I = intervention; IVIg = intravenous immunoglobulin; MC = multicentre; MG = myasthenia gravis; MP = methylprednisolone; NR = not reported; O = observational study; PE = plasma exchange; R = retrospective; RA = rheumatoid arthritis; RCT = randomised controlled trial; SC= single centre; SR = systemic review

## B.5.    OUTCOME MEASURES AND ANALYSIS

Tools used in the measurement of treatment outcomes discussed in this report are listed in Table 10.

Further details of the assessment domains are included in the discussion of outcomes in Section B.6.

The tools measure a range of outcomes including strength impairment, sensory dysfunction and disability, using a range of scales.

Version 3 of '*the Criteria*' restricts use of Ig in CIDP patients according to the tools Overall Neuropathy Limitations Scale (ONLS) or Medical Research Council (MRC) Sum Scores in adults, and the Modified Rankin Scale (MRS) score and walk time in children, as they do not require specialist equipment for patient evaluation. However, these tools were seen infrequently in the literature assessed for this update report.

**Table 10      List and description of currently validated scales suitable for use in CIDP**

| Scale | Scoring Range | Assessment area | Patient or physician reported |
|---|---|---|---|
| INCAT* | 0-10 overall score is sum of the two | Arm and leg disabilities | Patient |
| MRC sum score | Total out of 60 | Muscle strength | Physician |
| IRODS | Raw RODS score (0–48) transformed to final score 0–100 | Upper and lower limb disability | Patient |
| Grip Strength (Martin Vigorimeter) | Instrument-based scale | Hand grip Strength | Physician |
| RFSS | 9–63 | Fatigue and impact on lifestyle | Patient |
| SF-36 | 8 scaled scores, each directly transformed into a 0–100 scale | Physical, emotional and social functioning, mental health, general health perception | Patient |
| EQ-5D | 0 (no problems) - 2 (extreme problems) | Health related quality of life | Patient |
| EQ-VAS | 0 (worst health) – 100 (best health) | Overall health status | Patient |
| TQSM | 0 (poorest satisfaction) – 100 (perfect satisfaction) | Treatment satisfaction | Patient |
| WPAI-GH | 0 (best) – 100 (worst) | Work productivity | Patient |

Abbreviations: : CIDP = chronic inflammatory demyelinating polyneuropathy; EQ-5D = EuroQoL - dimension health profile, EQ-VAS = EuroQoL health status visual analogue scale; INCAT = Inflammatory Neuropathy Cause and Treatment; IRODS = Rasch-built Overall Disability Scale; MRC = Medical Research Council Sum Score; RFSS = modified Rasch-built Fatigue Severity Scale; SF-36 = 36-item short form health survey; TSQM = Treatment Satisfaction Questionnaire for Medicine; WPAI-GH = Work Productivity and Activity Impairment Questionnaire for General Health;

As there were only two trials with different comparisons identified in the safety and effectiveness section, no meta-analysis was performed and results were synthesised narratively. Outcomes from the extended assessment of harms section came largely from single arm studies and were also reported narratively. No pooling of data was conducted due to the heterogeneity of populations in the studies. Summary results were reported as ranges.

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

### IS IT SAFE?

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**What is the safety of Ig compared to steroids (oral and IV), plasma exchange, immunosuppressant and/or immunomodulatory drugs and therapies (not including steroids), a combination of two or more of the above therapies, or no active treatment?**

No additional RCT evidence was identified reporting the safety of Ig in comparison to steroids, PE, immunosuppressants, or combination therapies for CIDP.

**What is the safety of regular IVIg dose and interval compared to half IVIg dose and interval?**

In a cross-over design RCT in patients with CIDP, AEs were compared between two dosing regimens, in which patients received either their normal dose with regular interval, or half their normal dose at half the regular interval. The overall dose patients received was the same in both regimens. The frequency of AEs was similar between regimens, and the majority of patients had no preference for either dosing schedule. There were no serious AEs reported. The RCT provides evidence that there could be some flexibility in the dosing regimens that patients with CIDP are offered.

**What is the safety of low-dose SCIg (0.2 g.kg) compared to high-dose SCIg (0.4 g/kg) or placebo?**

In a randomised, three-armed comparison (PATH Trial), AE rates were higher in patients treated with SCIg (either dose) when compared to placebo. Treatment-related AEs occurred in 30% of patients receiving low-dose SCIg, 35% of patients receiving high-dose SCIg, and 18% of patients in the placebo group. Of 11 serious adverse events, 10 occurred in patients receiving SCIg. Only one serious AE (acute allergic skin reaction) was considered to be related to treatment, and led to discontinuation of SCIg. There were few differences in AE rates between low and high-dose treatment groups.

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One RCT (IVIg DOSE) met the majority of inclusion criteria for this review and reported on the safety of IVIg. While comparators in the PICO Confirmation for the 1564 review did not include dose comparisons, this study was included as it has the potential to inform clinical practice regarding dosing regimens. The study compared two different dosing regimens in a randomised cross-over trial (Kuitwaard et al. 2020b).

Safety data from the PATH trial was included from the study by van Schaik et al. (van Schaik, Ivo N. et al. 2018). Although this study did not meet the inclusion criteria for this update report due to its publication date, it was not included in the DCAR 1564 Review. Data regarding the safety of SCIg has the potential to inform the economic modelling for SCIg usage, and was specifically requested by MSAC for this update.

One single arm retrospective study was identified that reported on long-term AEs in patients with CIDP (Waheed et al. 2019). This study was included in Section B.7 Extended Assessment of Harms, in accordance with the protocol.

NORMAL IVIG DOSE AND INTERVAL COMPARED WITH HALF IVIG DOSE AT HALF THE INTERVAL IN CIDP PATIENTS ON INDIVIDUALISED MAINTENANCE TREATMENT

The IVIg DOSE RCT included 25 patients with CIDP who were IVIg dependent and receiving maintenance treatment with individualised dose and interval of IVIg (Kuitwaard et al. 2020b). Individualised patient doses ranged from 20 to 80 g, at intervals ranging from 14 to 35 days. All patients transitioned through a control phase in which they received their normal maintenance treatment, a wash-out phase, and an intervention phase in which they received half their normal IVIg dose at half the interval (thereby receiving the same amount of Ig but more frequent smaller doses). The "wash-out phase" consisted of two normal dose and interval treatment cycles. Half of the 25 randomised patients began with the control phase and half with the intervention phase. Patients were blinded to their treatment, and were given a placebo infusion at half intervals in the normal dose and interval phase.

The 10 most common AEs were compared between normal IVIg dose and interval and half IVIg dose at half the interval (Table 11). Both dosing regimens were tolerated equally well, and there were no significant differences in frequency of AEs between regimens. Fatigue, and muscle and joint ache were the two most frequently experienced AEs in both trial arms. Of the 25 patients, two preferred the intervention regimen, one preferred the control regimen, but the remainder had no preference between treatment regimens. There were no serious AEs reported (Kuitwaard et al. 2020b).

Table 11        Number of patients who reported common adverse events during blinded phase (Kuitwaard et al. 2020b)

| Adverse events | Regular IVIg dose and interval n (%) | Half IVIg dose and interval n (%) | Difference p |
|---|---|---|---|
| Fatigue | 19 (86) | 20 (91) | 1.0 |
| Muscle and joint ache | 17 (77) | 16 (73) | 1.0 |
| Headache | 11 (50) | 13 (59) | 0.69 |
| Warm feeling | 13 (59) | 11 (50) | 0.69 |
| Backache | 12 (55) | 10 (46) | 0.63 |
| Shortness of breath | 11 (50) | 9 (41) | 0.63 |
| Itching | 8 (36) | 8 (36) | 1.0 |
| Cold shivers | 8 (36) | 7 (32) | 1.0 |
| Dizziness | 10 (46) | 6 (27) | 0.13 |
| Malaise | 4 (18) | 6 (27) | 0.76 |

Abbreviations: IVIg = intravenous immunoglobulin therapy

**SCIg (0.2 g/kg) COMPARED WITH SCIg (0.4 g/kg) AND PLACEBO IN CIDP PATIENTS STABILISED ON IVIg**

Adverse events for the PATH trial were reported by van Schaik et al (van Schaik, Ivo N. et al. 2018) (Figure 2). The highest frequency for AEs occurred in the low-dose (0.2g/kg) SCIg group. There were 52 AEs over 1514 infusions (3.4%) in the placebo group, occurring in 21 (37%) patients. In the low-dose group, there were 158 AEs over 2007 infusions (7.9%), occurring in 33 (58%) patients. In the high dose group there were 114 AEs over 2218 infusions (5.1%) experienced by 30 (53%) of patients.

In a comparison of treatment "causally-related" AEs, the high-dose (0.4 g/kg) SCIg group experienced the highest frequency (20 patients, 35%). In the placebo group 10 (18%) patients, and in the low-dose (0.2 g/kg) SCIg treated group, 17 (30%) patients experienced treatment related AEs (Figure 3). Serious AEs (11 events) occurred in six patients: one receiving placebo, three patients (five events) receiving 0.2 g/kg SCIg, and two patients (five events) receiving 0.4 g/kg SCIg. Only one serious AE (acute allergic skin reaction in a patient on low-dose SCIg) that was considered to be related to treatment, eventually led to discontinuation. The study did not report any statistical comparison between event rates. A comparison of the frequencies of mild, moderate and serious AEs between groups can be seen in Figure 3 (van Schaik, Ivo N. et al. 2018).

| | Placebo (n=57)* | | Low-dose SCIg (n=57)† | | High-dose SCIg (n=58)‡ | |
|---|---|---|---|---|---|---|
| | Patients with an event (n) | Events (n)§ | Patients with an event (n) | Events (n)§ | Patients with an event (n) | Events (n)§ |
| Any adverse event (treatment emergent) | 21 (37%) | 52 (0·034) | 33 (58%) | 158 (0·08) | 30 (52%) | 114 (0·05) |
| General disorders and administration-site conditions¶ | 6 (11%) | 10 (0·007) | 16 (28%) | 60 (0·03) | 18 (31%) | 52 (0·02) |
| Fatigue | 1 (2%) | 1 (<0·001) | 5 (9%) | 5 (0·002) | 0 | 0 |
| Local reactions‖ | 4 (7%) | 7 (0·005) | 11 (19%) | 54 (0·03) | 17 (29%) | 49 (0·02) |
| Infusion-site erythema | 0 | 0 | 5 (9%) | 11 (0·005) | 10 (17%) | 28 (0·013) |
| Infusion-site swelling | 2 (4%) | 2 (0·001) | 5 (9%) | 8 (0·004) | 6 (10%) | 8 (0·004) |
| Infusion-site induration | 1 (2%) | 1 (<0·001) | 2 (4%) | 10 (0·005) | 3 (5%) | 3 (0·001) |
| Infusion-site warmth | 0 | 0 | 0 | 0 | 3 (5%) | 3 (0·001) |
| Infusion-site pain | 2 (4%) | 2 (0·001) | 3 (5%) | 15 (0·007) | 2 (3%) | 2 (<0·001) |
| Infusion-site pruritus | 0 | 0 | 0 | 0 | 2 (3%) | 3 (0·001) |
| Infusion-site extravasation | 0 | 0 | 0 | 0 | 1 (2%) | 1 (<0·001) |
| Infusion-site mass | 1 (2%) | 1 (<0·001) | 0 | 0 | 1 (2%) | 1 (<0·001) |
| Infusion-site haematoma | 1 (2%) | 1 (<0·001) | 2 (4%) | 2 (<0·001) | 0 | 0 |
| Infusion-site haemorrhage | 0 | 0 | 1 (2%) | 1 (<0·001) | 0 | 0 |
| Infusion-site oedema | 0 | 0 | 1 (2%) | 6 (0·003) | 0 | 0 |
| Infusion-site rash | 0 | 0 | 1 (2%) | 1 (<0·001) | 0 | 0 |
| Infections and infestations | 8 (14%) | 11 (0·007) | 13 (23%) | 18 (0·009) | 6 (10%) | 9 (0·004) |
| Nasopharyngitis | 1 (2%) | 1 (<0·001) | 4 (7%) | 6 (0·003) | 2 (3%) | 2 (<0·001) |
| Upper respiratory tract infection | 2 (4%) | 2 (0·001) | 3 (5%) | 3 (0·001) | 2 (3%) | 2 (<0·001) |
| Urinary tract infection | 3 (5%) | 3 (0·002) | 1 (2%) | 1 (<0·001) | 0 | 0 |
| Musculoskeletal and connective tissue disorders | 4 (7%) | 4 (0·003) | 10 (18%) | 14 (0·007) | 6 (10%) | 7 (0·003) |
| Arthralgia | 1 (2%) | 1 (<0·001) | 3 (5%) | 4 (0·002) | 1 (2%) | 1 (<0·001) |
| Back pain | 1 (2%) | 1 (<0·001) | 3 (5%) | 4 (0·002) | 1 (2%) | 1 (<0·001) |
| Pain in extremity | 0 | 0 | 1 (2%) | 1 (<0·001) | 3 (5%) | 3 (<0·001 |
| Nervous system disorder | 4 (7%) | 6 (0·004) | 6 (11%) | 9 (0·004) | 6 (10%) | 7 (0·003) |
| Headache | 2 (4%) | 2 (0·001) | 4 (7%) | 5 (0·002) | 4 (7%) | 4 (0·002) |
| Injury, poisoning, and procedural complications | 2 (4%) | 2 (0·001) | 7 (12%) | 16 (0·008) | 3 (5%) | 4 (0·002) |
| Fall | 0 | 0 | 3 (5%) | 8 (0·004) | 1 (2%) | 1 (<0·001) |

Data are n (%) or n (rate per infusion). SCIg=subcutaneous immunoglobulin. *1514 infusions. †2007 infusions. ‡2218 infusions. §The rate per infusion is calculated as the number of events divided by the overall number of infusions in the respective treatment groups. ¶During our study this system organ class also included some local reactions, but these are reported in the local reactions category to avoid repetition. ‖The virtual system organ class of local reactions included all adverse events reported within the Medical Dictionary for Regulatory Activities high-level terms "Administration Site Reactions Not Elsewhere Classified", "Infusion Site Reactions", and "Injection Site Reactions".

*Table 5:* All adverse events reported in at least 5% of patients in a treatment group (in an overall category)

**Figure 2        Adverse events reported in the PATH trial (van Schaik, Ivo N. et al. 2018)**

Abbreviations: SCIg = subcutaneous immunoglobulin therapy

| Category | Placebo | | Low-dose SCIg | | High-dose SCIg | |
|---|---|---|---|---|---|---|
| | Number (%) of patients N=57 | Number of events (rate/infusion) N=1514[#] | Number (%) of patients N=57 | Number of events (rate/infusion) N-2007[#] | Number (%) of patients N=58 | Number of events (rate/infusion) N=2218[#] |
| Any AE | 21 (36·8) | 52 (0·034) | 33 (57·9) | 158 (0·079) | 30 (51·7) | 114 (0·051) |
| Mild | 18 (31·6) | 34 (0·022) | 31 (54·4) | 130 (0·065) | 25 (43·1) | 88 (0·040) |
| Moderate | 11 (19·3) | 17 (0·001 | 13 (22·8) | 22 (0·011) | 9 (15·5) | 20 (0·009) |
| Severe | 1 (1·8) | 1 (0·001) | 4 (7·0) | 6 (0·003) | 3 (5·2) | 6 (0·003) |
| Local skin reactions | 4 (7·0) | 7 (0·005) | 11 (19·3) | 54 (0·027) | 17 (29·3) | 49 (0·022) |
| Any serious AE | 1 (1·8) | 1 (0·001) | 3 (5·3) | 5 (0·002) | 2 (3·4) | 5 (0·002) |
| Causally related and/or temporally associated serious AE | 1 (1·8) | 1 (0·001) | 1 (1·8) | 1 (<0·001) | 1 (1·7) | 1 (<0·001) |
| Causally related and/or temporally associated AE | 19 (33·3) | 37 (0·024) | 29 (50·9) | 118 (0·059) | 27 (46·6) | 95 (0·043) |
| Causally related AE | 10 (17·5) | 14 (0·009) | 17 (29·8) | 71 (0·035) | 20 (34·5) | 64 (0·029) |
| Temporally associated AE | 19 (33·3) | 37 (0·024) | 29 (50·9) | 115 (0·057) | 25 (43·1) | 88 (0·040) |
| AE leading to withdrawal of investigational product | 0 | 0 | 1 (1·8) | 1 (<0·001) | 2 (3·4) | 6 (0·003) |
| AE leading to subject discontinuation | 0 | 0 | 1 (1·8) | 1 (<0·001) | 1 (1·7) | 3 (0·001) |
| AE leading to death | 0 | 0 | 0 | 0 | 0 | 0 |

**Figure 3      Adverse events by severity and cause (van Schaik, Ivo N. et al. 2018)**

Abbreviations: AE = adverse event; SCIg = subcutaneous immunoglobulin therapy;
# number of infusions

Van Schaik et al also assessed the relationship between AE frequency and infusion volume and infusion rate (van Schaik, Ivo N. et al. 2018). The study found that patients receiving higher infusion rates reported similar proportions of AEs as those receiving lower infusion rates. However, patients receiving infusion volumes of ≥ 50 ml experienced a higher rate of AEs than those receiving maximum volumes of < 25 ml or 25-50 ml per infusion. Results can be seen in Figure 4.

| | Maximum Volume Infused per Site | | |
| --- | --- | --- | --- |
| | ≤25 mL | >25 – <50 mL | ≥50 mL |
| Number of Infusions, I | 4865 | 826 | 46 |
| Any AEs, n (n/I) | 271 (0·056) | 49 (0·059) | 4 (0·087) |
| Any Causally Related AEs, n (n/I) | 127 (0·026) | 19 (0·023) | 3 (0·065) |
| *Local* | 83 (0·017) | 11 (0·013) | 3 (0·065) |
| *Non-Local* | 44 (0·009) | 8 (0·010) | 0 |

| | Maximum Infusion Rate per Site | | |
| --- | --- | --- | --- |
| | <35 mL/h | 35 mL/h | >35 mL/h |
| Number of Infusions, I | 4617 | 890 | 229 |
| Any AEs, n (n/I) | 258 (0·056) | 54 (0·061) | 12 (0·052) |
| Any Causally Related AEs, n (n/I) | 132 (0·029) | 14 (0·016) | 3 (0·013) |
| *Local* | 89 (0·019) | 6 (0·007) | 2 (0·009) |
| *Non-Local* | 43 (0·009) | 8 (0·009) | 1 (0·004) |

**Figure 4      Adverse events in relation to infusion volume and infusion rate (van Schaik, Ivo N. et al. 2018)**

Abbreviations: AE = adverse event; I = number of infusions

> **What is the efficacy of IVIg compared to steroids (oral and IV), plasma exchange, immunosuppressant and/or immunomodulatory drugs and therapies (not including steroids), a combination of two or more of the above therapies, or no active treatment?**
>
> No additional RCT evidence was identified reporting the efficacy of Ig in comparison to steroids, PE, immunosuppressants, or combination therapies for CIDP.
>
> **What is the efficacy of IVIg (normal individualised dose and interval) compared to IVIg (half individualised dose at half the interval) in patients stabilised on individualised dose regimens?**
>
> The two dosing regimens showed no difference in efficacy for patients on IVIg maintenance. More flexibility may be made available to patients with respect to size and frequency of dose, to accommodate patient preference.
>
> **What is the efficacy of a lower SCIg dose (0.2 g/kg) compared to a higher SCIg dose (0.4 g/kg), and to placebo?**
>
> Quality of life (QoL) and other patient reported outcomes (PROs) were reported from the PATH[3] trial in subjects who were successfully re-stabilised on IVIg after relapse. There were some differences in efficacy when SCIg treated patients (either dose) were compared to placebo, but little difference was shown between the two treatment groups.
>
> Both SCIg doses were more effective than placebo for all domains of health-related quality of life (EQ-5D: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), but there were no differences between the two SCIg doses. Similarly, overall health (EQ-VAS) was significantly worse with placebo when compared to either SCIg dose. Treatment satisfaction (TSQM) did not show any differences in the domains of overall satisfaction and effectiveness. Work productivity (WPAI-GH) was worse for patients in the placebo group in domains of activity impairment, work impairment, and work productivity loss, than both dosage groups, for which productivity remained relatively stable.
>
> Both low and high-dose SCIg treatment reduced relapse rate when compared to placebo. There were fewest relapses in the high-dose SCIg treated group, but the difference between SCIg treatment groups did not reach statistical significance. More patients withdrew from the PATH trial in the high-dose treated group (nine out of the total 16 withdrawals). The most frequent reason given for withdrawal was "withdrawn consent":
>
> A lower SCIg dose may provide satisfactory effectiveness, including quality of life and work productivity, in some patients.

Two RCTs met the inclusion criteria for the update of effectiveness data on IVIg or SCIg (Hartung et al. 2019; Kuitwaard et al. 2020b). Kuitwaard et al (2020) performed an IVIg dose comparison in a randomised cross-over trial. Hartung et al (2019) reported on patient reported outcomes (PROs) and QoL from an RCT comparing two doses of SCIg with placebo (PATH trial).

Results were also included from van Schaik et al. (2018), who reported on the effectiveness and safety from the PATH trial. Although Schaik et al (2018) did not meet the inclusion criteria for this update report due to its publication date, the results were missing from the DCAR 1564 Review, and the data have the potential to inform the economic modelling for SCIg usage.

**IVIg (NORMAL INDIVIDUALISED DOSE AND INTERVAL) COMPARED WITH IVIg (HALF INDIVIDUALISED DOSE AT HALF THE INTERVAL) IN CIDP PATIENTS ON INDIVIDUALISED IVIg MAINTENANCE TREATMENT**

The IVIg DOSE RCT by Kuitwaard et al (2020) compared two dosing regimens in a cross-over design trial. Twenty-five patients stabilised on individualised IVIg maintenance regimens were included, but only when they showed an objectively measured deterioration (handgrip strength by Martin Vigorimeter) in association with a reduction of IVIg dose or lengthening of treatment interval. Individualised patient doses prior to randomisation ranged from 20 to 80 g, and intervals ranged from 14 to 35 days. Patients were randomised to either their own regular regimen (control) or the regimen of half dose at half the interval (intervention). A wash-out period of two cycles of normal dose and interval were given prior to crossing over to the second treatment phase. The treatment phases consisted of four infusion cycles each. Treatment efficacy was measured by handgrip strength using the vigorimeter (kPa). Secondary outcomes included the Rasch-built Overall Disability Score (IRODS), modified Rasch-built Fatigue Severity Scale (RFSS), and the 36-item Short-Form health survey (SF-36). The tools and scales are described in Table 12.

**Table 12      Tools used to compare efficacy in CIDP patients treated with two dosing regimens of IVIg**

| PRO Assessment area | Scoring range | Score interpretation |
|---|---|---|
| Vigorimeter Handgrip strength | 0-160 kPa | Higher kPa = greater strength |
| IRODS Overall disability | 0 - 100 centile metrics | Higher value = fewer limitations |
| RFSS Fatigue severity | 0 - 21 | Higher score = more fatigue |
| SF-36 Health survey | 0 - 100 | Higher score = better health or less bodily pain |

Abbreviations: CIDP = chronic inflammatory demyelinating polyneuropathy; EQ-5D = EuroQoL - dimension health profile, EQ-VAS = EuroQoL health status visual analogue scale; IRODS = Rasch-built Overall Disability Scale; IVIg = intravenous immunoglobulin; PRO = patient reported outcome; RFSS = modified Rasch-built Fatigue Severity Scale; SF-36 = 36-item short form health survey

The change from baseline to end of randomisation phases using each of the tools was compared between treatment groups. Handgrip strength was measured in triplicate for both hands prior to each infusion. According to the study authors, handgrip strength by vigorimeter is a simple measure that parallels or precedes improvement in the Inflammatory Neuropathy Cause and Treatment (INCAT) disability score. IRODS and RFSS questionnaires were completed after each infusion, and the SF-36 was completed four times in total.

There was no significant change from baseline for mean handgrip strength in either dosing regimen, and the outcome was similar when change from baseline was compared between regimens. There were no significant differences between groups in the secondary measures, although interestingly, all components of the SF-36 showed a worsening trend with half dose at half the interval. The worse SF-36 results could not be explained by more frequent doses as both groups received the same number of infusions; the full dose and interval group received placebo on at half intervals. Change from baseline in outcomes were reported as the coefficient of difference between treatment regimens (Table 13).

**Table 13  Comparison of efficacy of regular IVIg dose and interval and half IVIg dose at half the interval**

| Outcome | Coefficient | 95%CI | p |
|---|---|---|---|
| Vigorimeter score (kPa) | -2.71 | -5.4, 0.01 | 0.07 |
| RFSS | -0.01 | -0.2, 0.2 | 0.90 |
| IRODS | -0.02 | -0.4, 0.4 | 0.93 |
| SF-36<br>Physical functioning<br>Role-physical<br>Bodily pain<br>General health<br>Vitality<br>Social functioning<br>Role emotional functioning<br>Mental health score | -2.98<br>-5.32<br>-0.77<br>-0.28<br>-3.48<br>-3.70<br>-4.40<br>-4.22 | -8.0, 2.1<br>-12, 1.3<br>-22, 21<br>-10, 9.4<br>-7.3, 0.3<br>-15, 8.2<br>-13, 4.1<br>-10, 2.2 | 0.25<br>0.13<br>0.95<br>0.96<br>0.08<br>0.55<br>0.32<br>0.22 |

Abbreviations: CI = confidence interval; IRODS = Rasch-built Overall Disability Score; IVIg = intravenous immunoglobulin therapy; RFSS = modified Rasch-built Fatigue Severity Scale; SF-36 = 36-item Short-Form health survey

**SCIG (0.2 G/KG) COMPARED WITH SCIG (0.4 G/KG) AND PLACEBO IN CIDP PATIENTS STABILISED ON IVIG**

Hartung et al (2019) reported on the PATH trial[3], assessing QoL and other PROs in subjects who relapsed during the Ig dependency phase and successfully re-stabilised on IVIg. Re-stabilisation was invoked using an induction dose of 2 g/kg followed by 1 g/kg every 3 weeks as a maintenance dose of IgPro10 (Privigen®, CSL Behring). Stabilised subjects (n = 172) were randomised 1:1:1 to 20% SCIg 0.2 g/kg, 0.4 g/kg, or placebo.

Standardised tools were used to measure QoL and health status (EuroQoL - dimension health profile and visual analogue scale, EQ-5D and EQ-VAS), treatment satisfaction (Treatment Satisfaction Questionnaire for Medicine, TQSM), and work related impact (Work Productivity and Activity

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[3] The PATH (Polyneuropathy and Treatment with Hizentra®) trial included adults with CIDP. They progressed through three phases – an Ig dependency phase (up to 12 weeks); an IVIg re-stabilisation period (up to 13 weeks, and a randomised SCIg treatment phase (24 weeks).

Impairment Questionnaire for General Health (WPAI-GH)). Components of the tools and scales are described in Table 14.

**Table 14          PRO measurement tools**

| PRO Assessment area | Dimension/domain | Scoring range | Score interpretation |
|---|---|---|---|
| EQ-5D Health-related quality of life | Mobility<br>Self-care<br>Usual activities<br>Pain/discomfort<br>Anxiety/depression | 0 – 2 | 0 = no problems<br>1 = some/moderate problems<br>2 = extreme problems |
| EQ-VAS Health status | Overall health status | 0 – 100 | 0 = worst health<br>100 = best health |
| TSQM Treatment satisfaction | Medication<br>Effectiveness<br>Side effects<br>Convenience<br>Overall satisfaction | 0 – 100 | 0 = poorest satisfaction<br>100 = perfect satisfaction |
| WPAI-GH Work productivity | Absenteeism<br>Work impairment<br>Activity impairment<br>Work productivity | 0 – 100 | 0 = best<br>100 = worst |

Abbreviations: EQ-5D = EuroQoL 5-dimension health profile, EQ-VAS = EuroQoL health status visual analogue scale; PRO = patient reported outcome; TSQM = Treatment Satisfaction Questionnaire for Medicine; WPAI-GH = Work Productivity and Activity Impairment Questionnaire for General Health

PROs were assessed at baseline (after IVIg re-stabilisation), and at nine and 25 weeks following the start of SCIg treatment. Change in scores at final follow-up (25 weeks) were compared between randomised treatment groups. A full set of data was collected for 151 patients, but sensitivity analyses were performed using imputed data for 167 patients accounting for missing values. Drop-out rates were higher in the placebo group, signifying less perceived effectiveness and tolerance in this group. No explanation was given for the missing data, however, it was acknowledged by the authors that missing data points were a limitation in the study.

*EQ-5D*

The imputed data for the EQ-5D for 167 patients can be seen in Table 15. The number of patients (N, %) who maintained or improved their EQ-5D score were compared between treatment groups. Outcomes were better across all domains for both dosage groups than placebo. There was greater stability or improvement in mobility, self-care, usual activities, pain/discomfort, and anxiety/depression when treated with either 0.2 or 0.4 g/kg SCIg compared to placebo. When the two SCIg doses were compared, there was no difference in any domain. In the observed data analysis, the trends were similar but the only difference reaching statistical significance was in the usual activities domain, for the comparisons of 0.2 g/kg to placebo ($p = 0.039$) and 0.4 g/kg to placebo ($p = 0.006$).

**Table 15    Comparison of the number of patients who maintained or improved their EQ-5D at 25 weeks of SCIg (0.2 or 0.4 g/kg) or placebo, imputed data (Hartung et al. 2019)**

| EQ-5D dimension | Placebo N/55 (%) | 0.2 g/kg N/56 (%) | 0.4 g/kg N/56 (%) | Difference (p) 0.2 g/kg vs placebo 0.4 g/kg vs placebo 0.4 vs 0.2 g/kg |
|---|---|---|---|---|
| Mobility | 33 (60.0) | 48 (88.9) | 46 (82.1) | 0.002 0.009 0.780 |
| Self-care | 36 (65.5) | 48 (82.8) | 48 (85.7) | 0.011 0.011 0.606 |
| Usual activities | 31 (56.4) | 47 (83.9) | 49 (87.5) | 0.001 <0.001 0.394 |
| Pain/discomfort | 38 (69.1) | 51 (91.1) | 49 (87.5) | 0.003 0.016 0.820 |
| Anxiety/depression | 37 (67.3) | 48 (85.7) | 48 (85.7) | 0.019 0.019 0.606 |

Abbreviations: EQ-5D = EuroQoL 5-dimension health profile

*EQ-VAS*

There was a greater decline in overall health status for patients in the placebo group than in either treatment group. The differences in EQ-VAS were statistically significant in both instances (Wilcoxon $p \leq 0.005$). The median score declined in the 0.2 g/kg group (-5.0 points; Q1, Q3: -15.0. 6.0) as well as the placebo group (-10.0 points; Q1, Q3: -25.0, 0.0) but remained stable in the 0.4 g/kg group (0.0 points; Q1, Q3: -7.5, 5.5) (Hartung et al. 2019). Results are presented graphically in Figure 5. The observed data was used for this analysis.
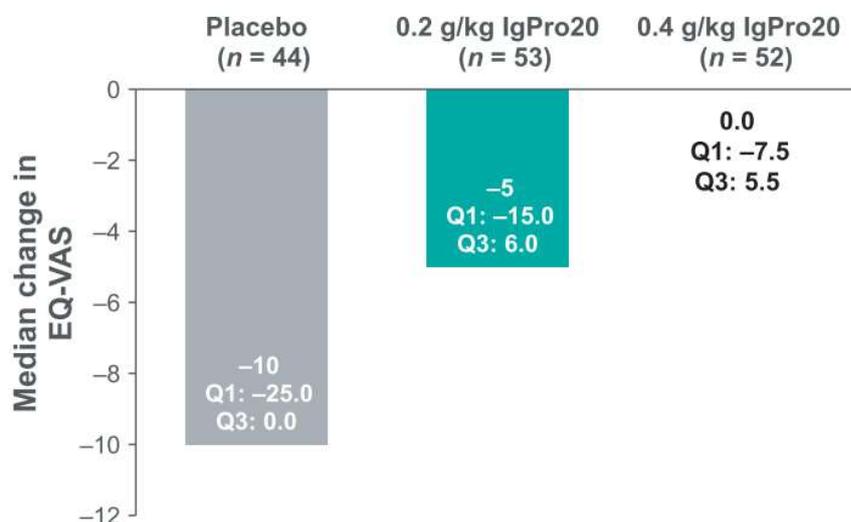
**Figure 5        EQ-VAS: median change from baseline to past post-dose observation (Hartung et al. 2019)**

Abbreviations: EQ-VAS = EurQoL health status visual analogue scale; Q = quartile

*TSQM*

There were some differences between treatment groups for change in TSQM domains, however none of them reached statistical significance. The largest differences were found for overall satisfaction and effectiveness. The greatest reduction for both of these domains was in the placebo group, but there was a reduction in all groups. There were only minor differences for the domains of side effects and convenience (Hartung et al. 2019). Results are reported graphically for overall satisfaction and effectiveness (Figure 6).
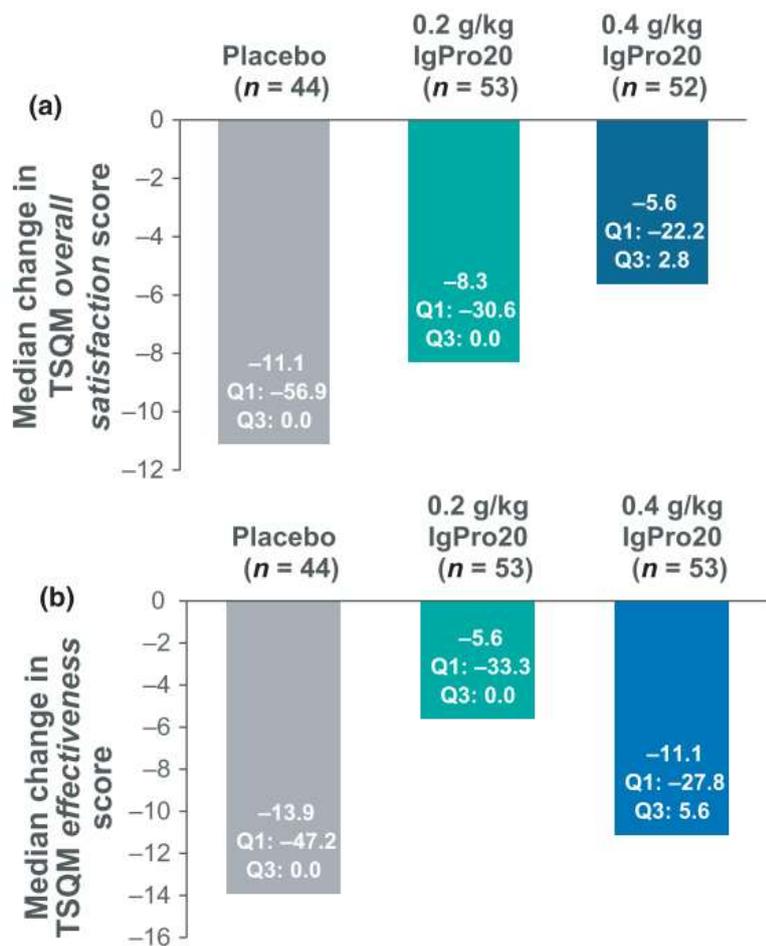


**Figure 6        Median change in TSQM from baseline to last post-dose observation for (a) overall satisfaction and (b) effectiveness (Hartung et al. 2019)**

Abbreviations: Q = quartile; TQSM = Treatment Satisfaction Questionnaire for Medicine

*WPAI-GH*

The domains of activity impairment, work impairment, and work productivity loss were relatively stable for the SCIg treated groups, showing little change from baseline. For the placebo group, reductions of 10%, 30%, and 23% from baseline for activity impairment, work impairment, and work productivity loss respectively were observed. The stability in those treated with either 0.2 g/kg or

0.4 g/kg SCIg dose appeared to be better than for those who received placebo, although the differences were not statistically significant for either dose compared to placebo (Hartung et al. 2019).

For the work impairment and work productivity loss domains there were fewer responses in the questionnaire (n = 56 and n = 49 respectively) when compared to 147 responses in the analysis of the activity impairment domain. The authors acknowledged that missing data points were a limitation of the study, but did not give reasons for their absence. There was no analysis with imputed data. There was further comment that the WPAI-GH, while accepted in the scientific community, may not be sensitive enough to capture specific characteristics of CIDP. There were no relevant differences between groups for the absenteeism domain (Hartung et al. 2019). The results are illustrated in Figure 7.
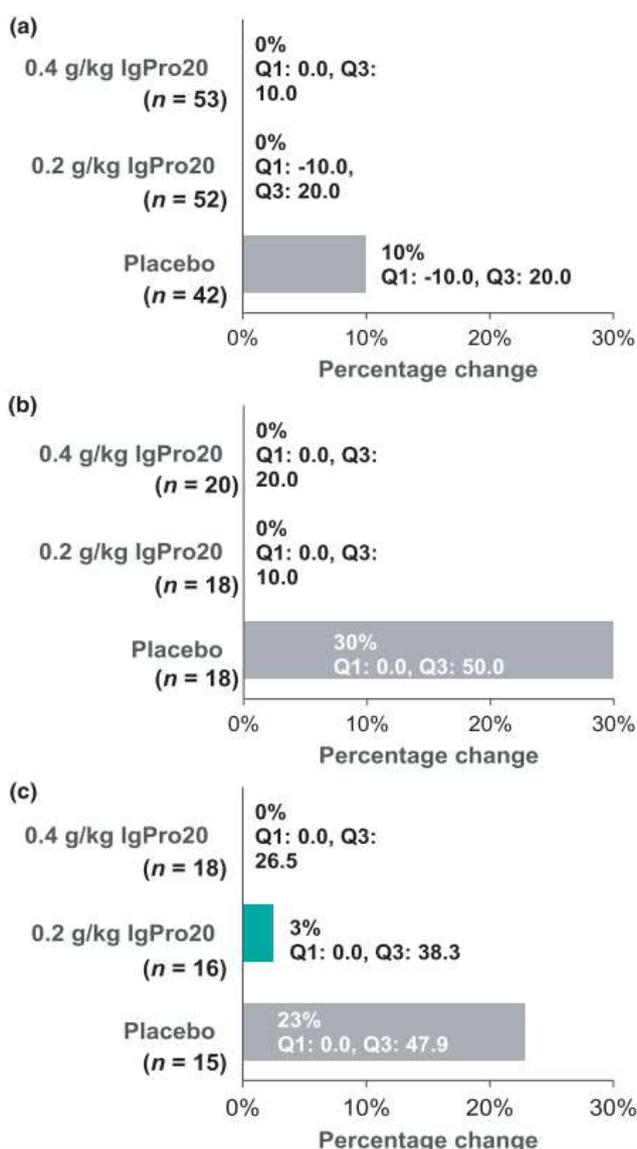


**Figure 7**     **Median change in WPAI-GH from baseline to last post-dose observation for (a) activity impairment (b) work impairment and (c) work productivity loss (Hartung et al. 2019)**

Abbreviations: Q = quartile; WPAI-GH = Work Productivity and Activity Impairment Questionnaire for General Health

*Time to relapse or withdrawal*

Results for the primary outcome from the PATH trial reported by van Schaik et al. (van Schaik, Ivo N. et al. 2018) are summarised in Figure 8 and Figure 9. The primary outcome was described as the proportion of patients with a CIDP relapse or who were withdrawn for any other reason during 24 weeks of treatment. There was a statistically significantly greater proportion of patients who relapsed or withdrew in the placebo group (63.2%) compared to either of the treatment groups (0.2 g/kg: 39.0%; 0.4 g/kg: 33.7%), but no difference between the treatment groups. The relapse rate was 58% in the placebo group, 35% in the low-dose group, and 22.4% in the high-dose group, showing an inverse relationship between dose and relapse rate (Figure 9).

The time to primary outcome was shorter for placebo compared to either dose of SCIg. The difference was statistically significant for the high SCIg dose (0.4 g/kg vs placebo: HR 0.38; 95%CI 0.22, 0.67; p = 0.005) and the low dose SCIg (0.2 g/kg vs placebo: HR 0.49; 95%CI 0.29, 0.84; p = 0.007). There was no difference shown between doses 0.2 g/kg and 0.4 g/kg of SCIg in time to reach the primary outcome (Figure 8). The authors noted that four (7%) patients in the placebo group, three (5%) in the low-dose group, and nine (16%) in the high-dose group withdrew for reasons other than relapse. The reasons given were AE (two patients), subcutaneous treatment related (one patient), withdrawn consent (13 patients), and physician's decision (one patient) (van Schaik, Ivo N. et al. 2018).
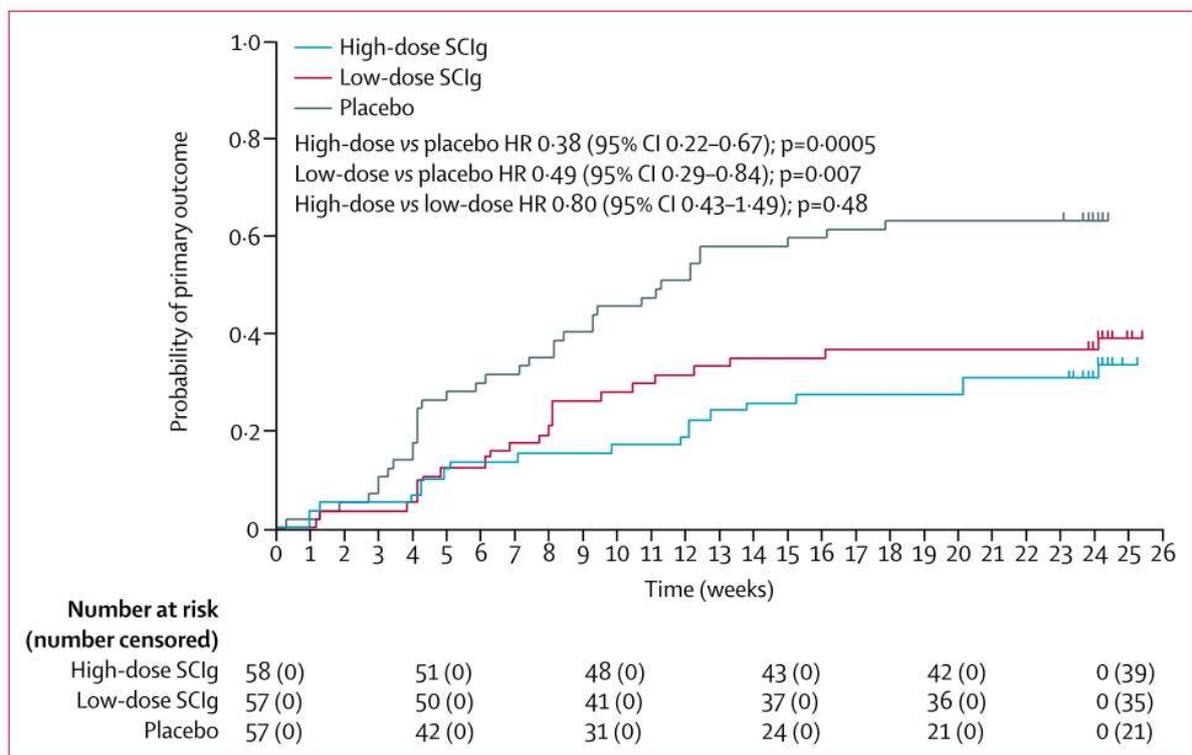


**Figure 8      Time to reach primary endpoint for high-dose-SCIg versus low-dose SCIg versus placebo (van Schaik, Ivo N. et al. 2018)**

Abbreviations: HR = hazard ratio; SCIg = subcutaneous immunoglobulin therapy

| | Placebo | Low-dose SCIg | High-dose SCIg | Overall p value* | Low-dose SCIg vs placebo | | High-dose SCIg vs placebo | | High-dose SCIg vs low-dose SCIg | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Hazard ratio | p value† | Hazard ratio | p value† | Hazard ratio | p value† |
| Primary outcome | 63·2% (50·9–75·4) | 39·0% (27·7–53·1) | 33·7% (22·8–47·8) | 0·0002 | 0·49 (0·29–0·84) | 0·007 | 0·38 (0·22–0·67) | 0·0005 | 0·80 (0·43–1·49) | 0·48 |
| Relapse | 58·8% (46·1–72·0) | 35·0% (23·9–49·3); | 22·4% (12·9–37·2) | <0·0001 | 0·48 (0·27–0·85) | 0·009 | 0·25 (0·12–0·49) | <0·0001 | 0·53 (0·25–1·12) | 0·09 |

Data in parentheses are 95% CIs. Data are Kaplan-Meier estimates. All tests are one-sided, with significance defined at a p value of less than 0·025. SCIg=subcutaneous immunoglobulin. *Log-rank test for trend. †Regular log-rank test.

*Table 3:* Probability of primary outcome or relapse at 24 weeks

**Figure 9** **Probability of primary outcome or relapse at 24 weeks (van Schaik, Ivo N. et al. 2018)**

Abbreviations: SCIg = subcutaneous immunoglobulin therapy

### *Secondary effectiveness outcomes*

Change from baseline was measured using the INCAT, IRODS, Hand-grip strength (dominant hand and non-dominant hand), and MRC. All scores were worse at the 24-week assessment time-point. All measures were worse in the placebo group when compared to either treatment group, and all differences were statistically significant. When the two SCIg doses were compared, only the change from baseline in the IRODS score gave a statistically significant difference, although all scores were worse in the group treated with the lower dose SCIg (van Schaik, Ivo N. et al. 2018). Change from baseline for the score can be seen in Figure 10.

| | Placebo (n=57) | Low-dose SCIg (n=57) | High-dose SCIg (n=58) | Overall p value* | Low-dose SCIg vs placebo | | High-dose SCIg vs placebo | | High-dose SCIg vs low-dose SCIg | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Difference | p value† | Difference | p value† | Difference | p value† |
| **INCAT (total score)** | | | | | | | | | | |
| Last postdose observation | 3·0 (3·0 to 4·0) | 3·0 (2·0 to 4·0) | 2·0 (1·0 to 3·0) | .. | .. | .. | .. | .. | .. | .. |
| Change from baseline | 1·0 (0·0 to 2·0) | 0·0 (0·0 to 1·0) | 0·0 (0·0 to 0·0) | <0·0001 | 0·0 (–1·0 to 0·0) | 0·0046 | –1·0 (–1·0 to 0·0) | <0·0001 | 0·0 (0·0 to 0·0) | 0·10 |
| **I-RODS (centile score)** | | | | | | | | | | |
| Last postdose observation | 60·0 (45·0 to 69·0) | 61·0 (55·0 to 69·0) | 65·0 (52·0 to 80·0) | .. | .. | .. | .. | .. | .. | .. |
| Change from baseline | –3·0 (–16·0 to 0·0) | –2·0 (–7·0 to 2·0) | 0·0 (–2·0 to 3·5) | 0·0002 | 3·0 (0·0 to 9·0) | 0·03 | 5·0 (2·0 to 9·0) | 0·0002 | 2·0 (0·0 to 4·0) | 0·04 |
| **Grip strength (dominant hand [kPa])** | | | | | | | | | | |
| Last postdose observation | 62·0 (36·0 to 75·3) | 64·0 (55·5 to 87·0) | 66·7 (43·3 to 90·7) | .. | .. | .. | .. | .. | .. | .. |
| Change from baseline | –6·6 (–21·6 to 0·3) | –0·6 (–8·9 to 7·0) | –2·7 (–6·6 to 2·0) | 0·0223 | 7·6 (2·0 to 14·0) | 0·004 | 5·7 (0·7 to 11·7) | 0·01 | –1·7 (–5·4 to 2·3) | 0·20 |
| **Grip strength (non-dominant hand [kPa])** | | | | | | | | | | |
| Last postdose observation | 60·0 (37·7 to 73·3) | 66·7 (52·7 to 85·0) | 65·2 (42·0 to 89·0) | .. | .. | .. | .. | .. | .. | .. |
| Change from baseline | –8·3 (–24·7 to 1·7) | –0·4 (–10·3 to 7·0) | –1·7 (–6·0 to 4·6) | 0·0026 | 8·3 (1·7 to 15·0) | 0·005 | 8·3 (2·4 to 15·6) | 0·002 | 0·3 (–4·1 to 4·9) | 0·46 |
| **MRC (sum score)** | | | | | | | | | | |
| Last postdose observation | 73·0 (66·0 to 77·0) | 74·0 (67·5 to 78·0) | 76·0 (68·0 to 80·0) | .. | .. | .. | .. | .. | .. | .. |
| Change from baseline | –2·0 (–6·0 to 0·0) | 0·0 (–2·0 to 2·0) | 0·0 (–2·0 to 1·0) | 0·0026 | 2·0 (1·0 to 4·0) | 0·003 | 2·0 (1·0 to 4·0) | 0·002 | 0·0 (–1·0 to 1·0) | 0·47 |

Data are median (IQR) or median (95% Moses CI). All tests are one-sided, with significance defined at an unadjusted p value of less than 0·025 (statistical testing was not adjusted for multiple testing for the secondary endpoints. These comparisons are therefore considered exploratory). SCIg=subcutaneous immunoglobulin. INCAT=Inflammatory Neuropathy Cause and Treatment. I-RODS=Inflammatory Neuropathy Rasch-Built Overall Disability Scale. MRC=Medical Research Council. *Asymptotic Jonckheere-Terpstra test. †Wilcoxon rank-sum test.

*Table 4:* Secondary outcomes

**Figure 10** **Secondary outcomes for the PATH trial (van Schaik, Ivo N. et al. 2018)**

Abbreviations: SCIg = subcutaneous immunoglobulin therapy

### B.7.    EXTENDED ASSESSMENT OF HARMS

Following advice from MSAC, targeted literature searches were performed to identify evidence for the long-term safety of the comparator treatments PE and corticosteroids, additional to that presented in the earlier review (DCAR 1564). Search terms and criteria used to guide the search were specified in the protocol for the current report (DCAR 1564 Update), and can be seen in **Appendix B**. Identified articles were screened to find the best quality data to represent the status of safety for PE and corticosteroids in patients with autoimmune neurological conditions. When there were no satisfactory data in CIDP patients, evidence was sought in broader populations who are treated with PE or corticosteroids, such as patients with rheumatoid arthritis (RA), giant cell arteritis (GCA) and systemic lupus erythematosus (SLE). Single arm and observational study designs were included, as these designs can have larger numbers and longer follow-up periods than some randomised study designs.

MSAC made the following specific requests for safety data:

•    "*Review evidence for safety of steroid use over the modelled lifetime of the disease and the appropriate utility decrements.*

•    *The DCAR reported insufficient evidence to make an assessment of the comparative safety between Ig and PE and this could be problematic for an economic comparison. Also review safety concerns resulting from vascular access for PE*" (MSAC 2020)

Articles were selected based on the applicability of the patient population, follow-up period, and steroid and PE dose and treatment regimens. Further considerations for selection were the size of the study population, date of publication, and risk of bias of the study[4], as these factors contribute to the reliability of the data. The studies included will be discussed under separate headings for each comparator treatment (PE and steroids).

#### ADVERSE EVENTS IN PATIENTS RECEIVING PLASMA EXCHANGE THERAPY

One SR was identified, published in 2016, which compared AEs in patients with Guillain-Barré syndrome (GBS) or myasthenia gravis (MG), receiving either IVIg or PE (Ortiz-Salas et al. 2016). Three additional studies reporting on AEs for patients receiving PE were single or multicentre retrospective analyses in mixed populations (Basic-Jukic et al. 2005; Mörtzell Henriksson et al. 2016; Nieto-Aristizábal, Vivas Á, et al. 2020). The multicentre study analysed data from the WAA apheresis registry[5], which assimilates data from national quality assessment apheresis registries developed in

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[4] Systematic reviews were appraised using the AMSTAR 2 checklist, and retrospective studies were appraised for using the SIGN 3 checklist for cohort studies.

[5] The World Apheresis Association (WAA) apheresis registry (https://www.waa-registry.org/)

Canada, France, Italy, Sweden, and Korea amongst other countries. Length of follow-up was not a consideration in selecting PE studies, as treatments during which AE data is collected occur over short periods of only a few days. All studies were assessed to be moderate for risk of bias. The essential details of the studies included, including the overall AE rates reported, and whether they were used to inform the economic modelling, are in Table 16.

**Table 16    Studies reporting adverse events for patients receiving PE**

| Study ID Country Study design ROB | Population/inclusion criteria n | Intervention Comparator (if applicable) | Overall adverse event rate |
|---|---|---|---|
| (Ortiz-Salas et al. 2016) Multinational SR Moderate | RCTs or analytical OS in patients with neurological disease (GBS or MG); comparison of IVIg and PE; publication up to 2014<br>Studies reporting AEs: k = 15 (published between 1994 and 2011)<br>Patients: n = 2,388 in studies reporting AEs | PE<br>Patients: n = 4,642<br>Cycles: typical strategy of 200-250 ml/kg over 10-14 days (5-6 cycles with 5% albumin)<br>IVIg<br>Patients: n = 1,600<br>Dosage: 0.4 g/kg/day or a total of 2 g.kg | PE 49/1656 (2.05%)<br>IVIg 41/732 (5.60%) |
| (Mörtzell Henriksson et al. 2016) Multinational R O MC Moderate | Patient data from the WAA apheresis registry (www.waa-registry.org ) between 2004 and 2014<br>Total patients n = 7,142<br>Diagnostic groups n (%):<br>  Malignancy 2,950 (41.8)<br>  Neurology 990 (14.0)<br>  Haematology 681 (9.6)<br>  Transplant and donors 576 (8.2)<br>  Rheumatology 501 (7.1)<br>  Endocrinology 446 (6.3)<br>  Other 958 (13.4) | PE by either filtration or centrifugation methods<br>procedures n = 50,846 | AEs / 10,000 procedures<br>Total 699 (6.99%)<br>Mild: 250 (2.5%)<br>Moderate: 281 (2.81%)<br>Severe: 168 (1.68%) |
| (Nieto-Aristizábal, Vivas Á, et al. 2020) Columbia R O SC Moderate | Patients receiving PE between 2011 and 2018, as prescribed by a neurologist<br>Patients: n = 187<br>Diagnoses n (%):<br>  MG 70 (37.4)<br>  GBS 53 (28.3)<br>  NMOSD 35 (18.7)<br>  CIDP 23 (12.3)<br>  AE 6 (3.2) | PE by centrifugation method<br>Average PE cycles per patient n = 5 (approx. 935) | AEs n/cycle<br>All patients 378/935 (40%)<br>CIDP 44/115 (38.2%) |
| (Basic-Jukic et al. 2005) Croatia R O SC Moderate | Data on PE procedures collected between 1982 and 2003 in a single dialysis centre<br>Patients: n = 507<br>Diagnoses n (%):<br>  MG 247 (48.7)<br>  TTP/HUS 19 (3.7)<br>  SLE 34 (6.7)<br>  GBS 60 (11.8) | PE by membrane/filtration method<br>Cycles n = 4857<br>Mean Session per patients 9.54 ± 13.71 (range 1 – 142) | AEs n (% of cycles)<br>All patients 231 (4.75%) |

| Study ID Country Study design ROB | Population/inclusion criteria n | Intervention Comparator (if applicable) | Overall adverse event rate |
|---|---|---|---|
| | CIDP 13 (2.5) ABO-incompatible BMT 23 (4.5) Other 94 (18.5) | | |

Abbreviations: AE = adverse event; BMT = bone marrow transplant; Ig = immunoglobulin; St = steroids; Pl = placebo; I = intervention; C = comparator; CI = confidence interval; CIDP = chronic inflammatory demyelinating polyneuropathy; GBS = Guillain Barre Syndrome; INCAT = Inflammatory Neuropathy Cause and Treatment; MG = myasthenia gravis; MRC = Medical Research Council; NDS = Neurological Disability Score; MD = mean difference; ODSS = INCAT overall disability sum score; NMOSD = neuromyelitis optica spectrum disorder; ROB = risk of bias; RODS = Rasch-built Overall Disability Scale; SLE = systemic lupus erythematosus; TTP/HUS = thrombotic thrombocytopenic purpura/haemolytic uremic syndrome

### Adverse events associated with PE compared with IVIg

RCTs and comparative observational studies were included in the SR by Ortiz-Salas et al (2016), with the inclusion period covering publications up to 2014. Of the 24 studies included, 15 reported on AEs - a total of 4,642 patients who received PE, and 1,600 who received IVIg. The typical PE strategy used across studies was replacement of 200 – 250 ml/kg body weight given over 10 – 14 days. This required approximately five to six cycles with 5% albumin replacement. The typical IVIg dosage was 0.4 g/kg body weight per day, to a total of 2g/kg body weight. There were fewer AEs overall in those receiving PE compared to those who received IVIg (2.05% versus 5.60%) (Table 16).

AEs fell into categories of respiratory, cardiovascular, genitourinary, central nervous system and other (including fever, temperature increase, chills, gastro-intestinal symptoms, phlebitis, haemolytic anaemia, allergic reactions, and elevated transaminases). In meta-analyses of clinical trials, the chance of AEs was lower for those treated with IVIg than those treated with PE but the difference was not statistically significant (patients with MG: OR = 0.65, 95%CI 0.16, 2.57; patients with GBS: OR = 0.76, 95%CI 0.38, 1.49) (Figure 11). When the outcomes were compared by study design, IVIg was favoured in comparative observational studies (OR 0.62; 95%CI0.41, 0.93; p = 0.023) but not in clinical trials (OR 0.81; 95%CI 0.45, 1.47; p = 0.496).

The frequency of AEs for both PE and IVIg was low in comparison to that reported in retrospective studies discussed below, and it is possible that the included studies underreported AEs, or did not report mild AEs. As an example, there is no mention of headaches in patients receiving IVIg, and yet this is one of the most commonly reported AEs for this treatment. As the comparison between IVIg and PE in this SR is not directly applicable to patients with CIDP, the results should be considered with caution and in conjunction with results from studies in CIDP populations where possible.
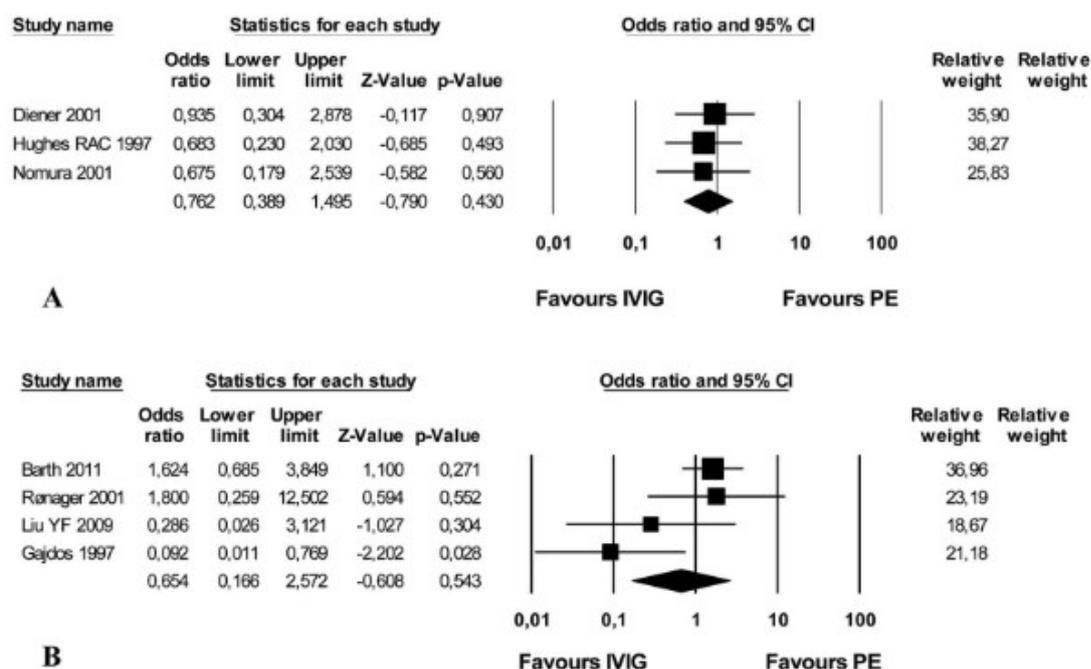
**Figure 11      A: Comparison of AEs for IVIg versus PE in clinical trials for GBS; B: Comparison of AEs for IVIg versus PE in clinical trials for MG**

Abbreviations: AEs = adverse events; GBS = Guillain Barre Syndrome; IVIg = intravenous immunoglobulin therapy; MG = myasthenia gravis; PE = plasma exchange therapy

### *Any adverse event in patients receiving PE*

There were a total of 49 AEs reported in 2,388 patients (2.05%) receiving PE in the SR (Ortiz-Salas et al. 2016). The severity of the AEs could not be determined by the authors due to the heterogeneity in primary study outcomes. The most frequently occurring AEs were arterial hypotension (n = 10), sepsis (n = 6), pneumonia (n = 5), alteration of coagulation (n = 4), nausea and vomiting (n = 4), and venous thrombosis (n =3). There were two incidences each of vasovagal reaction, poor venous access, acute renal failure, fever, and allergic citrate reaction, and one incident each of raised temperature, hypocalcaemia, haematoma, anaemia and skin eruption, vasospasm, syncope. The most frequently occurring AEs were cardiovascular events (which included occurrences of venous thrombosis and poor venous access), for which there were 21 events (42.8% of all AEs). Results for the most frequent AEs can be seen in Table 17.

### *Mild and moderate adverse events in patients receiving PE*

One large multicentre study (Mörtzell Henriksson et al. 2016) reported on registry data from the WAA. The number of patients included in the analysis was 7,142, and the number of PE procedures analysed was 47,856. The patient population was composed of patients from various diagnostic groups, the largest of which were malignancy (n = 2,950; 41.8%), neurology (n = 990; 14.0%) and haematology (n = 681; 9.6%). Because of the diversity of diagnostic groups, the applicability of data from the study is reduced. AEs were graded as mild, moderate and severe, where mild AEs were defined as those tolerated without medication, moderate AEs were those that required medication, and severe were

those events that interrupted the course of PE. Deaths due to AEs was a fourth grade. The severity of AEs was graded in sub-group of 2,760 procedures, and from the data, an AE rate for the total 47,856 procedures for each severity grade. There were 1,154 (2.4%) mild AEs, 1,438 (3.0%) moderate AEs, and 168 (0.35%) severe AEs.  The authors conducted further analyses, providing data on the number of AEs per 10,000 procedures.

Data for the most common AEs amongst 2,760 events were provided. The most common mild AE was an access problem, with 130 occurring every 10,000 procedures (1.3%). The next most common mild AE was hypotension, which occurred 36 times per 10,000 procedures (0.36%). The most commonly occurring moderate AEs were tingling (174/10,000 procedures, 1.74%), urticaria (45/10,000 procedures, 0.45%) and hypotension (30/10,000 procedures, 0.30%). There were severe AEs in 168 procedures, for which the primary reason for stopping PE was given. The most common reasons were hypotension (10/10,000 procedures, 0.1%), urticaria (6/10,000 procedures, 0.06%) and fever or chills (3/10,000 procedures, 0.03%) (Mörtzell Henriksson et al. 2016). The combined results for mild and moderate AEs are reported in Table 17.

Mörtzell Henriksson et al. also compared AEs between filtration and centrifugation methods of plasmapheresis, and the changes in AE frequency with number of treatments. AEs were reported as a number or rate per 10,000 procedures. The comparison showed frequency rates of 11% (membrane filtration) versus 6% (centrifugation), which was a statistically significant difference (95%CI 1.5, 2.3; p < 0.0001).

Two single centre retrospective studies (Basic-Jukic et al. 2005; Nieto-Aristizábal, Vivas, et al. 2020) provided AE data on 509 patients (4857 procedures) and 187 patients (approximately 935 procedures), respectively, receiving PE. The studies both included CIDP patients, albeit small proportions of the total populations: n = 13 (2.56%) (Basic-Jukic et al. 2005) and n = 23 (12.3%) (Nieto-Aristizábal, Vivas, et al. 2020). The earlier study included patients from a dialysis centre, so the patient diagnoses were broad. Despite this, more than half had autoimmune neurological disorders, and the majority were patients with MG (n = 247, 48.5%). The latter study included only patients who received PE prescriptions from a neurologist, and all had autoimmune neurological disorders (100%).

Basic-Jukic et al (2005) reported a total of 231 AEs, which occurred in 4.75% of procedures. The most common AE was thrombotic thrombocytopenic purpura/haemolytic uremic syndrome (TTP/HUS), which occurred in 5% of procedures. The next most common AEs were paraesthesia (2.7% of procedures) and haematoma at puncture site (2.4% of procedures). AEs were graded as mild to moderate, however five severe and potentially life-threatening anaphylactic reactions were recorded, and one case of respiratory arrest (n = 6, 0.12% of procedures) (see Table 18) (Basic-Jukic et al. 2005). By comparison, Nieto-Aristizabal et al (2020) reported higher rates of AEs, with high rates per patient of hypotension (56.6%), electrolytic disorders (54.5%), events related to Mahurkar catheters (45.4%), and bleeding (29.9%). Three hospitalised patients (1.6%) died with causes related to their neurological disease and septic shock (Nieto-Aristizábal, Vivas, et al. 2020).

The difference in AE rates between these two studies may be explained by the selection of patients at each setting, and/or by technical differences in procedure, setting, or experience of practitioner. Surprisingly, the more recent study, which used the centrifugation separation method (which reputedly has fewer AEs associated than the filtration method), had a higher rate of AEs than the older study, which used data from a centre which utilised the membrane filtration technique. It is possible that patients with autoimmune neurological disorders are more susceptible to safety issues with PE, or the patients included in the study had more severe illness, explaining the higher AE rate in the study by Nieto-Aristzabal et al (2020). Results are reported in Table 17.

**Table 17    The most common mild or moderate adverse events reported in patients receiving PE**

| Category/AE | Ortiz-Salas 2016[a] | | Mörtzell Henriksson 2016 | | Nieto-Aristizábal 2020 | | Basic-Jukic 2005 | |
|---|---|---|---|---|---|---|---|---|
| | N events | % procedures | N events/ 10,000 procds | % procedures | N events | % procedures | N events | % procedures |
| Cardiovascular | | | | | | | | |
| Hypotension | 10 | 0.04 | 66 | 0.66 | 106 | 11.3 | 29 | 0.6 |
| Vasovagal reaction, syncope | 3 | 0.012 | - | - | - | - | - | - |
| Poor venous access | 2 | 0.008 | 130 | 1.30 | 85 | 9[b] | - | - |
| Tingling, parasthesia, hypersensibility | - | - | 193 | 1.93 | 2 | 0.2 | 131 | 2.7 |
| Hypertension | - | - | 11 | 0.11 | - | - | - | - |
| Arrhythmia | - | - | 1 | 0.01 | 2 | 0.2 | - | - |
| Phlebitis | - | - | 2 | 0.02 | - | - | - | - |
| Electrolytic disorder | - | - | - | - | 102 | 10.9 | - | - |
| Chest pain | - | - | - | - | - | - | 15 | 0.3 |
| Gastrointestinal | | | | | | | | |
| Nausea and vomiting | 4 | 0.016 | 21 | 0.21 | - | - | 7 | 0.16 |
| Haematological | | | | | | | | |
| Haematoma, bleeding | 1 | 0.004 | 10 | 0.10 | 56 | 6.0 | 120 | 3.0 |
| Coagulation alteration, thrombosis | 7 | 0.027 | - | - | 4 | 0.4 | 83 | 1.7 |
| Systemic | | | | | | | | |
| Pneumonia | 5 | 0.020 | - | - | - | - | - | - |
| Fever | 5 | 0.008 | 8 | 0.08 | - | - | - | - |
| Sepsis | 6 | 0.024 | - | - | - | - | - | - |
| Infection | - | - | - | - | 21 | 2.2[c] | 2 | 0.04 |
| Immune | | | | | | | | |
| Allergic reaction | 23 | 0.008 | - | - | - | - | - | - |
| Urticaria | - | - | 57 | 0.57 | - | - | - | - |
| Other | | | | | | | | |
| Technical problems | - | - | 23 | 0.23 | - | - | - | - |
| Back pain | - | - | 1 | 0.01 | - | - | - | - |
| Flush | - | - | 2 | 0.021 | - | - | - | - |

Abbreviations: Ae = adverse event; PE = plasma exchange therapy; SR = systematic review
[a] Severity of events could not be established in the SR

*Severe adverse events in patients receiving PE*

Three studies reported the rate of most common severe AEs for patients receiving PE (Table 18). The most comprehensive severe AE reporting came from the WAA data base (Mörtzell Henriksson et al. 2016), who reported a per procedure rate of 1.68% for severe AEs overall. The most common severe AE was hypotension (11 events, 0.11% of procedures). Nieto-Aristizábal et al reported on three deaths, two of which occurred in patients currently receiving PE and the third occurring in a patient who had ceased PE several months prior. The deaths were stated to be caused by the patients' neurological disease and septic shock. Basic-Jukic et al reported five incidents of severe anaphylactic reaction requiring the use of aminophylline, epinephrine and steroid treatments. Two of these reactions occurred in one patient with TTP, and all cases were associated with the use of FFP (fresh frozen plasma). One patient with GBS with mild urticaria and hypotension experienced a respiratory arrest. The occurrence was explained by the combination of allergic reaction and respiratory insufficiency resulting from the patient's disease status.

**Table 18        The most common severe AEs reported for patients receiving PE**

| AE | Mörtzell Henriksson 2016[a] | | Nieto-Aristizábal 2020 | | Basic-Jukic 2005 | |
|---|---|---|---|---|---|---|
| | N events/ 10,000 procds | % procedures | N events | % procedures | N events | % procedures |
| Hypotension, Syncope | 11 | 0.11 | - | - | - | - |
| Urticaria | 6 | 0.06 | - | - | - | - |
| Fever, chills | 3 | 0.03 | - | - | - | - |
| Nausea vomiting | 2 | 0.02 | - | - | - | - |
| Access problem | 2 | 0.02 | - | - | - | - |
| Flush | 2 | 0.02 | - | - | - | - |
| Tingling, stitching | 2 | 0.02 | - | - | - | - |
| Arrhythmia | 2 | 0.02 | - | - | - | - |
| Bronchospasm | 1 | 0.01 | - | - | - | - |
| Quincke oedema | 1 | 0.01 | - | - | - | - |
| Anaphylactic reaction | - | - | - | - | 5 | 0.1 |
| Respiratory arrest | - | - | - | - | 1 | 0.02 |
| Death due to septic shock[b] | - | - | 3[b] | 0.32 | - | - |
| **Total** | **32** | **1.68** | **3** | **0.32** | **6** | **0.12** |

Abbreviations: AE = adverse event; PE = plasma exchange therapy
a Primary reason given in 168 procedures
b Two patients were receiving PE at the time of death, and one patient had finished PE three months prior to death.
c Only the 10 most frequently occurring severe adverse events have been tabulated

*Complications associated with access in patients undergoing PE*

The studies by (Mörtzell Henriksson et al. 2016) and (Basic-Jukic et al. 2005) analysed data for AEs associated with vascular access points for PE. Basic-Jukic et al found that peripheral venous access was

associated with haematoma in 5% of patients (n = 25). In 20% of these cases, the next session had to be delayed because of the haematoma. Of those receiving PE by central access, two patients experienced complication by occurrence of pneumothorax, which resolved spontaneously, and three developed a systemic infection at the catheter exit site (Basic-Jukic et al. 2005). Mörtzell Henriksson et al reported that procedures performed by central access were associated with more severe AEs, but there were more access problems associated with peripheral access. There were 130 mild AEs occurring every 10,000 procedures (1.3%) associated with access. Arteriovenous fistulae (AV-fistulae) and arteriovenous grafts (AV-grafts) were involved in the highest number of access problems compared to other access types (Mörtzell Henriksson et al. 2016).

### ADVERSE EVENTS IN PATIENTS RECEIVING CORTICOSTEROID THERAPY

The targeted literature search identified very few articles that reported on the long-term safety of steroids in patients with autoimmune neurological diseases, therefore the population was broadened to all autoimmune diseases that are treated with steroids. Three studies were identified for inclusion: one SR, one multicentre retrospective data analysis, and one single-centre retrospective analysis (Huscher et al. 2009; Rice et al. 2017; van Lieverloo et al. 2018). For comparison, data from the study by Wilson et al (2017), which was included in the original report on Ig for CIDP (DCAR 1564), were presented. Essential details of the four studies are given in Table 19. All studies were appraised as moderate for risk of bias.

One study was included that reported data from three large CIDP centres, in Serbia, Italy and The Netherlands (Nieto-Aristizábal, Vivas, et al. 2020). There were 125 patients in the study, and data were reported for up to 5 years from the start of steroid therapy. The treatments received were prednisone or prednisolone (n = 67, 54%), pulsed dexamethasone (n = 37, 30%), and pulsed intravenous methyl prednisolone (IV MP; n = 21, 17%). Neito-Aristizabal et al were the only authors to report AEs in categories of moderate and severe. The rate per patient of moderate AEs was 10%, and for severe AEs was 1.6%. This article was included because of the direct applicability of the patient population. However, there was insufficient detail to tabulate the rate of individual adverse events.

The SR (Rice et al. 2017) included full-text articles reporting indicators of long-term corticosteroid use in 40 cases or more, and published between the years 2007 to 2016 - 32 studies in all. Patients were from a diverse range of disease categories, but the largest proportion of studies were of patients with autoimmune disorders (31%). While patients were described as long-term users of GC, the follow-up period was not further described. An overall AE rate could not be calculated as only the most common AEs were reported. In addition, sleep disturbances were not reported, despite being a known side effect of GC. The most common AEs were hypertension (> 30% of cases) and fractures or osteoporosis (21% - 30%). A dose analysis was not performed, and AEs were not separated into categories of severity.

The single-centre retrospective study provided an analysis of data from a rheumatoid arthritis (RA) database in Germany (Huscher et al. 2009). Patients who had been treated with GC for a period of 6

months or longer were identified (n = 472) and AE data were collected. The overall AE rate was not reported, but individual AE rates are given in Table 20. A dose comparison was performed for dose categories of < 5 mg/day, 5 – 7.5 mg/day, and > 7.5 mg/day, and can be seen in Table 21.

Wilson et al (2017) performed a matched case-control analysis on patients with giant cell arteritis (GCA) from the Clinical Practice Research Datalink (CRPD) records in the UK. The analysis included 5011 GCA patients and 2011 matched controls that did not have the disease. Patients were required to have at least three years of recorded medical history to be eligible for the study. There was a total of 2190 (43.7%) GCA patients who experienced AEs, the most common of which were diabetes 321 (6.4%), osteoporosis 511 (10.2%), fractures 408 (8.1%), and infection 433 (8.4%). Death occurred in 517 (10.3%) of cases.

**Table 19**        **Studies reporting adverse events in patients receiving corticosteroid therapy**

| Study ID Country Study design | Population/inclusion criteria n | Intervention Comparator (if applicable) | Observation period | Adverse events overall n (%) |
|---|---|---|---|---|
| (Huscher et al. 2009) Germany R O SC Moderate | Patient data from a RA patient database, Patients taking ongoing GC > 6 months n = 472 | GC Dose categorisations: < 5mg/day 5-7.5 mg/day >7.5 mg/day | > 6 months | Overall AEs NR Dose comparison for individual AEs |
| (Rice et al. 2017) Multinational SR Moderate | Articles published between 2007 and 2016 reporting economic or utilisation data on CS Included studies: k = 32 Total patients: NR Diagnoses: Autoimmune diseases 31% Asthma 25% COPD & Lung diseases 19% Multiple disease areas 10% Other 15% | GC | "long-term" users of GC not further defined | Individual AE prevalence rates (most commonly reported AEs): 1% - > 30% |
| (van Lieverloo et al. 2018) Serbia The Netherlands Italy R MC Moderate | Patient data on from 3 large CIDP centres; Patients with treatment naïve CIDP; patients who underwent first-line treatment with corticosteroids; definite, probable or possible CIDP according to EFNS/PNS criteria. Patients: n = 125 CIDP subtype: Typical 98 (78%) Atypical 27 (22%) | Prednisone or prednisolone n = 67 (54%) Pulsed dexamethasone n = 37 (30%) Pulsed IV MP 21 (17%) | 5 years Median duration of treatment for responders (range): 6 (2-60) mo | AEs n (patient rate) Moderate: 10 (8%) Severe: 2 (1.6%) |
| (Wilson, J. C. et al. 2017b) UK R MCo Moderate | Patient data from a UK database CPRD on all patients 50 y and older who had a GCA diagnosis, at least one prednisolone prescription within 1 month of | Prednisolone | ≥ 3 years Median prednisolone duration (IQR): cases | AEs n (% patients) All 2190 (43.7%)[a] |

| Study ID Country Study design | Population/inclusion criteria n | Intervention Comparator (if applicable) | Observation period | Adverse events overall n (%) |
|---|---|---|---|---|
| | diagnosis, & 3 years medical history on the CPRD<br>Patients: n = 5011<br>Controls: n = 5011 | | 0.8 (1.9) y; controls 1.2 (2.1) y | |

Abbreviations: AE = adverse event; CIDP = chronic inflammatory demyelinating polyneuropathy; COPD = chronic obstructive pulmonary disease; CPRD = Clinical Practice Research Datalink; EFNS/PNS = The European Federation of Neurological Societies/Peripheral Nerve Society; GC = glucocorticoids; GCA = giant cell arteritis; MC = multicentre; MCo matched cohort study; NR = not reported; O = observational study; R = retrospective study; RA = rheumatoid arthritis
[a] Some patients may have more than one AE so 43.7% may not be a reliable proportion

AEs reported by Rice et al (Rice et al. 2017) and Wilson et al (Wilson, J. C. et al. 2017a) are compared in Table 20. Rice et al reported the prevalence rate of the most commonly reported AEs, but the number of events could not be calculated due to the lack of data. Wilson et al reported the incidence rates, focussing on a specific set of AEs commonly identified in patients with GCA. The two studies reported on rates of fractures and osteoporosis, and diabetes type II. Whereas Rice et al reported fractures and cases of osteoporosis together (prevalence 21% - 30%), Wilson et al reported these two events separately (incidence: fractures 16.5%, osteoporosis 22.9%), although it is likely that there was overlap between patients who experienced osteoporosis and fractures in the latter study. Rice et al (2017) reported diabetes prevalence to be up to four times greater than that in controls (from one study that reported this outcome), making it difficult to compare with the rate given in Wilson et al (14.2 %; 95%CI 12.7, 15.7). One of the studies reported that the prevalence of cataracts was between 1% and 3% in those taking GC (Rice et al. 2017), whereas the other reported on the incidence of glaucoma in GCA patients taking GC (10.2%; 95%CI 9.0, 11.5) (Wilson, J. C. et al. 2017a). The highest incidence for an AE was for serious infection (37.9% of GCA cases; 95%CI 34.7, 41.4) (Wilson, J. C. et al. 2017a), whilst the highest prevalence was for hypertension (> 30% of patients taking GC) (Rice et al. 2017).

AEs were not separated by severity, however Wilson et al (2017) reported an incidence of mortality of 23.4% (95%CI 34.7, 41.4).

**Table 20    AE rates reported for patients treated with steroids long-term**

| Category/AE | (Rice et al. 2017)<br>Prevalence range (%)[a] | (Wilson, J. C. et al. 2017a) | | |
|---|---|---|---|---|
| | | N events | Incidence (%) (95%CI)[b] | IRR[c] (95%CI) |
| Cardiac condition | 4 | - | - | - |
| Nausea, vomiting or other GI condition | 1-5 | - | - | - |
| Fracture or Osteoporosis | 21-30 | F: 433<br>O: 532 | F: 16.5 (15.0, 18.1)<br>O: 22.9 (21.1, 24.9) | 1.4 (1.2, 1.6)<br>2.4 (2.1, 2.8) |
| Cataracts | 1-3 | - | - | - |
| Glaucoma | - | 253 | 10.2 (9.0, 11.5) | 2.0 (1.6, 2.5) |
| Hypertension | > 30 | - | - | - |

| Category/AE | (Rice et al. 2017) | (Wilson, J. C. et al. 2017a) | | |
| --- | --- | --- | --- | --- |
| | Prevalence range (%)[a] | N events | Incidence (%) (95%CI)[b] | IRR[c] (95%CI) |
| Diabetes type II , hyperglycaemia | 8.3[b] | 340 | 14.2 (12.7, 15.7) | 1.4 (1.2, 1.7) |
| Serious infection | - | 476 | 37.9 (34.7, 41.4) | 1.5 (1.3, 1.7) |
| Mortality | - | 653 | 23.4 (21.7, 25.2) | 1.2 (1.0, 1.3) |

Abbreviations: AE = adverse event; CI = confidence interval; GI = gastro intestinal; GC = glucocorticoids; GCA = giant cell arteritis; IRR = incidence rate ratio; SLE = systemic lupus erythematosus

[b] Prevalence was compared between cases receiving GC and a cases not exposed to GC. The result reported by Rice et al (2017) came from one study, which also reported a prevalence of 8.3% , and a risk ratio for diabetes type II of 1 - 2 (Sarnes et al. 2011). A second study included in Rice et al (2017), found that amongst 989 patient with SLE using GC, there was a 1.5 times the risk of diabetes type II than controls (Shah et al. 2013).

[c] Incidence rate ratio, when compared to a control group without GCA and not taking long-term GC.

AEs identified in the large RA database (Huscher et al. 2009) were largely different to those reported by Rice et al and Wilson et al. Huscher et al conducted a dose comparison to determine the impact of GC dose on the rate of AEs (Table 21). The AE rates that increased in a linear pattern with increase in GC dose were Cushingoid phenotype, ecchymosis, leg oedema, mycosis, parchment-like skin, shortness of breath and sleep disturbance. Sleep disturbance was the most frequent AE, occurring at a frequency of 33.3% in the < 5mg/day dosage group and increasing to 44% in the > 7.5mg/day dosage group. A threshold effect was seen with other AEs. In these cases, the AE occurred at a consistent increased rate over the threshold dosage. Cataracts occurred at rates between 7.7% and 10.1% at doses over a low threshold of less than 5 mg/day. Epistaxis and weight gain occurred more frequently with GC doses over 5 mg/day. Depression, glaucoma and increased blood pressure had an increased incidence with doses over 7.5 mg/day. The overall incidence of increased blood pressure in patients with RA was 18.2%, which is lower than that reported in the SR of patients taking GC (> 30% prevalence) (Rice et al. 2017). However, the RA glaucoma incidence was similar (3.5% overall) to that reported for patients with GCA (2.0%; 95%CI 1.6, 2.5) (Wilson, J. C. et al. 2017a). Considering the variations between study populations, it is not unexpected to see some difference in AE rates.

**Table 21    AEs compared between GC doses for patients with RA treated with GCs longer than 6 months (Huscher et al. 2009)**

| Category/AE | Dose category (% patients) | | | |
| --- | --- | --- | --- | --- |
| | < 5 mg/day | %5 – 7.5 mg/day | > 7.5 mg/day | All |
| **Linear increase by dose** | | | | |
| Cushingoid phenotype | 4.3 | 15.8 | 24.6 | 15.0 |
| Ecchymosis | 17.4 | 23.5 | 24.6 | 22.1 |
| Leg oedema | 11.6 | 20.2 | 26.2 | 19.5 |
| Mycosis | 5.8 | 6.6 | 8.2 | 5.4 |
| Parchment-like skin | 10.1 | 15.8 | 21.3 | 16.6 |
| Shortness of breath | 10.1 | 12.6 | 16.4 | 12.8 |
| Sleep disturbance | 33.3 | 37.2 | 44.3 | 37.7 |

| Category/AE | Dose category (% patients) | | | |
|---|---|---|---|---|
| | < 5 mg/day | %5 – 7.5 mg/day | > 7.5 mg/day | All |
| **Threshold dose effect** | | | | |
| **< 5 mg/day** | | | | |
| Cataract | 10.1 | 7.7 | 8.2 | 8.3 |
| **5 – 7.5 mg/day** | | | | |
| Epistaxis | 1.4 | 6.6 | 4.9 | 5.1 |
| Weight gain | 8.7 | 22.4 | 21.3 | 19.6 |
| **> 7.5 mg/day** | | | | |
| Increased blood pressure | 18.8 | 16.4 | 23.0 | 18.2 |
| Depression, listlessness | 10.1 | 13.7 | 19.7 | 14.1 |
| Glaucoma | 2.9 | 2.7 | 6.6 | 3.5 |

Abbreviations: AE = adverse event; GC = glucocorticoids; RA = rheumatoid arthritis

The smaller study by van Lieverloo et al (van Lieverloo et al. 2018) included patients with CIDP, and analysed data from three treatment centres. Of the study population of 125 patients, 10 (8%) were reported to have experienced a moderate AE. Nine of the patients were treated with prednisolone, and one with dexamethasone. The AEs were not fully described, but included hypertension, diabetes mellitus de novo, glaucoma, depression, Cushingoid appearance, and gastro-intestinal complaints. Severe AEs occurred in two patients (1.6%) treated with prednisolone. One event was a severe case of hypertension, and the other was an acute myocardial infarction. Mild AEs were not reported, and no dose comparison was performed. The majority of patients were treated with oral prednisolone (53.6%), and the remainder were treated with either oral pulsed dexamethasone (29.6%), or pulsed IVMP (16.8%). The authors stated that the patients treated with prednisolone were more severely affected by their disease than the other treatment groups (MRC sum score p = 0.003; walking unassisted p = 0.01), which may have contributed to the higher rate of moderate and severe AEs in the prednisolone group.

#### ADVERSE EVENTS IN PATIENTS RECEIVING IVIG IN AN OUTPATIENT SETTING

One retrospective cohort analysis provided data on AEs for 438 patients with neuromuscular diseases receiving IVIg (Waheed et al. 2019). The patient group included 221 patients with CIDP (50.5%), data for whom were reported separately. The patients were treated at home by a specialty home infusion provider, or at a specialty home infusion pharmacy treatment centre within a seven month period in 2010. The specialty provider and treatment centres were jointly managed and operated by a company in the United States. Data for AEs related to IVIg were extracted from the company database in a standardised manner, so some infrequent observations were not considered in the analysis if they were not listed on the standardised data collection form. There were 5867 infusions in total, including 3256 infusions for patients with CIDP, within the data collection period. Other diagnostic categories within the population were MG (80 patients, 18.3%), and myositis (56 patients, 12.8%). The median follow-up time across the study was 21 weeks (IQR 7 – 27 weeks), however 8% of the overall

population had undergone their first-lifetime IVIg course at the time of data collection. A summary of essential characteristics of the study is found in Table 22.

**Table 22    Studies reporting adverse events in patients receiving IVIg therapy**

| Study ID<br>Country<br>Study design<br>ROB | Population/inclusion criteria | Intervention | Observation period | Adverse events overall n (%) |
|---|---|---|---|---|
| (Waheed et al. 2019)<br>United States<br>R O MC<br>Moderate | Database of an infusion provider company; infusions provided in homes or pharmaceutical centres (outpatient setting); patients with neuromuscular disorders<br>All patients : n = 438<br>CIDP = 221<br>Infusions all: 5867<br>Infusions CIDP: 3256 | IVIg | 7 months<br>Median follow-up (IQR): 21 (7, 21) weeks | AEs (16.9% of patients; 2.9% of infusions)<br>Serious AEs<br>Dose analysis<br>Treatment number analysis |

Abbreviations: AE = adverse event; CIDP = chronic inflammatory demyelinated polyneuropathy; IQR = interquartile range; IVIg = intravenous immunoglobulin therapy; MC = multicentre; O = observational; R = retrospective

AEs occurred in 2.9% of infusions and 16.9% of patients overall. By comparison, in the CIDP group, AEs occurred in 1.9% of infusions and 12.2% of patients. The most frequent AE was headache which occurred in 1.5% of infusions overall, and 0.8% of CIDP infusions. The next most commonly occurring AEs were hypertension (all infusions 0.5%; CIDP infusions 0.4%), rash (all infusions 0.5%; CIDP infusions 0.4%), and nausea (all infusions 0.4%; CIDP infusions 0.2%). Further AE frequencies can be seen in Table 23.

Four serious AEs were recorded, all of which were cases of aseptic meningitis (0.9% of patients). One of the cases occurred in a patient with CIDP (0.5% of patients).

**Table 23    Most common AEs in patients receiving IVIg in an outpatient setting**

| AE | All patients | | CIDP patients | |
|---|---|---|---|---|
| | Infusions n = 5867 | Patients n = 438 | Infusions n = 3256 | Patients n = 221 |
| Total | 172 (2.9) | 74 (16.9) | 63 (1.9) | 27 (12.2) |
| Headache | 90 (1.5) | 51 (11.6) | 26 (0.8) | 16 (7.2) |
| Hypertension | 28 (0.5) | 18 (4.1) | 14 (0.4) | 9 (4.1) |
| Rash | 27 (0.5) | 15 (3.4) | 12 (0.4) | 6 (2.7) |
| Other[a] | 23 (0.4) | 15 (3.4) | 9 (0.3) | 5 (2.3) |
| Nausea | 22 (0.4) | 14 (3.2) | 6 (0.2) | 4 (1.8) |
| Flu-like symptoms | 16 (0.3) | 13 (3.0) | 7 (0.2) | 6 (2.7) |
| Fever | 7 (0.1) | 5 (1.1) | 5 (0.2) | 3 (1.4) |
| Back pain | 4 (0.1) | 4 (0.9) | 0 (0.0) | 0 (0.0) |
| Aseptic meningitis Syndrome | 4 (0.1) | 4 (0.9) | 1 (0.1) | 1 (0.5) |
| Stiff neck | 3 (0.1) | 3 (0.7) | 0 (0.0) | 0 (0.0) |
| Shortness of breath | 3 (0.1) | 3 (0.7) | 1 (0.1) | 1 (0.5) |

Abbreviations: AE = adverse event; CIDP = chronic inflammatory demyelinating polyneuropathy; IVIg = intravenous immunoglobulin therapy
a Other AEs included achy feeling, diarrhoea, shaking, chills, dizziness, cold sweats, tight chest, pseudo-seizure, pain in neck and leg, pounding heart, heavy feeling, swollen lymph nodes, leg cramps, bruising at port site.

The authors performed a multivariate analysis to determine associations between patient and infusion characteristics and AE frequency per infusion. Associations that reached statistical significance are reported in Table 24. First lifetime course was strongly associated with a higher risk of any AE when compared to the frequency in subsequent courses. Higher IVIg dose, diagnosis of MG, and female sex were also found to be associated with a higher risk of any AE. For individual AE analyses, a higher risk of headache was associated with first-lifetime course of IVIg, and MG diagnosis. Higher frequency of hypertension was associated with first-lifetime dose and consecutive dosing. Older age was found to be associated with a lower chance of rash. When a per-patient multivariate analysis was performed, central line catheter was associated with higher rates of hypertension, when compared to the rate for peripheral catheters (OR 5.15, 95%CI 1.65, 16.1, p = 0.005).

**Table 24    ORs for AEs per infusion by multivariate logistic regression**

| Predictor (n events) | Any AE OR (95%CI), P | Headache OR (95%CI), p | Hypertension OR (95%CI), p | Rash OR (95%CI), p |
|---|---|---|---|---|
| First life-time course (116) Reference: subsequent courses (5751) | 3.74 (1.46, 9.58) 0.006 | 5.75 (2.16, 15.4) <0.001 | 13.99 (4.8, 41.8) <0.001 | - |
| IVIg dose >1.75 g/kg (1606) IVIg dose 1.00-1.75 g/kg (1056) Reference: 0.5-0.99 (1648) | 3.87 (1.73, 8.68) 2.34 (1.04, 5.30) 0.008 | - | - | - |
| Age, per 10 y increase (5867) | 0.81 (0.67, 0.97) 0.023 | 0.74 (0.61, 0.90) 0.003 | - | 0.73 (0.56, 0.97) 0.027 |
| Sex Women (3089) Reference: men (2778) | 1.85 (1.05, 3.27) 0.033 | - | - | - |
| Diagnosis MG (889) Reference: CIDP (3273) | 2.26 (1.09, 4.69) 0.035 | 4.19 (1.88, 9.30) 0.003 | - | - |
| Consecutive dosing (1915) Reference: non-consecutive (3953) | - | - | 2.15 (1.26, 3.69) 0.006 | - |

Abbreviation: AE = adverse event; CIDP = chronic inflammatory demyelinating polyneuropathy; OR = odds ratio

**SUMMARY OF EXTENDED SAFETY DATA**

A summary and comparison of AEs reported in retrospective cohorts of patients IVIg, PE or GC for neurological, autoimmune or other disorders can be seen in Table 25.

**Table 25    Comparison of adverse events reported in retrospective cohorts of patients receiving IVIg, PE or GC**

| Description | IVIg | PE | GC |
|---|---|---|---|
| Population | Outpatients with autoimmune neurological disorders including CIDP (50.5%) All patients : n = 438 CIDP = 221 | Patients with malignancy, neurological or haematological disorders | Autoimmune disorders including RA, SLE, GCA, and CIDP; asthma and lung diseases |

| Description | IVIg | PE | GC |
|---|---|---|---|
| | Infusions all: 5867<br>Infusions CIDP: 3256 | | |
| Observation period<br>Follow-up time | 7 months<br>Median follow-up (IQR): 21 (7, 21) weeks | NR | 6 months to 5 years |
| Mild or moderate AEs | 16.9% of all patients<br>2.9% of all infusions<br>12.2% of CIDP patients<br>1.9% of CIDP infusions | 2.05% of patients<br>4.75% to 40% of procedures | Up to 37.9% of patients per AE (only most common AEs were reported) |
| Serious AEs | 0.8% of all patients<br>0.5% of CIDP patients | 0.1% to 1.68% of procedures | 1.6% of CIDP patients |
| Most common AEs | Headache<br>Hypertension<br>Rash<br>Nausea | Hypotension<br>Poor venous access<br>Tingling, parasthesia<br>Infection<br>Urticaria<br>Nausea, vomiting<br>Electrolytic disorder<br>Haematoma | Serious infection<br>Sleep disturbance<br>Hypertension<br>Fracture and osteoporosis<br>Weight gain |

Abbreviations: AE = adverse event; CIDP = chronic inflammatory demyelinating polyneuropathy; GC = glucocorticoid therapy; GCA = giant cell arteritis; IVIg = intravenous immunoglobulin therapy; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus

## B.8.    INTERPRETATION OF THE CLINICAL EVIDENCE

### SAFETY

*Summary of DCAR 1564 Review outcomes*

The overall rate of serious AEs with any treatment (IVIg, steroids, PE, and immunosuppressant drugs) over the short to intermediate term is low. However, non-inferiority or superiority could not be determined due to the paucity of studies reporting safety outcomes and limitations in trial design. As CIDP usually requires long-term therapy and often multiple therapies, it would be helpful to consider long-term safety profiles. Side effects of IVIg frequently involve headache, fever, rash and infusion-like reactions that tend to be transient and non-severe. Steroids result in a similar number of patients experiencing adverse events, however, their frequency and their impact on quality of life is dependent on dose and duration of therapy. Based on a population with RA (Huscher et al. 2009) it is anticipated that the long-term adverse event profile of extended high-dose steroids is unfavourable relative to IVIg. Whether patients can be effectively titrated to low-dose steroids (< 7.5 mg/day of prednisone or equivalent) will impact the anticipated AE profile.

There was insufficient evidence to report on the safety of PE, immunosuppressants, or combination therapies for CIDP.

*What DCAR 1564 Update adds*

AE rates associated with Ig, PE and long-term steroid use have been identified, but not directly compared due to the disparate populations from which data were collected, which also impacts on the applicability of the evidence to the population of interest. The rates are compared in Table 25.

Adverse events associated with IVIg dosing regimen

The frequency of AEs was similar between two dosing regimens (normal individualised dose and interval, and half individualised dose at half the interval), and the majority of patients did not prefer either dosing schedule. There were no serious AEs reported. The evidence supports a flexible approach to the dosing regimens that patients with CIDP could be offered.

Adverse events associated with SCIg

The rate of AEs associated with SCIg was high. Over half of the patients who received SCIg in two different doses experienced an AE, with 4% experiencing a serious AE. Differences in rates between the two doses were small. Evidence for rates of AE associated with SCIg compared to other therapies was not identified in this review. A comparison of AEs between SCIg and IVIg was out of scope for this review. However, the recent TGA approval of SCIg for this population anticipates uptake into Australian clinical practice, and further data may be available in the future to investigate this comparison.

Adverse events associated with PE

The extended assessment of harms provided evidence of frequency per PE procedure of mild to moderate AEs of 2.05% of patients and ranging from 4.75% to 40% of procedures. The study reporting the higher rate of 40% was conducted in a population which included 12.5% CIDP patients and may initially have been thought to be more applicable to the population of interest. However the study found such a high rate of AEs in comparison to other studies, there is uncertainty around the selection of patients into the study and the technical characteristics of the treatment itself. The remaining two studies found mild and moderate AE rates of 4.75% of patients and 5.31% of PE procedures, the most common being hypotension and problems with venous access. The same two studies reported severe AEs at rates of 1.68% and 0.12% of procedures. Severe AEs were reported as hypotension, anaphylactic reaction, and death due to neurological disease and septic shock. In general, rates of AEs associated with PE were moderately low.

Adverse events associated with long-term steroid use

In the assessment of harms from long-term steroid use, there was considerable variability in the type of AEs reported. There was no separation of AEs by severity. Because the population was broadened to determine a bigger picture of harms from GC usage, the results may be less applicable to the CIDP population in Australia. The AE with highest incidence for patients taking long-term GCs was serious infection (37.9%), and the AE with highest prevalence was hypertension (> 30%). The next most frequently occurring adverse events were fracture and osteoporosis (prevalence 21% - 30%), diabetes type II (incidence 14.2%) and glaucoma (incidence 10%).

There was a dosage effect identified in the use of long-term GC. Several AEs increased linearly in rate with dose including sleep disturbance, ecchymosis and leg oedema. Other AEs demonstrated a threshold effect, including cataracts, weight gain, increased blood pressure and depression.

A severe AE rate of 1.6% (n = two patients) was reported in one study of CIDP patients. One event was a severe case of hypertension, and the other was an acute myocardial infarction.

Overall, the rate of AEs experienced by long-term steroid users is high; the evidence for severe AEs is less certain as only one small study contributed data. However it is likely that some of the adverse events reported in the other studies were severe, and this should be taken into account when interpreting this data. Additionally, as the clinical characteristics of the populations in these studies were diverse, the applicability of these rates of AEs to the population of interest is uncertain.

Adverse events associated with long-term Ig use

AEs occurred in 2.9% of infusions and 16.9% of patients with autoimmune neurological conditions receiving IVIg in an outpatient setting. In a CIDP sub-group, AEs occurred in 1.9% of infusions and

12.2% of patients. The most frequent AEs were headache, hypertension, rash and nausea, but the rates of these were generally low. Serious AEs were rare.

Multivariate analyses found that first lifetime course of IVIg and higher IVIg dose (0.5 – 0.99 g/kg) were found to be associated with a higher risk of some AEs.

Two SCIg doses (0.2 g/kg and 0.4 g/kg) had similar AE rates and serious AE rates over a 24-week randomised trial.

### EFFICACY

#### *Summary of the DCAR 1564 Review outcomes*

Ig is likely to have superior effectiveness (moderate-quality evidence) relative to no treatment. There is moderate evidence indicating that Ig has at least non-inferior effectiveness relative to steroids. The evidence may support a finding of superior effectiveness based on the relative number of patients discontinuing treatment. There was insufficient evidence on the comparison of Ig and plasma exchange to support a finding of non-inferiority. The relative long-term effectiveness of any of the active treatments for CIDP is uncertain as the evidence was limited and of mixed quality. There is some evidence to indicate there may be short-term (≤ six months) benefit from the addition of immunosuppressants to other treatments.

#### *What the DCAR 1564 Update adds*

Evidence from the PATH[3] trial, found that two SCIg doses (0.2 and 0.4 g/kg) were more effective than placebo in patients stabilised on IVIg after relapse, for relapse rate, time to relapse, and patient reported measures. Both SCIg doses were more effective than placebo for all domains of health related QoL and overall health, but there was no difference when the two doses were compared. The same trends were seen for treatment satisfaction and work productivity. A lower SCIg dose may provide satisfactory efficacy, quality of life and work productivity in some patients.

Two different IVIg dosing regimens (normal dose and interval, and half dose at half the interval) were found to have similar effectiveness in patients who were on individual maintenance regimens. There were no differences found in hand grip strength, disability, fatigue, and overall health. Patients may benefit from a more flexible approach to dose size and frequency, to fit in with service availability and patient preference.

There was no further evidence identified (from RCTs) comparing the effectiveness of IVIg with PE, steroids, or immunosuppressants.

It should not be necessarily assumed that the lack of high quality data on Ig equates to lack of effect, as with many rare diseases high quality evidence on treatments is often lacking. Real world evidence, such as from registries, can be helpful in these situations.

# SECTION C      TRANSLATION ISSUES

## C.1. OVERVIEW

The clinical conclusions were unchanged from DCAR 1564 (Duncan J et al. 2019). The relative safety of IVIg vs either corticosteroids, PE or immunosuppressants was uncertain. In terms of efficacy, the evidence suggests that Ig is superior to no treatment, and at least non-inferior (possibly superior) to steroids, but there is insufficient evidence to determine the relative efficacy vs plasma exchange or immunosuppressants.

Given the incomplete information available in the comparative evidence base, a modelled evaluation is constructed to quantitatively combine the otherwise disparate clinical information and to attempt estimation of overall long-term outcomes and costs.

The model structure used in this assessment (1564 Update) is different from the one used in the previous assessment (Duncan J et al. 2019). The revised structure addresses additional translational issues and updates the previously identified issues.

IVIg for the treatment of CIDP is already used in Australia and in order to assess the applicability of the available clinical evidence to the Australian setting, the following translation studies were considered in the revised model:

**Applicability issues**

- Does the patient profile in the clinical evidence match the demographic characteristics of patients with CIDP in Australia?
- Is the Ig dosing and frequency of administration schedule in the clinical trials consistent with the current recommendation in Australia (the Criteria V3)?
- Is the duration of Ig treatment in the clinical evidence consistent with use in the current Australian population?
- What is the optimum period of disease stability that would trigger a decision to reduce the maintenance Ig dose, in order to inform the Criteria V3?

**Extrapolation issues**

As the treatment duration in the trials is less than the expected duration of treatment in the current local setting, there is need for extrapolation of the trial results to address the following issue:

- What is the duration of the treatment effect (Ig and comparators) in patients with CIDP and was the duration of effect expected in the Australian setting captured in the available clinical evidence?

- How safe are intervention and comparator drugs when used for longer durations?

**Transformation issues**

Tools used in the measurement of treatment outcomes (including strength impairment, sensory dysfunction and disability) were discussed in section B.5 in the MSAC 1564 report. The Criteria V3 restricts use of Ig in CIDP patients according to the tools ONLS or MRC Sum Scores in adults, and MRS score and six minute walk in children. These outcome measures need to be transformed into health related quality of life utility scores and health states to estimate QALYs for the economic evaluation. The transformation issue addressed is:

- What are the utility/disutility values associated with various treatments and health states for patients with CIDP?

## C.2. APPLICABILITY ISSUES

### C.2.1. PATIENTS CHARACTERISTICS

**Does the patient profile in the clinical evidence match the demographic characteristics of patients with CIDP in Australia?**

This pre-modelling study addresses whether characteristics of participants in the key trials are representative of Australian CIDP patients currently using Ig; and whether the circumstances of use of Ig and comparators in trials are representative of how these products are being used in Australian clinical practice.

Patient characteristics in key trials, along with dose regimen and frequency, and setting were described in MSAC 1564 report (Duncan J et al. 2019) and are summarised in Table 26. The clinical trial comparing IVIg with plasma exchange (Dyck et al. 1994) was added to this pre-modelling study.

**Table 26    Patient characteristics in the key trials**

| Study | Inclusion criteria | Baseline | |
|---|---|---|---|
| | | Patient Characteristic | Disease Characteristic |
| IVIg vs Placebo<br>Hahn et al (Hahn, Bolton, Zochodne, et al. 1996)<br>Ig: n = 16<br>Placebo: n = 14 | Definite or probable CIDP (1991 AAN criteria). Continually progressive disease (>8 weeks) OR static or recently progressed disease; muscle weakness interferes with ambulation (NDS ≥ 40); patients with previous exposure to IVIg excluded. | Mean age (range):<br>52 (9–79)<br>% male: 37 | NDS<br>IVIg: 78.3 ± 27.5<br>Placebo: 76.6 ± 27.7<br>Clinical grade<br>IVIg: 4.6 ± 1.9<br>Placebo: 4.2 ± 1.9 |
| IVIg vs Placebo<br>ICE Study (Hughes et al. 2008)<br>Ig: n = 59<br>Placebo: n = 58 | Patients ≥18 years of age diagnosed with CIDP (motor and sensory dysfunction) and significant disability (INCAT 2-9); no steroids, IVIg or plasma exchange in previous 3 months; no | Mean age (sd):<br>IVIg: 50 (17)<br>Placebo: 53 (16)<br>% male<br>IVIg: 53 | INCAT disability score<br>IVIg: 4.2 ± 1.4<br>Placebo: 4.1 ± 1.5<br>MRC sum score<br>IVIg: 4.6 ± 1.9 |

| Study | Inclusion criteria | Baseline | |
|---|---|---|---|
| | | Patient Characteristic | Disease Characteristic |
| | immunomodulatory or immunosuppressive agents in previous 6 months. | Placebo: 79 | Placebo:: 4.2 ± 1.9 |
| IVIg vs Steroids<br>Nobile-Orazio et al (Nobile-Orazio et al. 2012)<br>IVIg: n = 24<br>IVMP: n = 21 | Typical CIDP according to EFNS/PNS criteria. Active or stationary phase but not in remission | Median age (years):<br>  IVIg: 54<br>  IVMP:66<br>% male:<br>  IVIg: 63<br>  Steroids: 71 | Rankin score (median)<br>IVIg: 2<br>Steroids: 3<br>ONLS (median)<br>IVIg: 3<br>Steroids: 4 |
| IVIg vs PE<br>Dyck et al (Dyck et al. 1994)<br>IVIg: n = 10<br>PE: n =9 | Definite CIDP with static or worsening neurological disability; no treatment with PE or Ig in the preceding six weeks | Age (years):<br>  IVIg: 51 ± 18<br>  PE: 39 ± 17<br>% male:<br>  IVIg: 60<br>  PE: 44 | NDS<br>IVIg: 68 ± 28<br>PE: 83 ± 40 |

**Abbreviations**: AAN = American Academy of Neurology; CIDP = Chronic inflammatory demyelinating polyneuropathy; Ig = Immunoglobulin; IV = Intravenous; EFNS/PNS = European Federation of Neurological Societies/Peripheral Nerve Society; MP = methylprednisolone; ONLS = Overall Neuropathy Limitations Scale; PE = Plasma Exchange; NDS = neurologic disability score; INCAT = Inflammatory Neuropathy Cause and Treatment; vs = versus; sd = standard deviation.

In summary, the characteristics of the patient populations and eligibility criteria in major trials (Dyck et al. 1994; Hahn, Bolton, Zochodne, et al. 1996; Hughes et al. 2008; Nobile-Orazio et al. 2012) appear to be aligned with the patient population currently eligible for IVIg according to Version 3 of *'the Criteria'*. Most of these trials exclude children. According to NBA Annual Report (2017–18), around 9% of the patients receiving Ig for any medical condition were aged ≤18 years (NBA 2018). Although the percentage of children with CIDP receiving Ig could not be determined from this report, it is assumed that children only comprise a small proportion of CIDP patients in Australia and therefore applicability of trial data should not be limited when age is considered.

One CIDP prevalence study using American Academy of Neurology (AAN) criteria in Newcastle, NSW, found the mean age of onset for CIDP was 48 years, with 51% of patients having relapsing-remitting CIDP over 7.1 years (McLeod et al. 1999). Data provided by the NBA (BloodSTAR) and analysed by the Department of Health indicate that the average age of new patients receiving Ig in 2019–20 was 65 years and average patient weight was 78 kg (Department of Health 2021c). Age range reported for patients using IVIg was 2–90 years in the NBA reports for 2018–19 and 2019–20 (NBA 2018, 2020). Age ranges of the participants in the key clinical trials are within the age range reported for patients with CIDP receiving Ig in Australian clinical practice.

### C.2.2.    IG AND COMPARATOR DOSING AND ADMINISTRATION FREQUENCY

**Is the Ig dosing and frequency of administration in the clinical trials consistent with the current recommendation in Australia (the Criteria V3), and are the doses of the comparators consistent with Australian clinical practice?**

This pre-modelling study compares the recommended IVIg doses in The Criteria V3, each RCT and the average dose used per patient based on the utilisation data from BloodSTAR (Department of Health 2021c). The comparator (corticosteroids and PE) dosing schedules in the RCTs are compared with those used in Australian clinical practice.

The recommendations outlined in the Criteria V3 differentiate between the induction phase and maintenance dosing of IVIg treatment. Initial treatment refers to patients commencing Ig treatment, and those who have relapsed within six months of a trial off-therapy. The recommendations are; **an induction dose of 2g/kg in 2–5 divided doses and a maintenance dose of 0.4–1 g/kg once every two to six weeks. A maximum dose of 2g/kg may be given in any four week period.** The Criteria V3 suggests the aim is to administer the lowest dose that achieves the appropriate clinical outcome for each patient.

The Criteria V3 recommendations are consistent with the clinical expert advice (Department of Health 2021a), that Australian neurologists generally authorise 2g/kg as an initial loading dose of IVIg followed by 0.4g/kg IVIg every four weeks as a maintenance dose. Dose and administration frequency are then titrated based on the patient's response. If the patient deteriorates, the maintenance dose is increased (mostly in the range 0.4–0.7 g/kg).

A summary of the dosing and frequency of administration in the key clinical trials is presented in Table 27.

**Table 27    IVIg and comparator dosing regimens in the key trials**

| Study | Intervention and Comparator |
|---|---|
| Hahn et al (Hahn, Bolton, Zochodne, et al. 1996) | IVIg: 0.4 g/kg daily for 5 consecutive days, once<br>Placebo: 10% dextrose daily for 5 consecutive days, once |
| ICE Study (Hughes et al. 2008) | IVIg: Baseline loading dose of 2.0 g/kg over 2–4 d, followed by a maintenance infusion of 1 g/kg over 1–2 d every 3 wk for 24 wk.<br>Placebo (0.1% albumin) |
| Nobile-Orazio et al (Nobile-Orazio et al. 2012) | IVIg: 0.5 g/kg/day for 4 consecutive days each month for 6 months<br>IVMP: 0.5g for 4 consecutive days each month for 6 months |
| Dyck et al (Dyck et al. 1994) | IVIg: 0.4 g/kg/week for first three weeks followed by 0.2 g/kg/week for the next three weeks.<br>PE: Twice per week for three weeks then once a week for next three weeks |

Abbreviations: Ig = Immunoglobulin; IV = Intravenous; MP = methylprednisolone; PE = Plasma Exchange; SCIg = subcutaneous immunoglobulin; wk = week.

A total induction dose of 2g/kg was consistent in three RCTs (Hahn, Bolton, Zochodne, et al. 1996; Hughes et al. 2008; Nobile-Orazio et al. 2012). Dyck et al (, 1994 #6} used a lower induction dose (total of 1.2g/kg over three weeks. None of the trials had a protocol that enabled them to distinguish response rates separately for the induction and maintenance phases.

The IVIg and comparator treatment doses and frequency for patients with CIDP in the Australian clinical practice are summarised in Table 28.

**Table 28** **Treatment doses and frequency depicted for patients with CIDP in the Australian clinical practice**

| Treatment | Induction dose and frequency | Maintenance dose and frequency | Source | Sensitivity analysis |
|---|---|---|---|---|
| IVIg | 4 infusions of 0.5 g/kg each (156 g for a 78 kg person per course) | 1 infusion of 0.70 g/kg each (54.6 g for a 78 kg person per course) | The Criteria V3 and clinical expert advice* | Induction: 2–5 infusions of 0.4–1.0 g/kg each  Maintenance: 1–2 infusions of 0.4–1.0 g/kg (31.2 – 78 g per course) every 3–8 weeks |
| Steroids (IV pulsed methylprednisolone) | 1g daily for 5 days | 1g every 28 days for a variable period | Clinical expert advice* | Induction: 1g daily for 3-5 days  Maintenance: 1g every 3–8 weeks |
| Plasma Exchange | 7 exchanges of 45 mL plasma per kg body weight (approximately 3.5 L) per treatment, 2–3 times per week | 1.5 sessions every 4 weeks | (Gwathmey 2020; Hahn, Bolton, Pillay, et al. 1996) | Induction: 5–10 exchanges of 40–50 mL/kg (~3.1 – 3.9 L) plasma volume  Maintenance: 1–2 sessions 3–8 weeks |

g = gram; Ig = immunoglobulin; IV = intravenous; kg = kilogram; L = litres; mL = millilitre; V = version
*Source: Clinical expert advice (Department of Health 2021a)

There appears to be differences in the Ig doses used in Australia and doses in the key trials. With respect to the modelled <u>comparison with steroids</u>, (Nobile-Orazio et al. 2012), the study maintains the high induction dose throughout the trial, whereas in Australia lower doses are used for maintenance therapy. It is appropriate that Australian doses are used in the economic model, however the lower dosing may be expected to be associated with a different (lower) treatment effect, therefore when moving from the trial-based analysis to the modelled analysis the estimated response rate to IVIg will become informed by the Australian data on response/continuations, rather than the trial.

For the modelled <u>comparison of IVIg with PE</u>, the clinical trial evidence base (Dyck et al. 1994) is only a six week study and it does not report absolute response rates – it merely describes the therapies as equivalent. For step 1 of the analysis trial-based doses will be costed, but no associated outcomes are known. Given neither the IVIg nor PE dosing is consistent with Australian practice the subsequent step in the economic model will replace the trial-based dosing with resource use consistent with Australian practice and Australian IVIg response rates will be used. As there are no alternative sources of relative treatment effect, the assumption that treatments are equivalent in terms of response will be maintained (although an overall difference in long-term outcomes will emerge due to differing adverse event profiles).

Sensitivity analyses will assess the impact of varying the dosage and frequency of intervention and comparators in section D.6.

*Validation of modelled Australian dosing*

The NBA provided summary level data from BloodSTAR on the use of Ig in CIDP patients in Australia (NBA 2018, 2020). These data suggest the average annual Ig use per Australian CIDP patient has increased from 437g in 2011–12 to 540g in 2019–20, and the average Ig use per treatment episode was 37.63g in 2019–20.

Under the Criteria V3, patients initiating treatment with Ig for CIDP are required to undergo clinical review by a neurologist after four months' of treatment to determine whether they have responded to therapy and are eligible to continue treatment. If response to treatment is satisfied at the four month review, patients are allowed to continue Ig for 12 months, at which time a second clinical review is conducted. Data from BloodSTAR were analysed by the Department of Health to distinguish Ig usage between those who continued beyond the first review period compared with those who didn't, based on utilisation data extracted for new patients who commenced Ig treatment for CIDP between 1 November 2018 and 30 April 2019 (Department of Health 2021c). This initiating cohort were followed through to 31 December 2020. The data extracted included all doses of Ig administered, date of authorisation and administration, reversals for doses not delivered, and patient characteristics such as age, gender and weight.

A total of 293 patients commenced Ig treatment between 1 November 2018 and 30 April 2019. Two patients had zero Ig dispensed by the cut-off date and were excluded from the analysis. Data for total grams of Ig dispensed (accounting for reversals) between initiation and day 120 were analysed. Patients received on an average 276 g of Ig in the first 120 days of treatment. Of the 291 patients who commenced therapy with Ig, 197 (68%) continued treatment beyond 140 days. Table 29 shows Ig dose for patients who did or did not continue treatment beyond 140 days.

**Table 29      Ig dose (g) for 120 days post-initiation of CIDP treatment for patients who did/did not continue Ig treatment beyond 140 days (after first clinical review)**

| Treatment continuation after 140 days | N (%) | Mean | Max | Min | Mode | Median |
|---|---|---|---|---|---|---|
| No | 94 (32) | 186.03 | 630 | 20 | 130 | 160 |
| Yes | 197 (68) | 318.98 | 1450 | 25 | 285 | 285 |
| Total | 291 | 276.04 | 1450 | 20 | 150 | 255 |

Source: Data and summary provided by the Department of Health (Department of Health 2021c)
CIDP = chronic inflammatory demyelinating polyneuropathy; g = grams; Ig = immunoglobulin; N = number of patients

The mean amount of Ig used by patients who did not continue treatment beyond 140 days was 186 g. This roughly equates to one loading dose of 156 g and a maintenance dose of 30 g indicating early treatment discontinuation (before four months review) due to lack of efficacy, adverse event or disease stability. For patients who continued treatment beyond the first review period the mean Ig used was 318 g equating to one loading dose of 156 g and four maintenance doses of 41 g each.

Of the 197 patients who continued to receive Ig following the first clinical review, 138 (70%) continued to receive Ig for over 16 months. 39 (13% ) of these 138 patients had at least one treatment break of greater than eight weeks during follow-up. Of those who continued to receive Ig for 16 months (after

second clinical review) or more without a break, the average amount of Ig supplied was 827 grams for a 12 month period (around 64 g every 4 weeks), and this amount ranged from 190 grams to 3,874 grams (15 g–298 g every four weeks) per patient. For those who did not continue treatment beyond second review and/or had treatment breaks between first and second review the average Ig ranged from 318 g–539 g per patient for a 12 month period (approximately 24 g–41 g every four weeks without accounting for breaks).

Table 30 summarises Ig use between first and second clinical review of Ig for CIDP as provided by NBA data (Department of Health 2021c).

**Table 30**     **Ig dose (g) supplied between first and second clinical review of Ig for CIDP**

| Description | N | Mean | Maximum | Minimum | Mode | Median |
|---|---|---|---|---|---|---|
| Not treated between first and second clinical review, but received treatment again more than 16 months after initiation | 4 | - | - | - | - | - |
| Ceased Ig treatment between first and second clinical review and had no treatment break | 48 | 317.58 | 1,440 | 30 | 60 | 215 |
| Ceased Ig treatment between first and second clinical review and had a treatment break | 7 | 373.21 | 1,120 | 140 | - | 250 |
| Received Ig after first and second clinical review without any treatment break | 99 | 827.15 | 3,874 | 190 | 455 | 645 |
| Continued beyond second clinical review (> 16 months) but had a break during this time | 39 | 538.64 | 1,820 | 75 | 200 | 420 |
| Total | 197 | | | | | |

CIDP = chronic inflammatory demyelinating polyneuropathy; Ig = immunoglobulin; N= number of patients
Note: The table above includes data for total Ig issued, that is intravenous Ig (IVIg) + subcutaneous Ig (SCIg). Updated data for IVIg issued excluding patients switching from IVIg to SCIg were provided by the Department on 31 March 2021. These are shown in Table 78 in Appendix G.

These summary statistics derived from the patient level analysis of BloodStar data (Department of Health 2021c) will be used for the model validation and calibration.

### C.2.3.     DURATION OF TREATMENT

**Is the duration of Ig treatment in the clinical evidence consistent with use in the current Australian population?**

Most of the RCTs are short-term (three to six weeks) or cease before one year of follow-up. This is not consistent with the duration of Ig treatment in the broader clinical evidence (observational studies) and the current Australian population. The Criteria V3 does not specify a maximum duration of treatment, rather it guides treatment based on specific time points (first clinical review at four months and second clinical review at 12 months) of clinical assessment to determine responsiveness and clinical benefit. BloodSTAR data for the mean duration of treatment in Australian patients receiving Ig for CIDP were not available. However, the utilisation data for 291 treatment naïve patients who commenced Ig treatment for CIDP between 1 November 2018 to 31 April 2019 (Department of Health 2021c) was summarised in Table 29 and Table 30 above.

In summary, of the 291 patients who commenced therapy with Ig, 197 (68%) continued treatment beyond 140 days (after first clinical review). Of the 197 patients who continued to receive Ig following the first clinical review, 138 (70%) continued to receive Ig for over 16 months, however during this follow-up 39 (28%) of these patients did have a break in treatment of greater than 56 days (8 weeks). A further 55 (28%) patients ceased Ig between the first and the second clinical review and did not reinitiate in the follow-up period. Four patients had a break of 12 months or more, but reinitiated more than 16 months after initiating Ig.

There is a considerable variation in the treatment durations among patients with CIDP in Australia, as observed in the BloodStar data (Table 29 and Table 30), therefore it was considered appropriate that additional information on long-term treatment response, remission and relapses in patients with CIDP should be incorporated from the long-term observational studies. These are discussed in section C.3.1.

### C.2.4.    TREATMENT WEANING

**What is the optimum period of disease stability that would trigger a decision to reduce the maintenance dose, in order to inform the Criteria?**

The Criteria V3 outlines continuation rules for CIDP patients who have responded to treatment with Ig as below.

> *"Review by a neurologist is required after four months of Ig therapy to determine whether the patient has responded. If there is no benefit after this period of treatment, IVIg therapy should be abandoned. Where treatment is continued, a review by a neurologist or general physician is required each 12 months. A trial of cessation should be considered each 12 months in patients in remission on maintenance therapy. Once a patient has relapsed in the first six months of a trial off therapy, a further trial might be considered after at least two years. Documentation of clinical efficacy is necessary for continuation of IVIg therapy. Clinical effectiveness of Ig therapy may be demonstrated by improvement in disability as measured by a reduction in the ONLS by at least one point; or by an increase in the MRC sum score by at least three points, as compared to the qualifying assessment (for adults and children 10 years or older)."*

Optimising the dose and dosing interval for each patient is challenging and is mainly trial and error (Lunn et al. 2016; Rajabally, Y. A., Wong & Kearney 2013). Currently no evidence supports weight-based dosing of maintenance treatment. Lower doses of treatment may be as effective as higher doses, considerable interpatient variability exists, and the required frequency of infusion appears patient-specific (Lunn et al. 2016; Rajabally, Y. A., Wong & Kearney 2013). Although the Criteria V3 and current guidelines recommend adjusting the dose and treatment interval for responsive patients in order to minimize the treatment required, limited information is available to guide the process (Lunn et al. 2016).

Recently, Lunn et al proposed a dosing algorithm to standardise the tapering of Ig doses in chronic inflammatory neuropathies based on patient response (Lunn et al. 2016). According to this treatment algorithm patients are treated with one or two initial IVIg doses of 2gm/kg at an interval of three weeks and their response is assessed, then a third dose is not administered until the patient's condition deteriorates, allowing a "dose interval" to be set. The dose is then reduced by 20% per course until relapse, allowing dose optimization. The authors individualized Ig doses for 71 chronic inflammatory neuropathy patients over five years using this algorithm. The majority of patients had CIDP (n = 39) or multifocal motor neuropathy (n = 24). The mean (standard deviation) dose of Ig administered in this study was 1.4 (0.6) g/kg, with a mean dosing interval of 4.3 weeks (median 4 weeks, range 0.5–10). Adaptation of this algorithm is specific to patient's response to treatment.

A sensitivity analysis will be performed using the mean dosing interval of four weeks and Ig dose reduction by 20% per course for four to six cycles for patients in the "Maintenance phase (on treatment more than four months)" health state in the model assuming that the Ig treatment effect will remain constant even on the lower doses.

## C.3. EXTRAPOLATION ISSUES

As the treatment duration in the trials is less than the expected duration of treatment in the current local setting, there is need to determine the appropriate time horizon for the analysis, and a need for extrapolation of the trial results.

### C.3.1. TIME HORIZON AND CYCLE LENGTH

**What is the appropriate time horizon and cycle length for the economic analysis of maintenance IVIg?**

The economic analysis for *Criteria V3* involves maintenance treatments for patients with CIDP who show improvement or are stable, which potentially are ongoing for as long as clinically required and there is a benefit. NBA data for the duration of treatment in Australian patients receiving IVIg for CIDP were not available, however average durations of IVIg used and mean/median follow-up (years) of the CIDP patients that were found in published literature (Table 79) suggest that patients with CIDP may receive treatment for long durations due to progressive nature of the disease. The longest mean follow-up of all the studies was 6.2 years. It is assumed that a time-horizon of ten years will sufficiently capture the treatment effect in the model. Treatment frequencies reported in the key trials, observation studies and indication in the Criteria V3 generally vary from two to six weeks. Therefore, a four weekly cycle-length is chosen in the model.

### C.3.2. DURATION OF THE TREATMENT EFFECT

**What is the expected duration of the treatment effect in patients with CIDP in the Australian setting, and is this captured in the available clinical evidence?**

The treatment duration reported from the RCTs described in Section C.2.3 (few weeks to 12 months), does not necessarily represent the actual treatment duration in the Australian setting. In fact, it is likely that a responder will receive active treatment for many years due to the chronic progressive nature of the disease. This is evident in data provided by NBA for Ig use in 2018–20. New patients using Ig represented 22% of the total patients receiving Ig in these two financial years, indicating 78% of the patients receiving Ig have received it in the past. The BloodStar data (Department of Health 2021c) provided assessment of Ig use 16 months post Ig initiation for treatment naïve patients initiating Ig for CIDP under the revised Criteria 3 (Table 29 and Table 30). The overall assessment of Ig supply from initiation to beyond second clinical review at 16 months suggested that of the 291 patients who initiated Ig for CIDP:

- 94 (32%) patients ceased Ig on or before the first clinical review at four months;

- 55 (19%) patients ceased Ig between the first and second clinical review and did not reinitiate in the follow-up period;

- 99 (34%) patients were continuously supplied beyond the second clinical review (16 months) date and without a break in supply

- 39 (13%) patients continued Ig therapy beyond the second review date, but did have at least one break of greater than two months during follow-up; and

- four (1.4%) patients had a break of 12 months or more, but reinitiated more than 16 months after initiating Ig.

The economic evaluation in Section D assumes that while patients are receiving treatment they are stable in their disease and will discontinue treatment if i) they have no response, ii) suffer an AE, or iii) initiate the trial of weaning off phase (for Ig only). Once a patient discontinues treatment (either due to an AE or non-efficacy) this patient can either progress through the disease or die due to other causes. The BloodStar data (Department of Health 2021c) above was converted into response, remission and relapse rates for use in the model.

The BloodStar rates were compared to response, remission and relapse rates identified in the long-term observational studies, see Table 79, in **Appendix G**. These studies were also used to identify appropriate response, remission and relapse rates for comparators, as equivalent Australian clinical practice data for corticosteroid use or plasma exchange was not available.

**Treatment response**

Recent studies focus increasingly on mid-term and long-term outcome in CIDP. Studies were highly heterogeneous regarding intervention, comparator, time point, and methodology. The definition of "treatment response" and "achieving remission" varied across studies.

IVIg generally achieved high rates of response to treatment (**54–88% response rate**), relative to placebo (Gorson et al. 2010; Hughes et al. 2008; Kuitwaard et al. 2015; Kuwabara et al. 2017; Lopate & Pestronk 2011; Nobile-Orazio et al. 2012; Querol et al. 2013; Rajabally, Yusuf A. & Afzal 2019; Viala et al. 2010). Where comparative data were reported, IVIg increased the proportion of patients with CIDP who responded to treatment, relative to comparators, including corticosteroids and plasma exchange (Dyck et al. 1994; Nobile-Orazio et al. 2012; Nobile-Orazio et al. 2015).

Although many patients responded to corticosteroid therapy (**48–81% response rate**, across eight studies), safety concerns were associated with their long-term use (Börü Ü et al. 2014; Eftimov et al. 2012; Lopate, Pestronk & Al-Lozi 2005; Nobile-Orazio et al. 2012; Nobile-Orazio et al. 2015; van Lieverloo et al. 2018; van Schaik, I. N. et al. 2010; Viala et al. 2010).

For PE, **44–85%** of patients across six studies responded (Choudhary & Hughes 1995; Codron et al. 2017; Dyck et al. 1994; Hahn, Bolton, Pillay, et al. 1996; Lieker et al. 2017; Viala et al. 2010).

Treatment response rates in the base-case economic analyses are based on estimates from BloodStar (Department of Health 2021c) and trial data (Nobile-Orazio et al. 2012), extrapolated over the modelled time horizon.

**Incidence of remission and relapse**

Few studies reported the remission and relapse rates; and the definitions of remission and relapse varied across the studies that did.

The ICE study re-randomised IVIg responders (N=75) to IVIg or placebo for an additional 24-week period. 56% of the patients who responded to IVIg and were re-randomised to placebo did not relapse (Hughes et al. 2008). In the IMC trial (Nobile-Orazio et al. 2012) patients with CIDP were randomised to receive IVIg or IVMP treatments for 24 weeks followed by 24 weeks off-treatment. 62% and 100% remained in remission (stable off treatment) in IVIg and IVMP arms respectively. In the extension phase of the IMC study (Nobile-Orazio et al. 2015), 86% of the patients relapsed over median 42 months off treatment compared with 77% of the patients relapsed over median 43 months in IVMP arm. In Table 31 these probabilities are shown converted to cyclic probabilities to apply in the trial-based analysis (Step 1 in the comparison 1).

The treatment regimens in IMC trial vary from the treatment regimens defined in the Criteria. All patients in the IVIg arm received high doses of 2g/kg IVIg every fourweeks for 24 weeks followed by no treatment period. In general practice only loading dose is high followed by lower maintenance doses (0.4–1g/kg) every two to six weeks. Therefore, the treatment effect, remission rate and relapse rate can vary from those observed in this trial. Further evidence for long-term IVIg treatment was found in retrospective case series; two studies showed remission in 26% of patients (Querol et al. 2013; Rajabally, Yusuf A. & Afzal 2019), and other one in 40% (Kuitwaard et al. 2015), all of which were

over a median follow-up of approximately four years. However, these remission rates did not capture patients who relapsed after remission.

Three studies reported remission for steroids treatment over long-term period. The extension study of the PREDICT trial (Eftimov et al. 2012) reported that 26% of patients were in remission over the median follow-up of 54 months. The extension study of the IMC trial (Nobile-Orazio et al. 2015) reported remission in 23% of the patients over median follow-up of 43 months. Van Lieverloo et al (2018) reported 61% of the patients in remission after steroids treatment over median follow-up of 43 months.

Long-term remission data for PE were not available. One study (Viala et al. 2010) investigated the treatment dependency (IVIg, prednisolone and PE) in 146 patients with CIDP. The treatment response and dependency rates for PE were 62% and 23% respectively. Overall, 18% of treated patients in this study stopped treatment within six months of initiation with no relapse during the median follow-up of three years. 29% of treated patients stopped treatment after mean treatment duration of 15 months. However, the treatment specific remission rates were not provided in this study.

In the absence of any data regarding remission rates for PE, the treatment remission rates are considered equivalent to those experienced with IVIg, consistent with the assumption of equivalent therapeutic effect.

Table 29 and Table 30 summarised Ig usage and treatment continuation data extracted from BloodStar for CIDP patients. Duration of treatment in these patients were discussed in Section C.2.3. Of the 291 patients who commenced therapy with Ig, 94 (32%) did not continue treatment beyond the first clinical review. As per the literature studies and clinical expert advice approximately 5% of the patients cease Ig treatment due to adverse events and 10% due to non-efficacy (Department of Health 2021a; Querol et al. 2013). Between 15% and 30% of patients require only a single course of IVIg (Van den Bergh, PYK et al. 2010). One study reported (Kuitwaard et al. 2015) that out of 86 treatment-naïve patients who were IVIg responsive and reached a documented clinical remission, 14 (16%) needed only one IVIg course, which is in line with the 15–30% reported in the literature. Therefore, it is reasonable to assume that the remainder of the patients (17%) are early responders who achieve remission within few Ig courses.

Of the 197 patients who continued Ig treatment beyond first review, 138 (70%) continued to receive Ig for over 16 months, however during this follow-up 39 (28%) of these patients did have a break in treatment of greater than 56 days (eight weeks). A further 55 (28%) patients ceased Ig between the first and the second clinical review and did not reinitiate in the follow-up period. Four patients had a break of 12 months or more, but reinitiated more than 16 months after initiating Ig. These data were used to estimate the probable remissions (51%) and relapses (49% of those in remission) over 12 months period (between first and second clinical review).

Remission and relapse incidences reported in the long-term studies and estimated from BloodStar data were converted to cyclic (four weekly) probabilities and compared across. Table 31 provides a summary of these estimates. These estimates should be interpreted with caution due to variability in the data reported, study structures and the assumptions made in deriving these probabilities.

**Table 31    Estimated probabilities for remission and relapse from the literature studies and BloodStar data**

| Study | Remission | Cyclic probability | Relapse | Cyclic probability |
|---|---|---|---|---|
| **Immunoglobulin** | | | | |
| Hughes (2008) | 56% of the patients who received IVIg and were re-randomised to placebo after 24 weeks, stayed in remission after 48 weeks.[1] | 0.0612 | 35% of the patients who received IVIg and were re-randomised to placebo after 24 weeks, relapsed before the end of the study period.[1] | 0.0326 |
| Nobile-Orazio (Nobile-Orazio et al. 2012) (IMC trial) | All patients in remission after 24 weeks of the treatment. | NC | 38% of the responders who were off treatment had a relapse over trial follow-up of 24 weeks. | 0.0768 |
| Nobile-Orazio (2015) (IMC extension study) | All responders in remission after 24 weeks of treatment. 14% of the patients stayed in remission after 3.5 years | NC | 86% of the responders relapsed over median follow-up of 42 months | 0.0419 |
| Querol (2013) | 25.6% in remission after 48 weeks | 0.0243 | NR | NC |
| Rajabally (2019) | 25.6% in remission after 4 years | 0.0057 | NR | NC |
| Kuitward (2015) | 40% in remission after median follow-up of 3.8 years | 0.0103 | NR | NC |
| BloodStar data (post-first review) | 17% over 20  weeks | 0.0366 | 4 patients relapsed after 16 months | 0.0150 |
| BloodStar data (post-second review) | 50.5% of patients reached remission at least once over 12 months | 0.0527 | 48.9% patients relapsed at least once over 12 months | 0.0380 |
| **Corticosteroids** | | | | |
| Nobile-Orazio (2015) | All patients in remission after 24 weeks of treatment. 23% of the patients stayed in remission after 3.5 years | NC | 77% of the patients relapsed over median follow-up of 43 months | 0.0310 |
| Van Schaik (2010) | 40% in remission after 52 weeks follow-up | 0.0385 | NR | NC |
| Eftimov (2012) | 62.5% stayed in remission after 4.5 years | NC | 50% of the patients relapsed over 13 months | 0.0480 |
| Van Lieverloo (2018) | 61% of the patients stayed in remission after 4.5 years | NC | 39% of patients relapsed over 4.5 years (69% of these within 6 months) | 0.0493 |

[1]. Probabilities were calculated over 48 weeks study period as all patients started in remission in second phase.
*Shaded cells* represent estimates from BloodStar data (Department of Health 2021c) and clinical study values that are used in the base case economic models

For IVIg, The cyclic **remission** probabilities for the induction and maintenance phases using BloodStar data (Department of Health 2021c) are estimated to be 0.0366 and 0.0527, respectively, which are within the range estimated from observational data (0.0057–0.0612). Trial based probabilities will be presented in Step 1 of the economic evaluation and then replaced by the probabilities estimated from BloodStar data in Step 2 and 3. Other values will be assessed in sensitivity analysis.

The cyclic **relapse** probability estimates from the two trials are 0.0419 (Nobile-Orazio et al. 2015) and 0.0326 (Hughes et al. 2008). Relapse probabilities estimated from BloodStar data are similar to these values (0.0150 and 0.0380 from first and second clinical review). The relapse probability (0.0419) estimated from the key comparative trial (Nobile-Orazio et al. 2015) is used in the Step 1 of the analysis (trial-based inputs), and estimates from BloodStar are applied in Step 2.

For steroids, the remission probability could only be estimated from one study (0.0385) (van Schaik, I. N. et al. 2010) and but relapse rates were estimated from three studies (0.0310–0.0493) (Eftimov et al. 2012; Nobile-Orazio et al. 2015; van Lieverloo et al. 2018). The probability for relapse estimated from study by Nobile-Orazio et al (0.0310) is used in the base case.

In the absence of any data regarding the remission and relapses observed with PE treatment, the remission and relapse probabilities estimated for Ig (0.0527 and 0.0419 respectively) are used, based on an assumption of equivalent therapeutic effect. Sensitivity analysis will assess varying these probabilities by ±50%.

### C.3.3.    LONG-TERM SAFETY IMPLICATIONS AND ADVERSE EVENTS

**What safety implications and adverse events are associated with the intervention and comparator treatments when used for longer durations?**

Several retrospective reviews have shown that long-term corticosteroids use, even in low doses, is a significant independent predictor of numerous adverse effects and that the risk is both dose and duration dependent (Curtis et al. 2006; Huscher et al. 2009; Wilson, J. C. et al. 2017b). In contrast rates of complications from long-term therapy are reportedly lower with either PE or Ig (Dyck et al. 1994; Kuitwaard et al. 2015). The key clinical trial comparing IVIg and IVMP captured safety events for first six months of trial only. Long-term adverse event rates associated with steroid use are required to capture the comparative safety of steroids and Ig and inform the model for longer time-horizon, beyond the trial period.

Long-term safety consequences associated with corticosteroids were identified and are reported in Table 20, section B.7 – Extended assessment of harms. These event rates need to be translated and extrapolated to inform the transition probabilities associated with adverse events in the economic evaluation.

Wilson et al performed a matched case-control analysis on patients with GCA from the Clinical Practice Research Datalink (CRPD) records in the UK (Wilson, Jessica C. et al. 2017). The analysis included 5011 GCA patients and 2011 matched controls that did not have the disease. Patients were required to have at least 3 years of recorded medical history to be eligible for the study. There was a total of 2190 (43.7%) GCA patients who experienced AEs, the most common of which were diabetes 321 (6.4%), osteoporosis 511 (10.2%), fractures 408 (8.1%), and infection 433 (8.4%). Death occurred in 517 (10.3%) of cases. These chronic conditions are prevalent in the general population irrespective of steroid use. Wilson et al reported incidence rates for both GCA and non-GCA groups for all these adverse events. Differences in the incidence rates for these events reported for GCA and non-GCA groups were used to estimate excess risk attributed to steroid use. This study also reported the incidence rate ratio for mortality of 1.2 for GCA vs non-GCA cohort. This rate ratio is applied to the background age-specific mortality risk to estimate the mortality risk associated with steroid use.

In a sub-study of the above cohort, Wilson et al analysed the effect of cumulative doses in the GCA cohort (Wilson, J. C. et al. 2017b). The study compared the event rates stratified by cumulative prednisolone dose. Five categories based on cumulative prednisolone dose (mg) were defined (≤3,000, 3,001–6,000, 6,001–10,000, 10,000–20,000 and ≥20,000). Adjusted odds ratio (AOR) for outcomes of interest were presented with cumulative dose ≤3,000mg as the reference category. The results of this study indicated that increasing cumulative doses of corticosteroids place patients at increased risk of serious individual adverse effects.

As per clinical expert advice (Department of Health 2021a), the main steroid protocol for CIDP in Australia is intravenous pulsed methylprednisolone – 1 g daily for three to five days as induction followed by 1g every 28 days for a variable period. Based on the above treatment regimen patients would be exposed to a cumulative dose of 10 g (10,000mg) within six months of starting steroids. The relative risk for cumulative prednisolone dose >10,000mg were estimated from AORs[6] provided in the above study (Wilson, J. C. et al. 2017b) and applied to respective adverse event risk to capture the dose effect in the model. The study reported the mean times for the occurrence of glaucoma, diabetes, osteoporosis, fractures and infection after beginning prednisolone were 2.7, 2.8, 3.0, 3.2 and 4.1 years, respectively, however the majority of cases of diabetes, glaucoma, and osteoporosis occurred within two years following treatment initiation, with over 40% of diabetes and glaucoma cases developing in the first year. The median total duration of prednisolone use in these cases was reported at 0.8 years. Therefore, in the model it is assumed that these adverse events can occur any time after induction treatment.

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[6] The adjusted odds ratio (AOR) were converted to relative risk (RR) using formula provided by Zhang et al (1998); $RR = AOR/((1-I_0) + (I_0 \times AOR))$, where $I_0$ indicates the incidence of the outcome of interest in the non-exposed group.

Table 32 summarises the estimated annual probabilities and relative risk for the adverse events diabetes, osteoporosis, fractures, glaucoma and severe infection.

**Table 32        Summary of adverse event risks associated with chronic corticosteroids use**

| Adverse event | GCA | Non-GCA | Rate difference | Annual probability[a] | RR for cumulative prednisolone dose >10,000 mg |
|---|---|---|---|---|---|
| Diabetes | 1.42% | 1.00% | 0.42% | 0.00035 | 1.78 |
| Osteoporosis | 2.29% | 0.94% | 1.35% | 0.00113 | 1.41 |
| Fractures | 1.65% | 1.23% | 0.42% | 0.00035 | 1.24 |
| Glaucoma | 1.02% | 0.51% | 0.51% | 0.00043 | 1.00 |
| Severe infection | 3.79% | 2.57% | 1.22% | 0.00101 | 1.32 |

[a] Rate differences were converted to annual probabilities using standard conversion formula; Probability = $1 - \exp(-\text{rate} \times \text{time})$.
Source: (Wilson, Jessica C. et al. 2017; Wilson, J. C. et al. 2017b)
GCA = giant cell arteritis; mg = milligram; RR = Relative risk

It is acknowledged that the estimated excess risk of adverse events and mortality attributed to steroid use based on this data may be confounded by the presence/absence of GCA disease, however no alternative comparative data were available and the extent of potential bias is unknown. To identify how sensitive the model is to the estimated adverse event rates, a sensitivity analysis is conducted that halves the excess adverse event rate and excess mortality.

## C.4.    TRANSFORMATION ISSUES

Version 3 of 'the Criteria' restricts use of Ig in CIDP patients according to the tools ONLS or MRS Sum Scores in adults, and MRS score and six minute walk in children. These outcome measures need to be transformed into utility estimates to estimate QALY for the cost-utility evaluation. The transformation issue addressed is:

### C.4.1.    UTILITY ESTIMATES TO ESTIMATE QUALITY-ADJUSTED LIFE YEARS

**What are the utility/disutility values associated with various treatments and health states for patients with CIDP?**

Patients with CIDP eligible for Ig treatment

McCrone et al measured HRQoL using EQ-5D at baseline (no treatment) and at six weeks in patients with CIDP who required treatment with IVIg or prednisolone (McCrone et al. 2003). The baseline HRQoL was 0.64 and 0.57 in groups treated with prednisolone or IVIg respectively. Whilst HRQoL was largely unchanged (0.64 to 0.63) for the prednisolone group, the effect of initiating treatment with intravenous Ig resulted in a non-statistically significant gain in QoL of 0.12 (0.57 to 0.69) (McCrone et al. 2003). Mahdi-Rogers et al studied the cost of illness and health related QoL in patients with chronic neuropathies (CIDP, multifocal motor neuropathy and paraproteinaemic demyelinating neuropathy) in Southeast England. The mean (SD) EQ-5D utility score reported for CIDP was 0.62 (0.23). The combined utility score in all three diseases was not significantly related to age, disease duration or sex (Mahdi-Rogers, McCrone & Hughes 2014). HRQoL values reported in studies by McCrone et al and

Mahdi-Rogers et al are similar for CIDP patients (0.57–0.64). It is assumed that CIDP patient entering in the model will have base line utility of 0.62. Sensitivity analysis will assess the baseline CIDP utility in the range 0.57–0.64.

Utility gain with Ig

Treatment response in CIDP is measured through reduction in disability scores which will indicate gain in health utility values. A meta-analysis of four-small short-term placebo-controlled clinical trials, found a significant reduction in disability score and improvement in strength in favour of IVIg (Gaebel et al. 2010). McCrone et al found that treatment with intravenous Ig over six weeks resulted in a non-statistically significant gain in QoL of 0.12 (0.57 to 0.69) (McCrone et al. 2003). The base-case analysis assumes that treatment with Ig results in utility gain of 0.12 in patients starting induction therapy. The utility gain with Ig beyond the study period of six weeks is uncertain, but the model assumes that this utility gain is maintained throughout the treatment. Sensitivity analysis will assess the impact of varying utility gain by ±50%.

Corticosteroids

Although steroids may be an efficacious first-line treatment for CIDP, they are associated with significant adverse events. The chronic use of steroids is associated with a number of potentially serious side effects including diabetes, increased risk of fracture, osteoporosis, hypertension, metabolic syndrome, weight gain, cataracts, glaucoma, gastrointestinal bleeds/ulcers, increased susceptibility to infection and psychological disorders. Sullivan et al assessed the HRQoL of patients taking systemic corticosteroids using data from the Medical Expenditure Panel Survey (MEPS) and EQ-5D tariffs for the USA and the UK (Sullivan et al. 2017). They performed regression analysis in order to control for confounding by indication (underlying medical conditions), other demographic characteristics and number of steroid prescriptions used. After controlling for sociodemographic characteristics, chronic comorbidity, the conditions for which steroids are used, and surrogate measures of severity and burden of disease, EQ-5D UK score for individuals using ≥4 prescriptions of steroids was –0.047 (–0.036 to –0.054). This disutility score is applied to patients who are on steroid treatment in the model. Observational data indicate that adverse physiological effects of steroid use last for a year (Wilson, J. C. et al. 2017b); therefore this disutility is applied to HRQoL values in the model for one year after stopping the steroid treatment. Sensitivity analysis assumes disutility associated with steroid use is only applicable while patients are on treatment and there is no treatment associated disutility after stopping the steroids.

Plasma exchange

Utility gain/loss associated with treatment with PE was not available in the literature. The base-case analysis assumes a utility gain of 0.12 similar to IVIg, based on an assumption of equivalent therapeutic effect. Sensitivity analysis will vary the utility gain from 0.0–0.18.

<u>Intravenous infusions</u>

Inconvenience associated with an uncomplicated intravenous infusion every few weeks was incorporated into the model. This was sourced from MSAC 1565 assessment report which used study by Weeks et al to estimate disutility (–0.0006) associated with intravenous infusion per day (Weeks, Tierney & Weinstein 1991; Wyndham et al. 2019). This disutility is applied for each infusion in the Ig, PE and IVMP treatment arms.

<u>Adverse events</u>

The most common AE with IVIg were headache, nausea, rash and hypertension (Table 25). These are considered to be short-term and transient. Therefore no additional disutility (beyond the disutility when having an IV infusion) is applied to the health states for the AE in Ig arm. There was one serious AE of aseptic meningitis (0.5% of patients) reported in one retrospective cohort analysis (Waheed et al. 2019) reporting data on AE for 221 patients with CIDP over a median follow-up of 21 weeks in year 2010. Study and adverse event details were described in Table 22 and Table 23 in section B.7. One cost-effectiveness study (Delgleize et al. 2016) of routine pneumococcal vaccination in the UK reported a short-term disutility of 0.023 for meningitis hospitalisation. This disutility will be applied in the sensitivity analysis for an adverse event with Ig.

Disutility associated with chronic steroid use was sourced from study by Sullivan et al as discussed above (Sullivan et al. 2017). This study cautioned that these estimates likely do not fully capture the longer term development of AEs associated with ongoing steroid use and their corresponding impact on HRQoL. This study suggested that long-term adverse effects associated with steroid use could be modelled by incorporating the disutility associated with the specific adverse effect from the catalogue of EQ-5D scores in an additive manner. A catalogue of EQ-5D index scores for a range of chronic conditions based on UK preferences was developed by Sullivan et al (Sullivan et al. 2011), including diabetes, osteoporosis and glaucoma. The study provided the marginal decrement in EQ-5D index scores for each condition after controlling for age, comorbidity, gender, race, ethnicity, income, and education. The marginal disutility for chronic adverse effects are sourced from this study for steroid treatment.

Abimanyi-Ochom investigated change in HRQoL in a cohort of Australian adults aged over 50 years with low to moderate impact fracture (hip, wrist, humerus, vertebral and ankle). The study concluded fractures reduce quality of life with the loss sustained at least over 12 months. The mean cumulative loss in QALYs for all fractures from pre-fracture to 12 months was 0.157, which represented an 18% loss in QALYs from baseline (Abimanyi-Ochom et al. 2015). A disutility of –0.157 is applied for patients experiencing fractures in the model. Disutility associated with severe infections (–0.410) was sourced from MSAC 1565 assessment report (Wyndham et al. 2019).

AEs of hypertension, fractures, osteoporosis, diabetes and glaucoma are categorised as moderate adverse events that result in treatment change. One retrospective analysis (van Lieverloo et al. 2018)

of corticosteroids use in 125 patients with CIDP reported moderate adverse events of hypertension, diabetes mellitus, glaucoma, depression, Cushingoid appearance, and gastro-intestinal complaints in ten (8%) patients. Additionally, serious AE occurred in two patients, one case of severe hypertension and one acute myocardial infarction. Key trial comparing IVIg with IVMP reported one severe AE of gastritis in a patient treated with IVMP. Disutility associated with gastritis (–0.0369) is sourced from the study by Sullivan et al (2011). Sensitivity analysis will include disutilities associated with AEs of severe hypertension (–0.0293) and acute myocardial infarction (–0.0577) sourced from the same study (Sullivan et al. 2011).

The rate of most common severe AEs for patients receiving PE were summarised in Table 18, Section B.7. A per procedure rate of 1.68% for severe adverse events was reported based on the WAA data base (Mörtzell Henriksson et al. 2016). The adverse events considered to have health impact are syncope, urticaria, arrhythmia, bronchospasm, oedema, anaphylaxis, chest pain, gastrointestinal bleeding and hypertension. The disutilities associated with these adverse events are sourced from Sullivan et al (2011) and are summarised in Table 34. Sullivan et al did not report disutility associated with anaphylaxis or severe allergies. Search of CEA registry for utility weights identified one cost-effectiveness study (Rognoni et al. 2019) of molecular profile patient selection for first-line treatment of recurrent/ metastatic head and neck cancer reporting disutility of 0.15 (for a month) associated with anaphylaxis or severe allergy. This disutility value is applied in the model for adverse events of anaphylaxis or severe allergy.

Remission and disease progression

It is assumed that patients in remission will have health similar to the general population and therefore age-specific utility scores summarised in Table 33 are used for the remission health state. It is assumed that the non-responders will stop treatment and have best supportive care. These patients are assumed to have gradual progression in their disease and thus have impact on their HRQoL due to increased disability. Ahmad et al quantified the impact of disability on health state utility values (HSUVs), and the physical and psychosocial health of people with multiple sclerosis (MS) using the Assessment of Quality of Life-8-Dimension (AQoL-8D) instrument (Ahmad et al. 2020). The estimates were compared to Australian general population norms and categorised by disability severity. The mean overall HSUV was estimated at 0.61 similar to that estimated for CIDP patients (Mahdi-Rogers, McCrone & Hughes 2014). HSUV decreased with increasing disability severity and was reported at 0.48 (95% CI: 0.46-0.50) for severe disability. In the absence of any estimate for HRQoL for patients with CIDP and severe disability, it is assumed that patients with CIDP who stop treatment as non-responders will have utility of –0.140 (estimated as 0.48 – 0.62 = –0.14).

General population

Clemens et al estimated Australian population norms for the EQ-5D-3L by age and gender based on a representative adult sample in Queensland, Australia (Clemens et al. 2014). The study also assessed

the differences in HRQoL by applying the Australian, UK and USA value sets to these data. Mean and significant differences for EQ-5D-3L index scores by age category–persons were similar across Australian and UK population norms and did not show statistical significance in the differences except for the age group 65–74 years (Table 33). However, this statistically significant difference was not observed in the index scores reported by age category–male or age category–female for Australia and UK HRQoL values. Age-specific utility scores for general Australian population are sourced from this study and are summarised in Table 33. Where utility values are not available in Australian context, UK values are considered applicable for the purpose of this assessment.

**Table 33    Mean and significant differences for EQ-5D-3L index scores for Australia and UK**

| Age group (years) | Australia Mean (95% CI) | UK Mean (95% CI) | Differences across value sets–p value (Australia to UK) |
|---|---|---|---|
| 18+ | 0.87 (0.86–0.87) | 0.86 (0.85–0.86) | **0.0010** |
| 18–24 | 0.91 (0.89–0.93) | 0.91 (0.89–0.93) | 0.873 |
| 25–34 | 0.91 (0.89–0.92) | 0.90 (0.88–0.92) | 0.433 |
| 35–44 | 0.89 (0.88–0.90) | 0.88 (0.86–0.89) | 0.279 |
| 45–54 | 0.85 (0.84–0.87) | 0.83 (0.82–0.85) | 0.078 |
| 55–64 | 0.85 (0.84–0.86) | 0.84 (0.82–0.85) | 0.055 |
| 65–74 | 0.82 (0.81–0.83) | 0.80 (0.78–0.81) | **0.029** |
| 75+ | 0.80 (0.78–0.81) | 0.78 (0.76–0.80) | 0.104 |

Source: (Clemens et al. 2014)
Note: values in bold represent statistical significance.
CI = confidence interval; EQ-5D = EuroQol- 5 dimensions; UK = United Kingdom

Table 34 summarises utility scores used in the economic evaluation along with their sources. These are applied as cyclical decrements in the model. The base-case utility for a patient entering in the model is assumed to be 0.62 which is a HRQoL value estimated for a patient with CIDP. All other utility or disutility values are applied as increments or decrements to this base-value in the model.

**Table 34    Utility scores[a] used in the economic model**

| Description | Utility adjustment | Sensitivity analysis | | Source |
|---|---|---|---|---|
| | | Lower value | Upper value | |
| Patient with CIDP | Baseline utility: 0.6200 | 0.5700 | 0.6400 | (Mahdi-Rogers, McCrone & Hughes 2014; McCrone et al. 2003) |
| Disease progression | –0.1400 | - | - | (Ahmad et al. 2020) |
| Effective treatment with Ig | +0.12 | 0.06 | 0.18 | (McCrone et al. 2003) |
| Effective treatment with steroids | –0.047 | 0.00 (disutility only associated with AEs) | –0.054 | (Sullivan et al. 2017) |
| Effective treatment with PE | +0.12 | 0.00 | 0.18 | Assumption |
| Intravenous infusion [b] | –0.0006 | - | - | (Weeks, Tierney & Weinstein 1991; Wyndham et al. 2019) |
| Diabetes mellitus | –0.0621 | –0.0697 | –0.0546 | (Sullivan et al. 2011) |

| Description | Utility adjustment | Sensitivity analysis | | Source |
|---|---|---|---|---|
| | | Lower value | Upper value | |
| Osteoporosis | –0.0418 | –0.0542 | –0.0294 | |
| Glaucoma | –0.0278 | –0.0401 | –0.0156 | |
| Arrhythmia | –0.0246 | –0.0351 | –0.0142 | |
| Chest pain | –0.0389 | –0.0511 | –0.0267 | |
| Haemorrhage | –0.0451 | –0.0996 | 0.0094 | |
| Hypertension | –0.0375 | –0.0456 | –0.0293 | |
| Syncope | –0.0039 | –0.0255 | 0.0178 | |
| Gastritis | –0.0369 | –0.0677 | –0.0061 | |
| Bronchospasm [c] | –0.0336 | –0.0451 | –0.0220 | |
| Anaphylaxis or severe allergy | –0.1500 | - | - | (Rognoni et al. 2019) |
| Aseptic meningitis | –0.023 | - | - | (Delgleize et al. 2016) |
| Severe infections | –0.4100 | - | - | (Wyndham et al. 2019) |
| Fracture | –0.1570 | - | - | (Abimanyi-Ochom et al. 2015) |
| Patient in remission | Revert to age-specific utility | - | - | Table 23 |

[a] Annual utility values are reported here unless specified. These are all adjusted for the cycle length in the model. Base-case utility for a patient entering in the model is assumed to be 0.62 which is health related quality of life value estimated for a patient with CIDP. All other utility or disutility values are applied to this base-value in the model.

[b] Value reported for marginal disutility per day of infusion.

[c] Disutility associated with bronchospasm was not found in the literature. Bronchospasm is similar to an asthmatic attack. Therefore disutility associated with asthmatic attack was used in the assessment.

AE = adverse events; CIDP = chronic inflammatory demyelinating polyneuropathy; Ig = immunoglobulin; PE = Plasma exchange

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

A summary of the results and implications is provided in Table 35.

**Table 35    Summary of results of pre-modelling studies and their uses in the economic evaluation**

| Section | Pre-modelling study | Results used in Section D | Cross-reference | Results used in sensitivity analyses | Cross-reference |
|---|---|---|---|---|---|
| **C.2.** | **Applicability issues** | | | | |
| C.2.1 | Does the patient profile in the clinical evidence match the demographic characteristics of patients with CIDP in Australia? | Patient weight: 78 kgs<br>Patient age: 65 years | D.4 | - | - |
| C.2.2 | Is the Ig dosing and frequency of administration schedule in the clinical trials consistent with the current recommendation in Australia (version 3 of 'the criteria')? | Treatment doses and frequency vary across trial and clinical practice. The base case uses doses based on the Australian BloodStar Criteria V3 and NBA data rather than clinical trial doses. Table 28 summarises the values used in the analyses. | D.4 | Alternative estimates of IVIg dosing (higher and lower per infusion doses and higher and lower infusion frequency) are tested in sensitivity analyses.. | D.6 |
| C.2.3 | Is the duration of Ig treatment in the clinical evidence consistent with use in the current Australian population? | There is little information on duration of treatment, therefore the modelled duration of treatment is driven by response, relapse and remission data synthesised from RCTs, observational studies and BloodStar data. | C.3.1 | - | - |
| C.2.4 | What is the optimum period of disease stability that would trigger a decision to reduce the maintenance dose, in order to inform the Criteria? | The base case dosing is based on Range of analysis presented using dose and frequency suggested in the Criteria V3. | D.5 | An Ig dose reduction by 20% per course for 6 cycles for Ig maintenance treatment is presented. | D.6 |
| **C.3** | **Extrapolation issues** | | | | |
| C.3.1 | What is the appropriate time horizon for the economic analysis of maintenance IVIg? | Follow-up in key trials and 10 year | D.3 | Results across variable time horizons | D.6 |
| C.3.2 | What is the duration of the treatment effect in patients with CIDP and was the duration of effect expected in the Australian setting captured in the available clinical evidence? | On and off-treatment transition probabilities estimated from RCTs, observational studies and BloodStar data (Table 31) and are extrapolated over the modelled time horizon. | D.4 | A range of alternative transition values (summarised in Table 31) are tested. | D.6 |
| C.3.3 | What safety implications and adverse events are associated with the intervention and comparator drugs treatments when used for longer durations? | Adverse events associated with long term corticosteroids and ongoing PE are included in the base case economic models. A summary is presented in Table 32 | D.4 | Alternative estimates of long-term adverse event rates are tested. | D.6 |

| C.4 | Transformation issues | | | | |
|---|---|---|---|---|---|
| C.4.1 | What are the utility/disutility values associated with various treatments and health states for patients with CIDP? | External literature identified estimates of utility and utility decrements associated with modelled health states and adverse events. A summary is presented in Table 33 and Table 34 | D.4 | Alternative health state utility values and decrements are tested. Summary presented in Table 33 and Table 34 | D.6 |

CIDP = chronic inflammatory demyelinating polyneuropathy; IVIg = intravenous immunoglobulin; PE = plasma exchange; RCT = randomised controlled trials

# SECTION D          ECONOMIC EVALUATION

## D.1.      OVERVIEW

A number of the revisions that the MSAC requested for the economic model in the original DCAR 1564 required significant change to the model structure and the approaches used to apply inputs. The changes essentially required the development of three distinct models; one for each of the three different comparators – Ig versus steroids; Ig versus therapeutic PE; and second line use of Ig in a steroid-resistant population versus placebo. The first two models are based on the non-inferior efficacy of Ig vs the comparators, but with further investigation of the comparative safety of each of the two therapies for each model. The third model assumes superior effectiveness and likely inferior or non-inferior safety for Ig use.

All models are structured to allow discontinuation of treatment due to remission, in addition to treatment failure. A stepped approach has been used to demonstrate the impacts of using the dose and time on treatment likely used in Australian clinical practice (based on BloodStar data and clinical opinion (Department of Health 2021c)), and important structural assumptions. Sensitivity analyses have been conducted around the uncertain parameters.

Ig versus steroids:

- Evidence around the safety of steroid use over the modelled lifetime of the disease and the appropriate utility increments/decrements have been carefully incorporated.
- The claim in the base case is non-inferiority based on Nobile-Orazio et al (2012), but a sensitivity analysis has been included to model superior efficacy of Ig as per the Reference Group clinical opinion.

Ig versus PE:

- Insufficient evidence was found in the original DCAR to assess the comparative safety of PE. The results of an expanded search on safety of PE (Section B.7) informed this model.
- The clinical effectiveness claim is non-inferiority based on Dyck (1994).

Ig versus placebo in steroid-resistant populations

- The clinical effectiveness claim is superiority over placebo based on trial evidence in steroid-resistant trial populations.

## D.2.      POPULATIONS AND SETTINGS

The use of IVIg and SCIg is funded in Australia by the NBA for patients with CIDP who qualify according to the Version 3 of '*the Criteria for the clinical use of immunoglobulin in Australia*'.

IVIg 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.

Clinical advisers on the Ig Review Reference Group[7] indicated that IVIg is infused predominantly in the public outpatient setting as a day procedure. 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; and 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 (approximately 5% as advised in PICO for DCAR 1564) 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.

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

A summary of the key characteristics of the economic evaluation is given in Table 36.

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[7] Document 1.0– 1564-Referral supplied by the Department in October 2020.

**Table 36      Summary of the economic evaluation**

| Perspective | Australian healthcare system |
|---|---|
| Comparator(s) | i)      Steroids<br>ii)     Therapeutic plasma exchange<br>iii)    Placebo (in steroids resistant subgroup) |
| Type of economic evaluation | Stepped cost-utility analysis |
| Sources of evidence | Systematic review, expert opinion (Ig review reference group) and data provided by NBA and Department of Health |
| Time horizon | 10 years |
| Outcomes | Cost per QALYs gained |
| Methods used to generate results | Decision analytic Markov model |
| Health states | A.   Active disease: treatment induction or a relapse after more than 6 months off treatment<br>B.   Active but stable disease: maintenance phase (on treatment more than 4 months)<br>C.   No active disease: in remission (off treatment)<br>D.   Treatment resistant/intolerant disease: best supportive care<br>E.   Dead |
| Cycle length | Four weeks |
| Discount rate | 5% |
| Software packages used | Microsoft Excel and TreeAge Pro |

AE = adverse event; Ig = immunoglobulin; NBA = National Blood Authority; QALY = quality-adjusted life year.

LITERATURE REVIEW

A search of the literature was conducted to identify cost-effectiveness analyses of Ig in CIDP published in 2019-20 (extending the search conducted in the previous DCAR 1564 report). Two cost studies were identified (Guptill et al. 2019; Querol et al. 2020). One was a retrospective cohort study that evaluated the treatment patterns and CIDP-related healthcare costs over a two-year follow-up period for patients with newly diagnosed CIDP who had commercial insurance, using claims data from the IMS LifeLink PharMetrics Plus Claims database between 2009 and 2014 (Guptill et al. 2019). Querol et al provided a systematic literature review of the burden of illness of CIDP (Querol et al. 2020). None of the studies identified in the previous or current extended search were applicable in the Australian context or addressed the research questions pertaining to the current assessment.

STRUCTURE OF THE ECONOMIC EVALUATION

As the studies identified in the search of the economic literature could not answer the question of the cost-effectiveness of Ig relative to steroids, PE and placebo (second line treatment in steroid- resistant subgroup) in the contemporary Australian setting, a Markov model was developed de novo to evaluate the cost effectiveness of intravenous Ig therapy compared to the alternative treatments. The Markov model structure with allowable transitions between health states is depicted in Figure 12. The five health states modelled are described in Table 37.
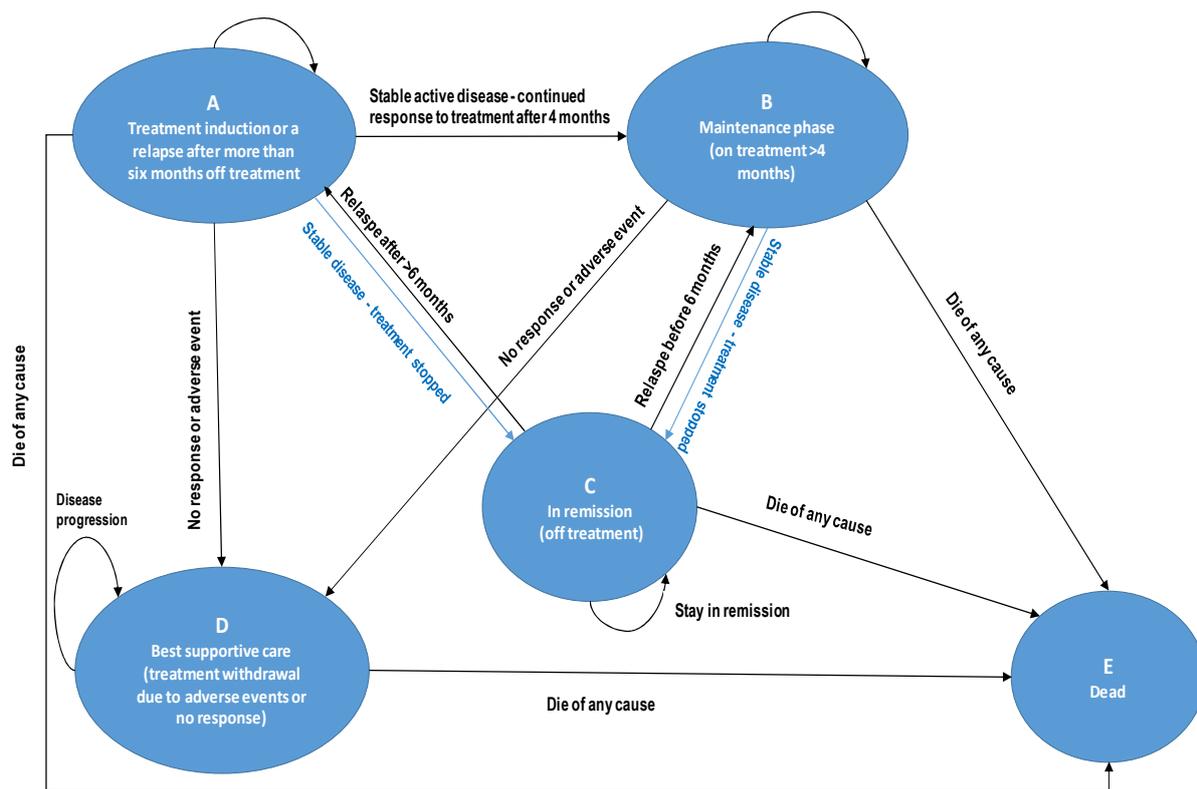
**Figure 12    State transition diagram for the Markov model**

Each oval (A to E) represents a chance node and the arrows represent the valid transitions between health states. All patients initially enter the Markov model at node "Treatment induction or relapse after six months off treatment".

**Table 37    Description of health states included in the Markov model**

|   | Health state | Description |
|---|---|---|
| A | Active disease: treatment induction or a relapse after more than 6 months off treatment | All patients enter model in this health state. This health state represents patients on induction treatment either being treatment naïve or experiencing a relapse after more than six months in remission.<br><br>Patients in this health state may stay on the induction treatment up to 4 months, continue to maintenance treatment after 4 months review, may have remission, withdraw from the treatment due to adverse events or no-response, or die. |
| B | Active but stable disease: maintenance phase of treatment (more than 4 months) (abbreviated as 'Maintenance phase' in the report) | This health state represents patients who are on maintenance treatment after showing response in the induction phase. Patients may stay in this health state, may have remission, withdraw from the treatment due to adverse event/no response, or die.<br><br>*This state will allow modelling weaning off trial for treatment (specifically Ig) by varying treatment dose or frequency in sensitivity analysis.* |
| C | No active disease: in remission (off-treatment) | This health state represents patients who have stopped treatment being in remission or due to stable disease. Patients may stay in this health state or reinitiate treatment (via State A if in relapse for more than 6 months or via State B if in relapse for less than 6 months), withdraw from the treatment due to adverse event/no response, or die. |
| D | Treatment resistant/intolerant disease: best supportive care | Patients in this health state include those who have discontinued treatment due to an adverse event or patients who have not responded to Ig.<br><br>It is assumed that patients who withdraw from the treatment due to non-response or adverse events will continue in this state and will accumulate disutility and costs associated with the long-term treatment side effects (such as with steroids) or disease |

| | Health state | Description |
|---|---|---|
| | | progression, or may die. Treatment switching (to a new treatment) or treatment cross-over is not allowed in the model. |
| E | Dead | Absorbing state (age-specific mortality or excess mortality associated with disease or treatment related adverse events) |

Abbreviation: Ig = immunoglobulin

To ease readability, the health state names for the model as described in full in Table 37 are abbreviated in the report here onwards. State A is referred to as 'Induction phase'; State B is referred to as 'Maintenance phase'; State C as 'In remission' and State D as 'BSC'.

As IVIg is mostly administered three to six weekly, a four weekly cycle length was chosen with a time horizon of 10 years (see section C.3). Half-cycle corrections are applied to all transitions in the model. Costs and outcomes are discounted at the standard discount rate of 5%.

The base-case will be generated using a modelled stepped evaluation with new step added for each new assumption added into the model, such as starting with a trial-based economic evaluation, presenting a modelled economic evaluation over a 10 year time horizon, changing resource use to Australian settings, adding utilities, assumptions regarding the side-effects, treatment switching etc. The model will include the costs and associated disutility of the serious adverse events that were identified in the review of extended safety and harm in Section B.7. Scenario analyses assuming the claim of superior safety and effectiveness of IVIg compared with steroids and plasma exchange will be performed. Due to the limited and poor quality evidence available for both intervention and comparators in CIDP, number of univariate sensitivity analyses will be performed and presented in Section D.6.

**Assumptions**

- Treatment effects are assumed to be constant throughout the model.

- Patients are 100% compliant to the treatment. It is assumed that non-compliance is captured in the estimated non-response, relapse and remission rates from the literature.

- Intra-patient variability is not considered in the model. Range of analysis will be presented to capture the effect of patient variability.

- Monitoring costs included in the cost analysis vary depending on treatments. While monitoring for liver function, renal function and blood disorders are included for all, dexascan, vitamin D testing and diabetes tests are only associated with steroids use.

- Transient (mild) AEs are not included in the model as these are considered to have no or very low cost or health consequences.

- Moderate AEs associated with chronic steroids use (diabetes, glaucoma, fractures, osteoporosis and serious infections) are assumed to have a health impact for one year after stopping the treatment. It is assumed that patients with these AEs will revert back to their original health one year after ceasing steroids therapy.

- No clinical evidence was identified regarding long-term treatment effect of PE. Utility gain with PE treatment is considered similar to IVIg and the transition probabilities for relapse are used from Ig studies.

## D.4.    INPUTS TO THE ECONOMIC EVALUATION

### PATIENT DEMOGRAPHIC INPUTS

Inputs regarding the patient population are show in Table 38.

**Table 38      Patient population inputs**

| Description | Input value | Source |
|---|---|---|
| Average patient weight (base case) | 78 kg | BloodStar data (Department of Health 2021c) |
| Average age (years) | 65 | BloodStar data (Department of Health 2021c) |
| Proportion of males | 58.8% | BloodStar data (Department of Health 2021c) |

Patients entering the model are assumed to be 65 years old and weigh 78 kg.

### Mortality

Two studies (Hafsteinsdottir & Olafsson 2016; Ryan & Ryan 2018) investigating survival in patients with CIDP have reported that the standardised mortality ratio for CIDP patients do not vary from mortality rate in general population (Querol et al. 2020). Therefore, the age-specific mortality rates of the general Australian population sourced from the Australian Life Tables (ABS 2020b) are applied in the model.

Incidence rate ratio (IRR) for mortality of 1.2 estimated from the study by Wilson et al (Wilson, Jessica C. et al. 2017) is applied to the background age-specific mortality risk to estimate the mortality risk associated with steroid use (see section C.3). Sensitivity analysis assesses the IRR of 1.1.

### TRANSITION PROBABILITIES

Transition probabilities for each treatment arm are estimated from studies reporting short-term and long-term treatment outcomes for patients with CIDP (Table 31).

Table 39 presents a summary of transition probabilities used in the model. Section D.6 presents sensitivity analyses using upper and lower bound of the parameter values found in these studies.

**Table 39    Transition probabilities in the economic models**

| Transition Parameter | Description | Analysis | Value(s) used | Source |
|---|---|---|---|---|
| *Intravenous Ig arm* | | | | |
| 'Initial phase' to 'Maintenance phase' (A→B) | Patients who respond to and tolerate initial treatment continue treatment (move to maintenance) after the first clinical review. | Trial-based | NA | No maintenance phase in clinical trial, (Nobile-Orazio et al. 2012) |
| | | Modelled | 1.0 | Assumption, consistent with treatment algorithms and BloodStar criteria. |
| 'Initial treatment' to 'In remission (off-treatment) (A→C) | Patients who respond to treatment, trial a cessation of therapy due to lack of disease activity/clinical need. | Trial-based | 1.0 | (Nobile-Orazio et al. 2012); all patients who responded to treatment were off treatment (in remission) at 24 weeks. |
| | | Modelled | 0.0527 | BloodStar data post second review, remission data – see Table 31 |
| | | Sensitivity Analysis | 0.0057, 0.0612 | Upper and lower remission rate estimates in Table 31; Kuitward (2015), Hughes (2008) |
| 'Initial treatment' to 'BSC' (A→D) | Patients who discontinue after initial use of therapy, due to either adverse events or lack of response. | Trial-based | 0.022 | (Nobile-Orazio et al. 2012); 12.5% of the patients withdrew from Ig treatment over first 24 weeks of the trial |
| | | Modelled | 0.0311 | Assumption of 10% non-response and 5% AE over 20 weeks (before first review) (0.0209 + 0.0102) (Department of Health 2021a) |
| | | Sensitivity Analysis | 0.0872 | Assuming all 33% patients who discontinued treatment after first review in the BloodStar data are non-responders + adverse event rate (0.0770 + 0.0102) |
| 'Maintenance phase' to 'In remission (off-treatment) (B→C) | Patients who respond to treatment then cease therapy due to lack of disease activity/clinical need. | Trial-based | NA | No maintenance phase in clinical trial, (Nobile-Orazio et al. 2012) |
| | | Modelled | 0.0527 | BloodStar data post second review, remission data – see Table 31 |
| | | Sensitivity Analysis | 0.0057, 0.0612 | Upper and lower estimates from Table 31; Rajabally (2019), Hughes (2008) |
| 'Maintenance phase' to 'BSC' (B→D) | Patients who are on treatment but stop therapy and move to BSC, due to adverse events (primarily) or loss of effect. | Trial-based | NA | No maintenance phase in clinical trial, (Nobile-Orazio et al. 2012) |
| | | Modelled | 0.0102 | Based on an estimated rate of adverse events resulting in discontinuation rate of 5% per twenty weeks (Department of Health 2021a) |
| | | Sensitivity Analysis | 0.0003 | Serious adverse event rate as reported in (Waheed et al. 2019) |
| 'In remission' to 'Initial / maintenance | Patients who have previously been successfully treated and stopped therapy who then experience disease relapse and need to re- | Trial-based | 0.0768 (short-term) - 0.0419 (long-term) | Relapse rates from Nobile-Orazio (2012) and Nobile-Orazio (2015), Table 31 |

| Transition Parameter | Description | Analysis | Value(s) used | Source |
|---|---|---|---|---|
| treatment' due to relapse (C →A or B) | start treatment. The allocation to state A or B is time-dependent; where remission is <6 months patients restart treatment in B, where remission is >6 months patients restart in A. | Modelled | 0.0380 | BloodStar data post second review, relapse data – see Table 31 |
| | | Sensitivity Analysis | 0.015 – 0.0419 | BloodStar data post first review, relapse data, and Nobile-Orazio (2015), see Table 31 |
| Death from all health states (A/B/C/D→E) | All patients are at risk of all-cause mortality (background mortality) at all times in the model. | Trial-based | NA | Not identified in clinical trial, (Nobile-Orazio et al. 2012) and Nobile-Orazio (2015) |
| | | Modelled | ASM | Australian Life Tables (ABS 2020b) |
| *Corticosteroid arm* | | | | |
| 'Initial treatment' to 'Maintenance phase' (A→B) | Patients who respond to and tolerate initial treatment who continue treatment after the first clinical review. | Trial-based | NA | No maintenance phase in clinical trial, (Nobile-Orazio et al. 2012) |
| | | Modelled | 1.0 | Structural assumption: patients with a response to initial therapy continue to maintenance therapy after 4 months. |
| 'Initial treatment' to 'In remission (off-treatment) (A→C) | Patients who respond to treatment then cease therapy due to lack of disease activity/clinical need. | Trial-based | 1.0 | (Nobile-Orazio et al. 2012); all patients in remission at 24 weeks. |
| | | Modelled | 0.0385 | Remission rate in Van Schaik (2010), see Table 31. |
| | | Sensitivity Analysis | ±50% | Arbitrary estimate of plausible range. |
| 'Initial treatment' to 'BSC' (A→D) | Patients who discontinue after initial use of therapy, due to either adverse events or lack of response. | Trial-based | 0.1103 | (Nobile-Orazio et al. 2012); 52.38% of the patients withdrew from steroids treatment either due to intolerance (4.76%) or non-response (47.62%) over first 24 weeks of the trial (sum of cyclic probabilities: 0.0081 and 0.1022 for AEs and non-efficacy) |
| | | Modelled | 0.1082 | (Nobile-Orazio et al. 2012); 47.64% non-responders over 24 weeks (0.1022) Waheed et al (2019) reported severe adverse events in 1.6% patients over 21 weeks (0.00307 per cycle probability for AE) AE associated with chronic use (cumulative higher doses) of steroids (0.0030), Table 32 : (Wilson, Jessica C. et al. 2017; Wilson, J. C. et al. 2017b) Estimated transition probability: 0.1022 + 0.00307 + 0.0030 |
| | | Sensitivity Analysis | 0.0497 | Assuming 81% response rate (upper limit of response rate reported in the literature, see Section C.3.1) over 20 weeks (0.0436) + AE (0.0031) + dose based AE (0.0030), Table 32 : (Wilson, Jessica C. et al. 2017; Wilson, J. C. et al. 2017b) |

| Transition Parameter | Description | Analysis | Value(s) used | Source |
|---|---|---|---|---|
| 'Maintenance phase' to 'In remission (off-treatment) (B→C) | Patients who respond to treatment then cease therapy due to lack of disease activity/clinical need. | Trial-based | All | (Nobile-Orazio et al. 2012); all patients who responded to treatment were off treatment (in remission) at 24 weeks. |
| | | Modelled | 0.0385 | Remission rate in Van Schaik (2010), see Table 31 |
| | | Sensitivity Analysis | ±50% | Arbitrary estimate of plausible range. |
| 'Maintenance phase' to 'BSC' (B→D) | Patients who are on treatment but stop therapy and move to BSC, due to adverse events (primarily) or loss of effect. | Trial-based | - | No maintenance phase in clinical trial, (Nobile-Orazio et al. 2012) |
| | | Modelled | 0.0071 | Sum of probabilities for experiencing treatment associated adverse event (0.00307) and adverse events due to chronic use of steroids (0.00407) (based on cumulative doses of steroids); Table 32 : (Wilson, Jessica C. et al. 2017; Wilson, J. C. et al. 2017b) |
| | | Sensitivity Analysis | 0.0031 | No excess risk of AE based on higher cumulative doses of steroids. This adjustment will be made to transition A→D as well. |
| 'In remission' to 'Initial / maintenance treatment' due to relapse (C →A or B) | Patients who have previously been successfully treated and stopped therapy, who then experience disease relapse and need to re-start treatment. The allocation to state A or B is time-dependent; where remission is <6 months patients restart treatment in B, where remission is >6 months patients restart in A. | Trial-based | 0.000 (short-term) – 0.0310 (long-term) | (Nobile-Orazio et al. 2012) and Nobile-Orazio (2015); Table 31 |
| | | Modelled | 0.0310 | Nobile-Orazio (2015); Table 31 |
| | | Sensitivity Analysis | 0.0310 – 0.0493 | Upper and lower estimates of relapse rates from Table 31; Nobile-Orazio (2015), Van Lieverloo (2018). |
| Death from all health states (A/B/C/D→E) | All patients are at risk of background mortality at all times, with an increased risk associated with taking corticosteroids in the base case analysis. | Trial-based | NA | Not reported |
| | | Modelled | ASM × 1.2 (for patients taking steroids) | Australian Life Tables (ABS 2020b) Excess risk of death associated with steroids (Wilson, Jessica C. et al. 2017) |
| | | Sensitivity Analysis | ASM, no excess death | Test of the effect of the applied excess death rate |
| *Plasma Exchange arm (no trial based data inputs)* | | | | |
| | | Modelled | 1.0 | Structural assumption: all responders continuing treatment move to maintenance health state after 4 months. |

| Transition Parameter | Description | Analysis | Value(s) used | Source |
|---|---|---|---|---|
| 'Initial treatment' to 'Maintenance phase' (A → B) | Patients who respond to and tolerate initial treatment who continue treatment after the first clinical review. | Sensitivity Analysis | - | |
| 'Initial treatment' to 'In remission (off-treatment) (A → C) | Patients who respond to treatment then cease therapy due to lack of disease activity/clinical need. | Modelled | 0.0209 | Assumed equivalence with Ig response and remission rates, see Table 31 |
| | | Sensitivity Analysis | 0.0057 – 0.0612 | Assumed equivalence with Ig response and remission rates, see Table 31 - upper and lower remission rates identified in Ig |
| 'Initial treatment' to 'BSC' (A → D) | Patients who discontinue after initial use of therapy, due to either adverse events or lack of response. | Modelled | 0.0377 | Assumption of 10% non-response over 20 weeks as in Ig arm and 1.68% AE per PE procedure sourced from Mörtzell Henriksson (2016) |
| | | Sensitivity Analysis | ±50% | Assumed plausible range |
| 'Maintenance phase' to 'In remission (off-treatment) (B → C) | Patients who respond to treatment then cease therapy due to lack of disease activity/clinical need. | Modelled | 0.0527 | Assumed equivalence with Ig response and remission rate |
| | | Sensitivity Analysis | 0.0057 – 0.0612 | Assumed equivalence with Ig response and remission rates, see Table 31 - upper and lower remission rates identified in Ig. |
| 'Maintenance phase' to 'BSC' (B → D) | Patients who are on treatment but stop therapy and move to BSC, due to adverse events (primarily) or loss of effect. | Modelled | 0.0168 | Mörtzell Henriksson (2016), 1.68% severe AE reported per PE procedure |
| | | Sensitivity Analysis | 0.001 | Serious AE rate in PE, reported in Table 25 |
| 'In remission' to 'Initial / maintenance treatment' due to relapse (C → A or B) | Patients who have previously been successfully treated and stopped therapy, who then experience disease relapse and need to re-start treatment. The allocation to state A or B is time-dependent; where remission is <6 months patients restart treatment in B, where remission is >6 months patients restart in A. | Modelled | 0.0380 | Assumed equivalence with Ig relapse rates. |
| | | Sensitivity Analysis | 0.015 – 0.0419 | Assumed equivalence with Ig relapse rates: BloodStar data post first review, relapse data, and Nobile-Orazio, see Table 31. |
| Death from all health states (A/B/C/D →E) | All patients are at risk of all-cause (background) mortality at all times in the model. | Modelled | ASM | Australian Life Tables (ABS 2020b) |

ABS = Australian Bureau of Statistics; AE = adverse event; ASM = age-specific mortality; BSC = best supportive care; Ig = immunoglobulin; MSAC = Medical Services Advisory Committee; NA = not applicable; NBA = National Blood Authority; SA = sensitivity analysis

Note: the modelled health state names are abbreviated in the table. State A 'Active disease: treatment induction or a relapse after more than 6 months off treatment' is referred as 'Induction phase'; State B 'Active but stable disease: maintenance phase (on treatment more than 4 months)' as 'Maintenance phase'; State C 'No active disease: in remission (off treatment)' as 'In remission' and State D 'Treatment resistant/intolerant: best supportive care' as 'BSC'.

**CLINICAL MANAGEMENT INPUTS**

Inputs (including assumptions) relating to the clinical management of CIDP, including the doses and administration patterns of therapies were described in section C.2.2. The dosing regimen and amount of drugs to be infused for initial and maintenance CIDP treatment are summarised in Table 28.

**ADVERSE EVENT AND CLINICAL OUTCOME INPUTS**

Summary of differences in safety consequences associated with IVIg, corticosteroids and PE were summarised in Table 25 in Section B.7. The modelling studies associated with translating these inputs for economic evaluation were described in section C.3.3 and C.4.1.

**RESOURCE USE AND COSTS**

Resource use associated with the treatment of patients with CIDP 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 report and the Australian Refined Diagnosis Related Groups (AR-DRG) for hospitalisations (IHPA 2021). All costs were measured and valued in 2021 Australian dollars. 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 below for each treatment.

**Ig**

The cost per gram of Ig used in the base case analysis is $60.41. This cost was provided by the Applicant to inform the economic and financial analyses and had been estimated retrospectively based on the reported total domestic product cost in 2017/18 ($195 million) minus domestic SCIg product costs ($4 million) in that same year, divided by the number of IVIg domestic grams issued (3,161,673) as published in the National Blood Authority (NBA) report on the Issues and Use of Ig in 2017/18 (NBA 2018) (see also Table 80, **Appendix G**). Additional analyses will be presented assuming:

- The highest cost per gram of Ig (i.e. domestic IVIg, including the cost of plasma fractionation), $140.18

- The lowest cost per gram of Ig (i.e. imported IVIg), $44.94

- The weighted average cost per gram of Ig across all indications, $94.51.

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. While there are slight variations between the prices per gram used in the model to that published on the NBA website (e.g. domestic IVIg has a current published price per gram of $58.20 as of 1 July 2020), as all costs (including that of plasma fractionation) could be sourced from the same year, for consistency the

prices retrospectively estimated from the NBA report are used. A sensitivity analysis will be presented using the current published price of domestic IVIg.

Resources and costs associated with IVIg administration such as infusion equipment, administrative and clinician time (e.g. resources associated with requesting, and authorising, access to Ig), nursing time (for initiation and monitoring) are implicitly captured in the hospitalisation or outpatient service episode costs, relevant to the setting under which IVIg is supplied.

The frequency with which a patient must be reviewed whilst receiving IVIg is specified in Version 3 of 'the Criteria' (NBA 2018). Patients receiving IVIg as first-line treatment for CIDP or following a CIDP relapse within six months of commencing a trial off Ig therapy, must be reviewed by a neurologist after four months of Ig therapy to determine patient response. Those who have responded to IVIg must be reviewed by a neurologist or general physician every 12 months. Specialist review may happen more frequently then suggested in the Criteria. Clinical expert advice (Department of Health 2021a) was that for a treatment-naïve patient clinical reviews may be performed as frequently as every three months and thereafter reduced to once – twice per year in order to assess the optimum dose and disease activity.

It is assumed that a patient on IVIg treatment for CIDP treatment will have two GP visits, four specialist consultations and four pathology tests (two to assess liver and renal function, and two whole blood examinations) annually as a part of disease management and treatment effect monitoring. Cost of Ig treatment per cycle is estimated based on the induction/maintenance dose as (base-case 2g/kg infused over four days and 1g/kg over two days, Table 28) and average patient weight (78 kg, Table 38).

During long-term IVIg therapy, intravenous access can become difficult due to obliteration of the veins and may necessitate catheterisation of the external jugular vein in some patients (Markvardsen et al. 2013). The clinical expert advice was that approximately 10% (1% peripherally inserted central catheter (PICC) line and 9% port-a-cath) of the patients may have placement of vascular access devices in first four to six months. Whereas, nearly 20% (1% PICC line and 19% port-a-cath) of the patients may have placement of vascular access devices for more than six months on IVIg treatment (Department of Health 2021a). The detailed cost estimation for long-term vascular access requirements by delivery mode are provided in Table 81 and Table 82, **Appendix G**.

Resource use and costs associated with the IVIg treatment and disease monitoring included in the model are summarised in Table 40. Cost of Ig per cycle in the model is calculated based on the dose of Ig used per infusion, cost per gram of Ig, average patient weight and number of infusions needed, therefore the Ig treatment costs may vary across different cycles/analyses.

**Table 40    Resource use and costs associated with IVIg treatment and monitoring**

| Description | Value | Source |
|---|---|---|
| **Induction treatment** | | |
| Cost per gram of Ig | $60.41 | Provided by the applicant; varied from $44.94 – $140.18 per gram in the sensitivity analysis |
| Administration cost per episode, outpatient hospital costs and consumables | $693 | NWAU calculator 2020-21 (IHPA)[a]; non-admitted service 10.13 Minor medical procedures |
| **Monitoring costs** | | |
| General Practitioner visitations | $39 | Scheduled fee for MBS 23 (2 units annually) |
| Neurologist consultation [b] | $191.68 | Weighted scheduled fees for MBS items 110 and 132 (1 unit annually) |
| Neurologist consultation - follow up [c] | $83.41 | Weighted scheduled fees for MBS items 116 and 133 (3 units annually) |
| Pathology tests - liver and renal function | $17.70 | Scheduled fee for MBS 66512 (2 units annually) |
| Pathology tests - Blood examination | $16.95 | Scheduled fee for MBS 65070 (2 units annually) |
| Total monitoring costs per cycle | $45.29 | For a cycle length of 4 weeks |
| **Severe adverse event costs** | | |
| Acute aseptic meningitis | $4,796 | Weighted cost of AR-DRG B73A and B73B |
| **Vascular access for Ig use (per patient)** | | |
| First 4–6 months | $146.66 | Table 81 and Table 82 |
| More than 6 months | $294.16 | Table 81 and Table 82 |

Source: Online schedule for MBS available at <http://www9.health.gov.au/mbs/search.cfm>
[a] National weighted activity unit (NWAU) calculators, available at < https://www.ihpa.gov.au/what-we-do/pricing/national-weighted-activity-unit-nwau-calculators/nwau-calculators-2020-21> .
[b] Scheduled fees for MBS items 110 ($157.95) and 132 ($276.25) weighted based on the Medicare statistics for years 2018–20.
[c] Scheduled fees for MBS items 116 ($79.05) and 132 ($138.30) weighted based on the Medicare statistics for years 2018–20.
AR-DRG = Australian Refined Diagnosis Related Groups; Ig = immunoglobulin; IHPA = the Independent Hospital Pricing Authority; g = grams; kg = kilograms; MBS = Medicare Benefits Schedule; NBA = National Blood Authority; NWAU = national weighted activity unit

**Corticosteroids**

Table 26, section C.2 summarised steroid doses used in the key trial. Table 28 summarised steroid doses used in the Australian practice. It is assumed that a patient on steroids treatment will have two GP visits, four specialist consultations and four pathology tests (two to assess liver and renal function, and two whole blood examinations) annually as a part of disease management and treatment effect monitoring. Chronic use of steroids is associated with serious side effects such as diabetes, glaucoma and osteoporosis (Curtis et al. 2006; Huscher et al. 2009; Wilson, J. C. et al. 2017b). Patients on long term steroid treatment are usually prescribed prevention treatment such as vitamin D, calcium and alendronate to prevent osteoporosis and incidence of fractures. Regular tests for diabetes mellitus, glaucoma and bone densitometry are performed to detect early signs of these diseases.

Patient on steroids treatment are assumed to have– two GP visits, four specialist consultations and four pathology tests (two to assess liver and renal function, and two whole blood examinations), one test each for vitamin D deficiency and open angle glaucoma, three tests for the diagnosis of diabetes, 0.33 (once in three years) dual-energy X-ray absorptiometry (DEXA) test, in a year as a part of disease

management and treatment effect monitoring. In addition, these patients will have prophylactic treatment with alendronate, vitamin D and calcium supplements.

Table 41 summarises resource use and costs associated with the steroid treatment and disease monitoring used in the model.

**Table 41** **Resource use and cost associated with corticosteroids treatment and monitoring**

| Description | Cost per unit | Source | Units per year | Cost per cycle |
|---|---|---|---|---|
| **Treatment costs** | | | | |
| Intravenous methylprednisolone | $44.52 | PBS 5264C, 1gram vial | 4 per induction course | $178 |
| Administration cost per episode, outpatient hospital costs and consumables | $693 | NWAU calculator 2020-21 (IHPA)a; non-admitted service 10.13 Minor medical procedures | 4 per induction course | $2,772 |
| Total cost per induction treatment (base-case) | | | | $2,950 |
| Intravenous methylprednisolone | $44.52 | PBS 5264C, 1gram vial | 1 per maintenance course | $44.52 |
| Administration cost per episode, outpatient hospital costs and consumables | $693 | NWAU calculator 2020-21 (IHPA)a; non-admitted service 10.13 Minor medical procedures | 1 per maintenance course | $693 |
| Total cost per maintenance treatment | | | | $738 |
| **Monitoring costs** | | | | |
| GP visits | $39 | MBS 23 | 2 | $5.96 |
| Neurologist consultation b | $191.68 | Weighted scheduled fee for MBS items 110 and 132 (1 unit annually) | 1 | $14.74 |
| Neurologist consultation - follow up c | $83.41 | Weighted scheduled fee for MBS items 116 and 133 (3 units annually) | 3 | $19.25 |
| Pathology tests - liver and renal function | $17.70 | MBS 66512 | 2 | $2.72 |
| Pathology tests - Blood examination | $16.95 | MBS 65070 | 2 | $2.61 |
| Test for open angle glaucoma | $42.05 | MBS 11200 | 1 | $3.23 |
| Test for diabetes | $16.80 | MBS 66841 | 3 | $3.88 |
| Vitamin D | $30.05 | MBS 66833 | 1 | $2.31 |
| DEXA scan | $105.60 | MBS 12312 (once every three years) | 0.33 | $2.68 |
| Alendronate + cholecalciferol (and) calcium carbonate | $23.76 | PBS 9351E (28 days; 4 weeks) | 13 | $23.76 |
| Total monitoring costs per cycle | | | | $81.15 |

Source: Online schedule for MBS available at <http://www9.health.gov.au/mbs/search.cfm>; PBS fee accessed at <https://www.pbs.gov.au/pbs/home>

a National weighted activity unit (NWAU) calculators, available at < https://www.ihpa.gov.au/what-we-do/pricing/national-weighted-activity-unit-nwau-calculators/nwau-calculators-2020-21>

b Scheduled fee for MBS items 110 ($157.95) and 132 ($276.25) weighted based on the Medicare statistics for years 2018–20.

c Scheduled fee for MBS items 116 ($79.05) and 132 ($138.30) weighted based on the Medicare statistics for years 2018–20.

DEXA = dual-energy X-ray absorptiometry; IHPA = the Independent Hospital Pricing Authority; MBS = Medicare Benefits Schedule; NBA = National Blood Authority; NWAU = national weighted activity unit; PBS = Pharmaceutical Benefits Schedule

*Costs associated with steroid associated adverse event management*

Adverse events associated with chronic use of steroids were described in Section C.3.3. Costs associated with managing these events are described below. Cost of all of these events (diabetes, glaucoma, fractures, osteoporosis and severe infections) were weighted based on their relative frequency to estimate cost per adverse event of $5,182 (Table 42) in the model.

Diabetes: The Australian Diabetes, Obesity and Lifestyle study collected data on the use of health services and health related expenditure in 2004–05 (Lee et al. 2013). Age- and sex-adjusted direct healthcare costs, direct non-healthcare costs and government subsidies were estimated according to glucose tolerance status for 6,101 participants. Annual direct per person costs was $4,763 ($2,081 in 2005$ indexed to 2020$).

Glaucoma: One study (Dirani et al. 2011) reported the economic impact of primary open-angle glaucoma (POAG) in Australia. The medication costs associated with POAG for 65–74 year old person was estimated to be $1,271 in 2005$, that is $2,908 in 2020 Australian dollars (indexed to current year using Health Price Index for Australia (ABS 2020a)).

Fractures: Watts et al (2013) used a bottom-up costing approach to determine the total burden attributable to fractures based on service utilisation data reported to the AusICUROS study. Fractures included hip, wrist, vertebral and 'other'. The study predicted annual total cost of all fractures (direct and indirect costs) for years 2013–2022. The projected total direct cost of all fractures for year 2021 was $12,892.

Osteoporosis: Tatangelo et al determined the direct economic cost of osteoporosis, osteopenia, and fractures among Australians aged 50 years and older in 2017 (Tatangelo et al. 2019). The study reported that the direct health-care costs associated with the ongoing management of osteoporosis (excluding any fracture treatment) include the use of anti-osteoporosis medications (denosumab)[8] and vitamin D and calcium supplements, 2.5 medical visits per year, a general blood test for renal function and serum calcium twice a year, serum 25-hydroxyvitamin D test once every two years, dual-energy X-ray absorptiometry (DEXA) once every three years, and pharmaceuticals for bone health. These resources were costed according to their use to estimate the annual cost of $872.87 per person for the management of osteoporosis. Table 83, in Appendix G presents the derivation of this cost.

Severe infection: Cost associated with managing severe infection was estimated to be $8,378 from the AR-DRG data. Cost of AR-DRGs B72 (nervous system infection), T60 (septicaemia), I64

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[8] Feedback from clinical expert advice provided to the Department of Health to the second draft report on 24th March 2021 suggested use of denosumab for osteoporosis management.

(osteomyelitis) and E62 (respiratory infections) were weighted based on the number of separations to estimate cost for managing severe infection (Table 84, in **Appendix G**).

**Table 42    Cost associated with moderate AEs observed with chronic use of steroids**

| Cost of moderate AE | Annual cost | Relative weight* | Source |
|---|---|---|---|
| Diabetes | $4,763 | 0.106 | Lee (2013). |
| Osteoporosis | $872.87 | 0.345 | Tatangelo (2019), Table 83 |
| Fractures | $12,892 | 0.108 | Watts (2013) |
| Glaucoma | $2,908 | 0.131 | Dirani (2011) |
| Serious infection | $8,378 | 0.311 | AR-DRGs B72, T60, I64 and E62 |
| **Estimated cost per AE** | **$5,182** | | Sum-product of annual costs and relative weights |

*Relative weights estimated from incidence of events reported in Table 32.
AE = adverse event; AR-DRG = Australian Refined Diagnosis Related Groups

<u>Severe adverse events:</u> Costs of AR-DRGs F67A, F65A, F65B, G61A and G61B (IHPA 2021) were used for managing severe adverse events (severe hypertension, myocardial infarction and gastritis) reported in the literature.

**Plasma exchange**

PE is generally administered as a day therapy in the outpatients department. Five to 10 exchanges of 40–50 mL/kg plasma volume on alternate days are initiated within two to four weeks as induction therapy, followed by one to two sessions every three to four weeks as maintenance therapy (Gwathmey 2020). The dose and schedule applied in the economic model are described in Table 28, section C.2.2. Plasma exchange requires volume replacement, most commonly with albumin, which is provided and paid for by the NBA (PICO 1564). Expert opinion suggested that while some patients may receive long-term plasma exchange, this would most commonly be provided in combination with an immunosuppressant (PICO 1564). The cost of azathioprine tablets is included in the maintenance treatment costs. The cost associated with disease and treatment monitoring is considered similar to Ig, as estimated in Table 40.

The number of severe AEs per PE procedure were reported in Table 18. The cost associated with treatment of these AEs were sourced from IHPA cost report (IHPA 2021). The cost of treating each AE, the AR-DRG code used and the estimated total cost associated with AEs per PE procedure are described in Table 85, Appendix G. The average cost of AEs per PE procedure was estimated to be $8.28.

PE requires adequate venous access for the collection and return of fluids; inadequate blood flow may result in longer procedure times and procedure cessation before the target PE volume has been reached. To achieve adequate venous access, patients may have large-bore peripheral cannulation or insertion of a central venous catheter. For longer-term treatment, such as required for patients with CIDP, implantation of an AV fistulae (surgically created connection between an artery and a vein) may be the most appropriate option for some patients. Resource use associated with the placement of

venous access devices was sourced from the MSAC 1566 report (Milverton et al. 2019) and is summarised in Table 81, **Appendix G**. The clinical expert advice was that approximately 50% of the patients may have placement of tunnelled large bore catheters in the first four to six months. For patients who need chronic vascular access for more than six months on treatment, nearly 20% may have placement of tunnelled large bore catheters and 10% may have implantation of an AV fistulae (Department of Health 2021a). The detailed cost estimation for long-term vascular access requirements by delivery mode for PE is provided in Table 82, **Appendix G**.

Table 43 presents a summary of resource costs associated with plasma exchange procedure.

**Table 43: Resource prices associated with Plasma exchange**

| Resource | Cost | Source |
|---|---|---|
| **Treatment costs** | | |
| Albumin (Albumex 4) | $70.01 / 500mL or $0.14 /mL | NBA product list[1] |
| Plasma volume exchanged (mL/kg) | 45 | Table 28 |
| Total volume exchanged (mL) | 3,510 | Product of average patient weight (78kgs) and plasma volume exchanged per kg of body weight |
| Administration, inpatient hospital costs and consumables | $1,477 | AR-DRG B40Z, Plasmapheresis (IHPA 2021) |
| **Disease and treatment monitoring costs** | | |
| Total monitoring costs per cycle | $45.29 | For a cycle length of 4 weeks, same as Ig (Table 40) |
| **Severe adverse event costs** | | |
| Cost of adverse event per procedure | $8.28 | Table 85, Appendix G |
| **Vascular access for Ig use (per patient)** | | |
| First 4–6 months | $737.50 | Table 81 and Table 82, Appendix G |
| More than 6 months | $1,345.84 | Table 81 and Table 82, Appendix G |

[1] Source: NBA product list accessed on 10 March 2021; <https://www.blood.gov.au/national-product-price-list#note-1>
AR-DRG = Australian Refined Diagnosis Related Groups; IHPA = the Independent Hospital Pricing Authority; Ig = immunoglobulin; kg = kilograms; MBS = Medicare Benefits Schedule; mL = millilitres; NBA = National Blood Authority;

**Best supportive care**

The cost of the 'Best supportive care' in health state D is comprised of disease monitoring and applies to both treatment arms. Of note, 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 physical disabilities due to muscle weakness. Such resources may include allied health services, use of walking aids such as electric wheelchairs and walking frames, additional rehabilitation and physiotherapy sessions, social work services, residential admissions, etc. 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. However, the negative health impact of disease progression is accumulated in the model by applying utility decrements in each cycle.

## HEALTH OUTCOMES

The utility values applied in the model are described in Section C.4.1. A baseline utility value of 0.62 is assumed for all patients entering the model. Patients who respond to intravenous Ig or PE either in the 'Induction phase'(A) or Maintenance phase'(B) have a utility gain of 0.12 (0.0092 per cycle). Patients in 'In remission (off-treatment)' health states, revert back to age-specific utility for the general population for their time in those states. A utility decrement of –0.0036 is applied to patients who are on steroids per cycle. Utility values are adjusted for aging (a decrement of –0.0002 in the model). Utility values for adverse events were calculated as a product of the incidence of specific AEs and the associated disutilities described in Table 34. Table 44 presents a summary of utility weights used in the modelled base-case economic evaluations.

**Table 44    Utility weights[a] used in the modelled base-case economic evaluation**

| Description | Health States | Ig | Corticosteroids | PE |
|---|---|---|---|---|
| Baseline utility with disease | Applies in A/B/C/D | 0.0477 | 0.0477 | 0.0477 |
| In remission | C | Age-specific utility weights | Age-specific utility weights [b] | Age-specific utility weights |
| **Utility adjustments** | | | | |
| Utility gain/loss with treatment | A and B | 0.0092 | –0.0036 | 0.0092 |
| Severe AE | Applied on transition to D | –0.0108 | –0.0466 | -0.0108 |
| Chronic AE | Applied on transition to D | 0.0000 | –0.1690 | 0.0000 |
| Treatment resistant or intolerant disease / Progression | D | –0.0108 | –0.0108 | –0.0108 |
| IV infusion (per procedure) | A and B | -0.0006 | -0.0006 | -0.0007 [c] |

[a] Utility weights are adjusted for cycle length or time period applied for in the model.
[b] Disutility associated with steroid use is applied for one year after stopping treatment when in remission (see section C.4.1 for details).
[c] Disutility associated with adverse events per procedure of plasma exchange are added to the disutility per infusion in the model.
Source: Section C.4.1 and Table 34.
Abbreviations: AE = Adverse events; Ig = immunoglobulin; IV = intravenous; PE = plasma exchange

## D.5.    RESULTS OF THE ECONOMIC EVALUATION

### D.5A. IG COMPARED WITH CORTICOSTEROIDS

#### D.5A.1.    Stepped economic evaluation

A summary the steps in the stepped economic evaluation is presented below:

- Step 1: Trial-based analysis. This step will apply the dose, dose frequency, relative adverse events, trial time horizon and Ig treatment duration from the Nobile-Orazio et al (2012) trial.

- Step 2: Trial-based analysis, extrapolated. The second step of the model will continue to apply the trial doses, dose frequency and treatment duration as mentioned in the Nobile-Orazio et al (2012). However, relapse rates as reported in the extension study to the above trial (Nobile-

Orazio et al. 2015) are applied in the model assuming relapse rates stay constant over the modelled time horizon. All patients in the trial stopped treatment after 24 weeks and were considered in remission. The extension study only studied for relapses in these patients for the median follow-up of 3.5 years. The time horizon is 10 years and the model allows for the patients to relapse, be retreated or have remission.

- Step 3: Modelled base case analysis. The final step of the analysis models the benefit of Ig relative to corticosteroids based on the pooled response, remission, relapse and adverse event rates estimated in Section C.3.1, The dose and frequency of Ig modelled is that described in the version 3 of the Criteria. This is compared with the average dose estimated from the BloodSTAR data (Department of Health 2021c).

Table 45 presents the results of the stepped analysis.

**Table 45     Results of the stepped economic analysis: IVIg vs corticosteroids**

|  | Inc. cost | Inc. QALYs | ICER |
|---|---|---|---|
| Step 1 – Trial-based analysis.<br>Applies the dose (2. g/kg), dose frequency (q4w), non-responder rates, adverse event rates, time horizon (48 weeks) and treatment duration (24 weeks) as per the Nobile-Orazio et al (2012) study. | $63,315 | 0.1320 | $479,635 |
| Step 2 – Trial-based dosing, extrapolated outcomes analysis<br>Applies the dose, dose frequency, response rate, adverse event rates from step 1. Relapse rates, and re-remission rates are estimated from the Nobile-Orazio (2015) study, with the model time horizon extrapolated to 10 years. | $702,576 | 0.9982 | $703,839 |
| Step 3 – Modelled economic evaluation<br>Applies the dose and frequency based on the Criteria version 3 (2g/kg loading dose and 0.7g/kg maintenance dose for Ig), the best estimates of transitions for remission, relapse and adverse events as described in section C.3.2 and Table 39, with the model time horizon of 10 years. | $137,443 | 1.1840 | $116,088 |

ICER = incremental cost-effectiveness ratio; Ig = immunoglobulin; Inc = Incremental; QALY = quality-adjusted life years.

In Step 1 of the analysis the ICER of Ig is $479,635 due to the higher doses of Ig used compared with the Criteria and no treatment stopping rules applied. In Step 2, the time horizon is extrapolated to 10 years. All responders are off treatment (in remission) after the 24 weeks treatment period as per the Nobile-Orazio et al (2012) study. However, model allows for the retreatment, relapse and re-remission in this step. Severe adverse events as well as the chronic adverse event rates (specific to corticosteroid treatment) are applied in this analysis. The ICERs substantially increase due to the increased use of Ig based on trial doses. Further improvements in the ICER are observed when the treatment doses used are based on clinical practice (the Criteria for Ig) and the best estimates of baseline adverse event rates and treatment effect are included in the modelling.

**D.5A.2.    Modelled base case analysis**

*Disaggregated costs and outcomes*

The costs and outcomes disaggregated for the base case analysis are presented in Table 46 and Table 47.

**Table 46    Disaggregated costs, Ig versus corticosteroids**

|  | Ig | Corticosteroids | Increment |
|---|---|---|---|
| Drug costs | $131,280 | $1,080 | $130,200 |
| Monitoring costs | $4,454 | $7,912 | –$3,457 |
| Administration costs | $28,293 | $16,805 | $11,488 |
| Adverse event costs | $0 | $788 | –$788 |
| **Total costs** | **$164,027** | **$26,584** | **$137,443** |

Ig = immunoglobulin.

The cost of Ig was the main driver of the incremental cost, with offsets related to a reduction in the number of adverse events and costs associated with it.

**Table 47    Disaggregated QALYs, Ig versus corticosteroids**

|  | Ig | Corticosteroids | Increment |
|---|---|---|---|
| On treatment (induction /maintenance phase) QALYs | 2.066 | 0.879 | 1.188 |
| 'In remission' QALYs | 2.560 | 1.253 | 1.307 |
| 'BSC' QALYs | 0.753 | 2.080 | –1.327 |
| Adverse event QALYs | 0.000 | –0.016 | 0.016 |
| **Total QALYs** | **5.379** | **4.195** | **1.184** |

BSC = best supportive care (this represents health state with treatment failure/withdrawal due to adverse events or non-efficacy); Ig = immunoglobulin; QALY = quality-adjusted life years.

The incremental QALYs were primarily accrued in the on treatment (induction/maintenance phase) health states due to improved QALYs with Ig treatment. As Ig was associated with higher response rate and fewer adverse events, less time was spent in the 'BSC (treatment failure/withdrawal due to AE or non-efficacy)' health state with Ig.

*Incremental cost-effectiveness*

The ICER per additional QALYs gained is presented in Table 48.

**Table 48    Incremental cost-effectiveness ratios, Ig versus corticosteroids**

|  | Ig | Corticosteroids | Increment |
|---|---|---|---|
| Total cost | $164,027 | $26,584 | $137,443 |
| Total QALYs | 5.379 | 4.195 | 1.184 |
| **ICER per additional QALY gained** | | | **$116,088** |

ICER = incremental cost-effectiveness ratio; Ig = immunoglobulin; QALY = quality-adjusted life years.

Markov traces depicting health state membership over time for Ig and steroid treatment arms are presented in Figure 13.
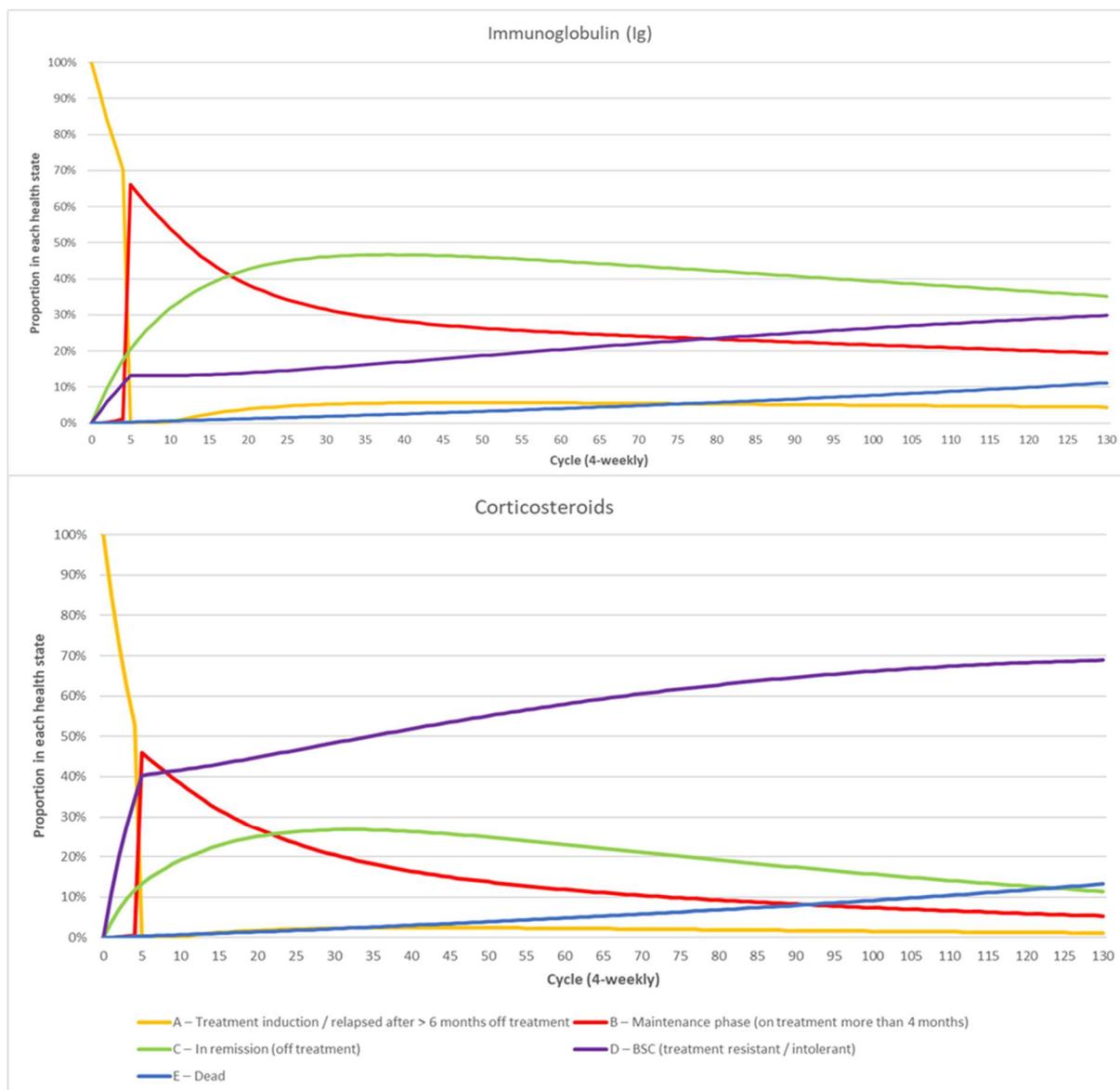
**Figure 13    Markov model traces, Ig versus corticosteroids**

Abbreviation: AE= adverse event; BSC = best supportive care; Ig = immunoglobulin

*Scenario analyses*

Scenario analysis for the modelled base-case varying the maintenance dose for Ig and using alternative cost per gram of Ig are presented in Table 49.

**Table 49    Scenario analyses, Ig versus corticosteroids, alternative cost per g of Ig and alternative maintenance dose**

| Step 3 – Modelled economic evaluation | Inc. cost | Inc. QALYs | ICER |
|---|---|---|---|
| Base-case, maintenance dose for Ig: 0.7g/kg/infusion every 4 weeks, cost $60.41 per gram of Ig | $137,443 | 1.1840 | $116,088 |
| Maintenance dose for Ig: 0.4g/kg/infusion every 4 weeks | $87,628 | 1.1840 | $74,013 |
| Maintenance dose for Ig: 1.0g/kg/infusion every 4 weeks | $187,259 | 1.1840 | $158,163 |

| Step 3 – Modelled economic evaluation | Inc. cost | Inc. QALYs | ICER |
|---|---|---|---|
| High cost (domestic IVIg, including cost of plasma), $140.18 per gram of Ig | $310,795 | 1.1840 | $262,505 |
| Low cost (imported IVIg), $44.94 per gram of Ig | $103,825 | 1.1840 | $87,693 |
| weighted average across all indications, $94.51 per gram of Ig | $211,540 | 1.1840 | $178,672 |

g = grams; ICER = incremental cost-effectiveness ratio; Ig = immunoglobulin; Inc = Incremental; IV = intravenous; kg = kilograms; QALY = quality-adjusted life years

The ICERs vary substantially in the range of $74,013– $158,163 per QALY gained when maintenance dose for Ig infusion is varied from 0.4–1.0 g/kg. ICERs are highly sensitive to the cost per gram of Ig used (range $87,693 – $262,505).

## D.5B. IG COMPARED WITH PLASMA EXCHANGE

There was insufficient evidence on the comparison of Ig and PE to support a finding of non-inferiority. The long-term effectiveness of PE treatment for CIDP is uncertain as the evidence was limited and of mixed quality. As such, only exploratory analyses could be conducted for this comparison.

### D.5B.1. Stepped economic evaluation

A summary the steps in the stepped economic evaluation is presented below:

- Step 1: Trial-based analysis. This step will apply the dose, dose frequency, time horizon from the Dyck et al (1994) trial (see Table 27). This study was conducted over six weeks with 20 patients. This study claimed equivalent effectiveness for Ig and PE. As there were no differences in the health outcomes, only a cost analysis is presented in Step 1.

- Step 2: Modelled base case analysis. The final step of the analysis models the benefit of Ig relative to PE based on the exploratory data analyses and pooled adverse event rates as summarised in Section D.4. The dose and frequency of Ig modelled is that described in the version 3 of the Criteria and PE as described in (Gwathmey 2020), see Table 28.

Table 50 presents results for step 1: Trial-based analysis.

**Table 50      Results for step 1 of the analysis, immunoglobulin versus plasma exchange**

| | NTE | Dose (g) | Drug cost | Administration cost | Total cost |
|---|---|---|---|---|---|
| *Immunoglobulin* | | | | | |
| Induction treatment | 3 | 93.6 | $5,654 | $2,079 | $7,733 |
| Maintenance treatment | 3 | 46.8 | $2,827 | $2,079 | $4,906 |
| Total cost, immunoglobulin | | | | | $12,640 |
| *Plasma exchange* | | | | | |
| Induction treatment | 6 | 3,510 | $2,949 | $8,860 | $11,809 |
| Maintenance treatment | 3 | 3,510 | $1,474 | $4,430 | $5,904 |
| Total cost, plasma exchange | | | | | $17,713 |
| **Incremental cost** | | | | | **–$5,074** |

g= grams; NTE = number of treatment episodes

Table 51 presents the results of the stepped analysis.

**Table 51 Results of the stepped economic analysis: IVIg vs PE**

| | Inc. cost | Inc. QALYs | ICER |
|---|---|---|---|
| Step 1 – Trial-based analysis.<br>IVIg: 0.4 g/kg/week for first three weeks followed by 0.2 g/kg/week for the next three weeks.<br>PE: Twice per week for three weeks then once a week for next three weeks (Dyck et al. 1994) | –$5,074 | - | - |
| Step 2 – Modelled economic evaluation<br>Applies the dose and frequency based on the Criteria V3 for Ig and for PE from Gwathmey et al (2020) (Table 28), the best estimates of transitions for remission, relapse and adverse events as described in section C.3.2 and Table 31, with the model time horizon of 10 years. | $49,991 | 0.5316 | $94,038 |

ICER = incremental cost-effectiveness ratio; Ig = immunoglobulin; Inc = Incremental; PE = plasma exchange; QALY = quality-adjusted life years.

In Step 1 of the analysis the treatment with Ig results in cost savings of $5,074 due to the lower doses of Ig used compared with the Criteria and shorter treatment duration (6 weeks in the trial). In Step 2, the exploratory modelled base-case analysis, the ICER of Ig is $94,038 due to the higher doses of Ig used compared with the trial based doses and for longer treatment duration.

### D.5B.2. Modelled base case analysis

*Disaggregated costs and outcomes*

The costs and outcomes disaggregated for the base case analysis are presented in Table 52 and Table 53.

**Table 52 Disaggregated costs, immunoglobulin versus plasma exchange**

| | Immunoglobulin | Plasma exchange | Increment |
|---|---|---|---|
| Drug costs | $131,280 | $22,183 | $109,097 |
| Monitoring costs | $4,454 | $4,454 | $0 |
| Administration costs | $28,293 | $86,652 | -$58,359 |
| **Total costs** | **$164,027** | **$114,036** | **$49,991** |

Note: Totals may not add up due to rounding off.

The cost of Ig was the main driver of the incremental cost, with offsets related to a reduction in the administration costs.

**Table 53 Disaggregated QALYs, immunoglobulin versus plasma exchange**

| | Immunoglobulin | Plasma exchange | Increment |
|---|---|---|---|
| On treatment (induction /maintenance phase) QALYs | 2.033 | 1.336 | 0.698 |
| 'In remission' QALYs | 2.560 | 1.843 | 0.717 |
| 'BSC' QALYs | 0.753 | 1.600 | -0.846 |
| **Total QALYs** | **5.346** | **4.778** | **0.568** |

BSC = best supportive care (this represents treatment resistant or intolerant health state); QALY = quality-adjusted life years.

The incremental QALYs were primarily accrued in the on treatment (induction/maintenance phase) health states due to more patients continuing treatment with Ig. As Ig was associated with higher response rate and fewer adverse events, less time was spent in the 'BSC' health state with Ig.

### *Incremental cost-effectiveness*

The ICER per additional QALYs gained is presented in Table 54.

**Table 54    Incremental cost-effectiveness ratios, immunoglobulin versus plasma exchange**

|  | Immunoglobulin | Plasma exchange | Increment |
|---|---|---|---|
| Total cost | $164,027 | $114,036 | $49,991 |
| Total QALYs | 5.346 | 4.848 | 0.532 |
| **ICER per additional QALY gained** | | | **$94,038** |

ICER = incremental cost-effectiveness ratio; Ig = immunoglobulin; QALY = quality-adjusted life years.

Markov traces depicting health state membership over time for Ig and PE arms are presented in Figure 18 and Figure 20 in **Appendix G**.

### *Scenario analyses*

Scenario analysis for the modelled base-case varying maintenance dose for Ig and using alternative cost per gram of Ig are presented in Table 55.

**Table 55    Scenario analyses, Ig versus PE, alternative cost per g of Ig and alternative maintenance dose**

| Modelled economic evaluation | Inc. cost | Inc. QALYs | ICER |
|---|---|---|---|
| Base-case, maintenance dose for Ig: 0.7g/kg/infusion every 4 weeks, cost $60.41 per gram of Ig | **$49,991** | **0.5316** | **$94,038** |
| Maintenance dose for Ig: 0.4g/kg/infusion every 4 weeks | $176 | 0.5316 | $331 |
| Maintenance dose for Ig: 1.0g/kg/infusion every 4 weeks | $99,807 | 0.5316 | $187,745 |
| High cost (domestic IVIg, including cost of plasma), $140.18 per gram of Ig | $223,343 | 0.5316 | $420,129 |
| Low cost (imported IVIg), $44.94 per gram of Ig | $16,373 | 0.5316 | $30,799 |
| weighted average across all indications, $94.51 per gram of Ig | $124,088 | 0.5316 | $233,422 |

g = grams; ICER = incremental cost-effectiveness ratio; Ig = immunoglobulin; Inc = Incremental; IV = intravenous; kg = kilograms; PE = plasma exchange; QALY = quality-adjusted life years

The ICERs vary substantially in the range of $331 –$187,745 per QALY gained when maintenance dose for Ig infusion is varied from 0.4–1.0 g/kg. The ICERs are highly sensitive to the cost per gram of Ig used in the model, with values ranging from $30,799 – $233,422 across the prices tested.

### D.5C. IG COMPARED WITH PLACEBO IN STEROID RESISTANT SUBGROUP

There was insufficient evidence on the comparison of Ig and placebo in steroid resistant population. Data from Ig versus placebo study (Hughes et al. 2008) are used for the trial-based analysis. Modelled base-case analysis use estimates for Ig as used in the other two comparisons. For placebo (best supportive care) assumptions are made that patients do not switch to other treatment, as such there

is no treatment effect and no transitions to 'In remission' health state are made in the modelled analysis.

### D.5C.1. Stepped economic evaluation

A summary the steps in the stepped economic evaluation is presented below:

- Step 1: Trial-based analysis. This step will apply the dose, dose frequency, time horizon from the Hughes et al (Hughes et al. 2008) trial (see Table 27). This study was conducted over 48 weeks with 117 patients. Patients were categorised as responders or non-responders after 6 weeks on treatment. Non-responders were allowed to cross-over.

- Step 2: Modelled base case analysis. The final step of the analysis models the benefit of Ig relative to placebo using Ig estimates based on NBA data (as used in previous comparisons) and extrapolating placebo estimates for time horizon of 10 years. The dose and frequency of Ig modelled is that described in the version 3 of the Criteria and placebo arm is supposed to have no treatment.

Table 56 presents the results of the stepped analysis.

**Table 56    Results of the stepped economic analysis: Ig vs best supportive care**

| | Inc. cost | Inc. QALYs | ICER |
|---|---|---|---|
| Step 1 – Trial-based analysis. IVIg: Baseline loading dose of 2.0 g/kg over 2–4 d, followed by a maintenance infusion of 1 g/kg over 1–2 d every 3 wk for 24 wk. Placebo (0.1% albumin) (Hughes et al. 2008) | $40,873 | 0.1266 | $322,801 |
| Step 2 – Modelled economic evaluation Applies the dose and frequency based on the Criteria version 3 for Ig and no treatment for placebo, the best estimates of transitions for remission, relapse and adverse events as described in section C.3.2 and Table 31, with the model time horizon of 10 years. | $159,573 | 1.7162 | $92,983 |

ICER = incremental cost-effectiveness ratio; Ig = immunoglobulin; Inc = Incremental; PE = plasma exchange; QALY = quality-adjusted life years.

In Step 1 of the analysis, the ICER of Ig is $322,801 due to the higher and more frequent doses of Ig used compared with that in the modelled base-case. Improvements in the ICER are observed when the treatment doses used are based on clinical practice (the Criteria V3 for Ig) and the best estimates of baseline adverse event rates and treatment effect are included in the modelling (step 2, the exploratory modelled base-case analysis.

### D.5C.2.    Modelled base case analysis

#### Disaggregated costs and outcomes

The costs and outcomes disaggregated for the base case analysis are presented in Table 57 and Table 58.

**Table 57    Disaggregated costs, Ig vs best supportive care**

|  | Ig | Placebo | Increment |
|---|---|---|---|
| Drug costs | $131,280 | $0 | $131,280 |
| Monitoring costs | $4,454 | $4,454 | $0 |
| Administration costs | $28,293 | $0 | $28,293 |
| **Total costs** | **$164,027** | **$4,454** | **$159,573** |

Ig = immunoglobulin.

The cost of Ig and the administration costs were the main driver of the incremental cost.

**Table 58    Disaggregated QALYs, Ig vs best supportive care**

|  | Ig | Placebo | Increment |
|---|---|---|---|
| On treatment (induction /maintenance phase) QALYs | 2.066 | 0.128 | 1.938 |
| 'In remission' QALYs | 2.560 | 0.054 | 2.505 |
| 'BSC' QALYs | 0.753 | 3.481 | −2.728 |
| **Total QALYs** | **5.379** | **3.663** | **1.716** |

BSC = best supportive care (this represents the treatment resistant or treatment intolerant health state); Ig = immunoglobulin; QALY = quality-adjusted life years.

The incremental QALYs were primarily accrued in the on treatment (induction/maintenance phase) and 'in remission' health states due to more patients continuing treatment or in remission with Ig. As placebo was associated with higher relapse rate and no treatment after relapse, more time was spent in the 'BSC' health state with placebo.

*Incremental cost-effectiveness*

The ICER per additional QALYs gained is presented in Table 59.

**Table 59    Incremental cost-effectiveness ratios Ig vs best supportive care**

|  | Ig | Placebo | Increment |
|---|---|---|---|
| Total cost | $164,027 | $4,454 | $159,573 |
| Total QALYs | 5.379 | 3.663 | 1.716 |
| **ICER per additional QALY gained** |  |  | **$92,983** |

ICER = incremental cost-effectiveness ratio; Ig = immunoglobulin; QALY = quality-adjusted life years.

Markov traces depicting health state membership over time for Ig and placebo arms are presented in Figure 18 and Figure 21 in **Appendix G**.

*Scenario analyses*

Scenario analysis for the modelled base-case varying maintenance dose for Ig and using alternative cost per gram of Ig are presented in Table 60.

**Table 60    Scenario analyses, Ig vs BSC, alternative cost per g of Ig and alternative maintenance dose**

| Modelled economic evaluation | Inc. cost | Inc. QALYs | ICER |
|---|---|---|---|
| Base-case, maintenance dose for Ig: 0.7g/kg/infusion every 4 weeks, cost $60.41 per gram of Ig (domestic IVIg, excluding cost of plasma) | **$159,573** | **1.7162** | **$92,983** |

| Modelled economic evaluation | Inc. cost | Inc. QALYs | ICER |
|---|---|---|---|
| Maintenance dose for Ig: 0.4g/kg/infusion every 4 weeks | $109,757 | 1.7162 | $63,955 |
| Maintenance dose for Ig: 1.0g/kg/infusion every 4 weeks | $209,388 | 1.7162 | $122,010 |
| High cost (domestic IVIg, including cost of plasma), $140.18 per gram of Ig | $332,925 | 1.7162 | $193,995 |
| Low cost (imported IVIg), $44.94 per gram of Ig | $125,954 | 1.7162 | $73,393 |
| Weighted average across all indications, $94.51 per gram of Ig | $233,670 | 1.7162 | $136,159 |

BSC = best supportive care; g = grams; ICER = incremental cost-effectiveness ratio; Ig = immunoglobulin; Inc = Incremental; IV = intravenous; kg = kilograms; QALY = quality-adjusted life years

The ICERs vary substantially in the range of $63,955 –$122,010 per QALY gained when maintenance dose for Ig infusion is varied from 0.4–1.0 g/kg. The ICERs are highly sensitive to the cost per gram of Ig used in the model, values ranging from $73,393 – $193,995.

## D.6.  SENSITIVITY ANALYSIS

### ADMINISTRATION COSTS PER IG INFUSION

The base case estimates the administration cost per Ig infusion as $693. Sensitivity analyses were performed varying the administration cost; as expected, decreasing this cost reduces the ICERs in favour of Ig, to varying extents across the different comparisons. There is minimal impact for the Ig versus corticosteroids comparison (as the same administration cost is applied to both IVIg and corticosteroid (IVMP) infusions). The impact in the Ig versus BSC comparison is also fairly small. However, in the Ig versus PE comparison, the ICER is more sensitive to this variable; reducing the administration cost per Ig infusion to values between $200 – $500 reduces the ICERs by 15%–39%. Table 61 presents a summary of results for sensitivity analyses changing the administration cost of Ig per infusion.

**Table 61       Sensitivity analyses, administration costs per Ig infusion**

| | Inc. cost | Inc. QALYs | ICER | %Change |
|---|---|---|---|---|
| **Ig versus corticosteroids (base case: $693)** | **$137,443** | **1.1840** | **$116,088** | |
| $200 | $129,664 | 1.1840 | $109,517 | –6% |
| $371 (used in the previous DCAR 1564) | $132,362 | 1.1840 | $111,796 | –4% |
| **Ig versus PE (base case: $693)** | **$49,991** | **0.5316** | **$94,038** | |
| $200 | $30,257 | 0.5316 | $56,916 | –39% |
| $371 (used in the previous DCAR) | $37,102 | 0.5316 | $69,792 | –26% |
| **Ig versus BSC (base case: $693)** | **$159,573** | **1.7162** | **$92,983** | |
| $371 (used in the previous DCAR 1564) | $146,683 | 1.7162 | $85,472 | –8% |
| $200 | $139,838 | 1.7162 | $81,483 | –12% |
| $400 | $147,844 | 1.7162 | $86,148 | –7% |
| $500 | $151,847 | 1.7162 | $88,481 | –5% |

BSC = best supportive care; Ig = immunoglobulin; ICER = incremental cost-effectiveness ratio; Ig = immunoglobulin; Inc = Incremental; IV = intravenous; kg = kilograms; PE = plasma exchange; QALY = quality-adjusted life years

Sensitivity analyses were performed for both models for the inputs related to Ig dose and interval length between doses; varying the average patient age and weight; utility gain/loss associated with treatment; discount rates (0% and 3%); modelled time horizon; varying transition probabilities for treatment response, treatment effect and treatment associated severe AEs.

**Ig versus corticosteroids**

Key sensitivity analyses (i.e. those which changed the ICER by more than 25%) are presented in Table 62, below. All other sensitivity analyses conducted around areas of uncertainty in the model are presented in Table 86, **Appendix G**.

**Table 62      Key sensitivity analyses, Ig versus corticosteroids**

|  | Inc. cost | Inc. QALYs | ICER | %Change |
|---|---|---|---|---|
| **Cost per gram of Ig** | | | | |
| **Base case modelled analysis** | **$137,443** | **1.1840** | **$116,088** | **-** |
| **Maintenance dose intervals for Ig (base case: 4 weeks)** | | | | |
| 3 weeks | $184,329 | 1.1772 | $156,582 | 35% |
| 6 weeks | $90,558 | 1.1907 | $76,053 | -34% |
| 8 weeks | $67,115 | 1.1941 | $56,206 | -52% |
| **Weaning off trial for Ig** | | | | |
| Starting dose in maintenance phase- 1g/kg, then applying 20% dose reduction for 5 cycles | $100,559 | 1.1840 | $84,934 | -27% |
| **Modelled time horizon (base case: 10 years)** | | | | |
| 1 year | $31,109 | 0.1616 | $192,522 | 66% |
| 3 years | $64,521 | 0.4355 | $148,140 | 28% |
| 5 years | $106,839 | 1.0259 | $104,145 | 12% |
| 7 years | $130,976 | 1.3438 | $97,465 | 5% |
| **Health state transitions, Ig** | | | | |
| Proportion of patients relapsing in remission health state (base case: 3.8%) | | | | |
| 1.50% | $91,384 | 1.3294 | $68,740 | -41% |
| Treatment to in remission - off treatment health state (base case: 5.3%) | | | | |
| 0.57% | $276,595 | 1.0566 | $261,775 | 125% |
| 1.03% | $252,055 | 1.0763 | $234,185 | 102% |
| 3.66% | $166,243 | 1.1522 | $144,284 | 24% |
| **Health state transitions, steroids** | | | | |
| Treatment to in remission - off treatment health state (base case: 3.85%) | | | | |
| 0.56% | $127,179 | 1.4804 | $85,909 | -26% |

Ig = immunoglobulin; ICER = incremental cost-effectiveness ratio; Ig = immunoglobulin; Inc = Incremental; IV = intravenous; kg = kilograms; QALY = quality-adjusted life years

The cost of Ig is a key driver in the model. Any reduction in Ig use, either by increasing the interval length between doses or decreasing the maintenance dose (such as with weaning off trial or using

lower maintenance dose of 0.4g/kg) reduces the ICER substantially. Decreasing the time horizon below five years increases the ICERs substantially. The ICER reduces when the probability of remission on steroid treatment is lowered.

*Ig versus plasma exchange therapy*

Sensitivity analyses also included varying the administration cost per PE procedure; number of exchanges per maintenance treatment course.

Key sensitivity analyses (i.e. those which changed the ICER by more than 25%) are presented in Table 63, below. All other sensitivity analyses conducted around areas of uncertainty in the model are presented in Table 87, **Appendix G**. Generally the ICER for Ig vs PE is less stable (more sensitive to changes in inputs and assumptions) than the previous comparison.

**Table 63      Key sensitivity analyses, Ig versus plasma exchange**

| | Inc. cost | Inc. QALYs | ICER | % Change |
|---|---|---|---|---|
| **Base case results** | **$49,991** | **0.5316** | **$94,038** | |
| **Maintenance dose intervals for Ig (base case: 4 weeks)** | | | | |
| 3 weeks | $96,877 | 0.5249 | $184,579 | 96% |
| 6 weeks | $3,106 | 0.5384 | $5,769 | -94% |
| 8 weeks | -$20,337 | 0.5417 | Dominant (ICER: − $37,541) | Dominant |
| **Weaning off trial for Ig** | | | | |
| Starting dose in maintenance phase- 1g/kg, then applying 20% dose reduction for 5 cycles | $13,107 | 0.5316 | $24,656 | -74% |
| **Utility gain with Ig (base case:0.12)** | | | | |
| 0.06 | $49,991 | 0.3616 | $138,253 | 47% |
| 0.18 | $49,991 | 0.7016 | $71,251 | -24% |
| **Modelled time horizon (base case: 10 years)** | | | | |
| 1 year | $3,590 | 0.0164 | $218,409 | 132% |
| 3 years | $12,974 | 0.1025 | $126,578 | 35% |
| **Health state transitions, Ig** | | | | |
| Treatment failure (base case: 3.1% per cycle in State A) | | | | |
| 8.72% per cycle in State A | -$2,030 | -0.0357 | Less costly, less effective (ICER: $56,869) | Less costly, less effective (ICER: $56,869) |
| Proportion of patients relapsing in remission health state (base case: 3.8%) | | | | |
| 1.50% | $3,932 | 0.6771 | $5,807 | -94% |
| 4.12% | $55,633 | 0.5165 | $107,710 | 15% |
| Treatment to in remission - off treatment health state (base case: 5.3%) | | | | |

| | Inc. cost | Inc. QALYs | ICER | % Change |
|---|---|---|---|---|
| 0.57% | $189,143 | 0.4043 | $467,878 | 398% |
| 1.03% | $164,603 | 0.4240 | $388,257 | 313% |
| 3.66% | $78,791 | 0.4998 | $157,633 | 68% |
| 6.12% | $38,407 | 0.5464 | $70,294 | -25% |
| **Health state transitions, PE** | | | | |
| Adverse event per PE procedure (base case: 1.68%) | | | | |
| 0.10% | -$6,561 | -0.0702 | *Less costly, less effective (ICER: $93,483)* | *Less costly, less effective (ICER: $93,483)* |
| Proportion of patients relapsing in remission health state (base case: 3.8%) | | | | |
| 0.015 | $75,651 | 0.3025 | $250,127 | 166% |
| Treatment to in remission - off treatment health state (base case: 2.09%) | | | | |
| 0.57% | $6,747 | 0.9414 | $7,167 | -92% |
| 6.12% | $54,845 | 0.4826 | $113,655 | 21% |
| **Number of plasma exchanges per maintenance treatment (base case: 1.5)** | | | | |
| 1 | $73,833 | 0.5233 | $141,078 | 50% |
| 2 | $26,150 | 0.5399 | $48,437 | -48% |
| **PE administration cost (base case: $1,477)** | | | | |
| $738 | $83,317 | 0.5316 | $156,726 | 67% |
| **Utility gain with PE treatment (base case: 0.12)** | | | | |
| 0.0 | $49,991 | 0.7654 | $65,316 | -31% |

Ig = immunoglobulin; ICER = incremental cost-effectiveness ratio; Ig = immunoglobulin; Inc = Incremental; IV = intravenous; kg = kilograms; PE = plasma exchange; QALY = quality-adjusted life years

Due to the lack of evidence, most treatment effect parameter values (i.e. except treatment costs and treatment associated severe adverse events) in the base-case are assumed similar for Ig and PE, based on the clinical claim of non-inferior efficacy. The cost of Ig and the administration cost per PE procedure are the key cost drivers in the model. Any reduction in the Ig doses either by increasing the interval length between doses or decreasing the maintenance dose (such as with weaning off trial or using lower maintenance dose of 0.4g/kg) favours Ig and reduces the ICERs substantially. Reducing the administration cost per PE procedure by 50% favours PE and increases the ICER by 67%. When the number of PEs are decreased to one per four weeks the ICER increases by 50% due to significant reduction in costs associated with PE. In contrast, when the number of plasma exchanges increases to two per four weeks, the ICER reduces by 48%. The base case assumes the utility gain with Ig and PE treatment is same (0.12); reducing the utility gain with PE treatment naturally reduces the ICER. The base case modelled time horizon is 10 years; decreasing the time horizon below five years increases the ICERs substantially. Varying the transition probabilities (treatment response, remission

probability, relapse probability and adverse events) for Ig or PE all have a substantial impact on the ICERs.

***Ig versus BSC***

Sensitivity analyses conducted around areas of uncertainty in this model are presented in Table 88, **Appendix G**.

# SECTION E

A market-based approach has been used to estimate the financial implications of Ig in CIDP, based on current utilisation of Ig products in patients with CIDP. As data available on utilisation were only available for use under the Criteria V2 or when patients were transitioning to the Criteria V3, the impact of transitioning to the Criteria V3 could not be captured in the analysis. There is also uncertainty as to whether the trends observed in the past would continue in the future.

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

The primary sources of data used in the estimates of the financial impact of Ig in CIDP are:

- NBA (2021a) National reports on the issue and use of Ig, which report the number of patients and Ig use from 2009–10 to 2017–18.

- The 'HTA Data 31 Dec 2020.xlsx' workbook provided by the Department (NBA 2021b) – which reports use, by indication and delivery mode (IVIg and SCIg), for the full financial years 2017–18 to 2019–20, and for the 2020–21 partial year to December 31, 2020.

The data available from these sources are summarised in Table 64.

**Table 64      Number of patients and grams issued for patients with CIDP who received Ig, 2011-12 to 2017-18**

|  | 2009–10 | 2010–11 | 2011–12 | 2012–13 | 2013–14 | 2014–15 |
|---|---|---|---|---|---|---|
| Ig grams issued | 541,206 | 599,181 | 677,458 | 758,271 | 857,533 | 974,258 |
| Number of patients | NR | NR | 1,551 | 1,754 | 1,903 | 2,054 |
|  | 2015–16 | 2016–17 | 2017–18 | 2018–19 | 2019–20 | 2020–21 |
| Ig grams issued | 1,071,135 | 1,171,581 | 1,290,730 | 1,359,604 | 1,494,448 | 825,641 |
| Number of patients | 2,250 | 2,379 | 2,595 | 2,682 | 2,712 | 2,507 |

CIDP = chronic inflammatory demyelinating polyneuropathy; Ig =immunoglobulin; NBA = National Blood Authority; NR = not reported.
Source: NBA (2021a) National Reports on the issue and use of immunoglobulin (Ig), 2009–2010, 2010–11, 2011–12, 2012–13, 2013–14, 2014-15, 2015-16 and 2016–17, and the 'HTA Data 31Dec 2020.xlsx' workbook provided by the Department (NBA 2021b). Shaded cells represent only six months data were available.

## E.2.    USE AND COSTS OF IG FOR CIDP

### ESTIMATED NUMBER OF PATIENTS WHO RECEIVE IG

The current eligible population and their extent of Ig use is well-defined in the BloodSTAR database, therefore a ground-up epidemiological approach to estimating the size of the relevant population is not required.

National reports on the issue and use of immunoglobulin provide data on Ig use under Criteria V2 from 2009–10 to 2017–18 (NBA 2021a). The NBA provided data to the Department of Health on the issue

and use of Ig to CIDP patients in Australia from years 2017–18 to 2020–21 (but only six months data for the last year)(NBA 2021b). This included disaggregated Ig use across the Criteria V2 and the Criteria V3 in years 2018–19 and 2019–20. In addition, the use of SCIg is reported for years 2019–20 and the partial year 2020–21. The Criteria V3 was introduced in October 2018 and the use of SCIg for CIDP was funded in August 2019. It is uncertain how the changes in eligibility and dosing (from Version 2 to Version 3 of the Criteria) and funding of SCIg (discussed below) in addition to IVIg would impact the projected future Ig use for patients with CIDP.

The total number of patients with CIDP receiving Ig has increased from 1,551 in 2011–12 to 2,250 in 2015–16 and 2,712 in 2019–20. The rate of growth for CIDP patients were 3.4% and 1.1% for the years 2018–19 and 2019–20 respectively. It is uncertain if this reduction in growth rate is attributed to the introduction of Version 3 Criteria or patient numbers switching from alternate therapies have stabilised. Due to non-linear trend observed in the growth of the number of patients using Ig over the past 10 years, patient numbers were projected using non-linear extrapolations (second order polynomial) fitted to the observed data presented in Table 64 (Figure 14). The projected estimated number of patients with CIDP requesting Ig are presented in Table 65.
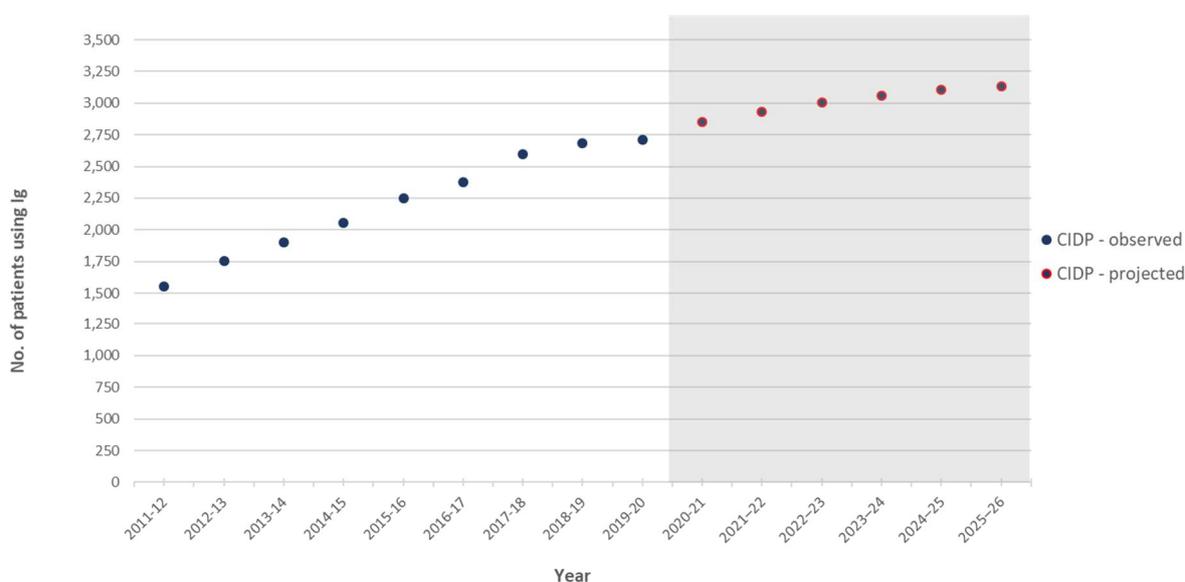


**Figure 14     Number of patients with CIDP requiring Ig therapy; projected patient numbers to 2025–2026**

CIDP = chronic inflammatory demyelinating polyneuropathy; Ig =immunoglobulin.
Source: 'Estimated patient numbers' worksheet in 'MSAC 1564.1 Financials.xlsx' workbook.

**Table 65     Number of patients with CIDP projected to receive Ig, 2021–22 to 2025–26**

|  | 2021–22 | 2022–23 | 2023–24 | 2024–25 | 2025–26 |
|---|---|---|---|---|---|
| Number of patients | 2,934 | 3,003 | 3,059 | 3,102 | 3,133 |

CIDP = chronic inflammatory demyelinating polyneuropathy; Ig =immunoglobulin.
Source: 'Estimated patient numbers' worksheet in 'MSAC 1564.1 Financials.xlsx' workbook.

**Use of Ig for IV and SC administration**

In Australia, the majority of patients who currently receive Ig for CIDP do so by intravenous infusion. SCIg was approved in August 2019 for use for the treatment of CIDP under the national blood arrangements pending the outcome of a current Health Technology Assessment review evaluating the use of immunoglobulin in the treatment of CIDP[9]. There was an uptake of 2.3% in 2019–20 (from November 2019 to June 2020), which had increased to around 4.7% in 2020–21 (July to December 2020) for SCIg for CIDP (NBA 2021b). It is uncertain to what extent the increase in SCIg uptake is attributed to the COVID-19 pandemic, or patient preference for home-based treatment. In Criteria V3 the minimum and maximum doses are equivalent (IVIg 0.4-2g/kg, 2-6 weekly and SC 0.2-1g/kg weekly, both with a maximum of 2g/kg/4-weeks). The mean dose equivalence of IV and SC Ig in practice is not well defined; in the US a SC:IV dose ratio of 1.37:1 is recommended, whereas the European Union approves a 1:1 ratio. In a small UK study of eight patients with CIDP/ multifocal motor neuropathy (Hadden & Marreno 2015) who switched from IVIg to SCIg, the ratio was 1.024:1, and a larger US analysis of real-world data in 278 switching patients (albeit, Primary Immunodeficiency Disease patients, not CIDP) indicated a stabilised ratio of 1.05:1, four months after switching. Updated BloodStar utilisation data (Department of Health 2021b) presented in Table 78, **Appendix G,** identifies that the average Ig use per patient is lower when patients receiving SCIg are excluded, suggesting higher doses are used in SCIg patients in Australia. However this is based on a small, non-comparative, short-term data set and so should be interpreted with caution (the higher average dose appears to be driven, at least in part, by the particularly large maximum dose in a single patient). Overall, the impact of dosing route on total Ig use is uncertain, but it appears more likely subcutaneous administration would be associated with increased use rather than decreased use. This is discussed further below.

IN ADDITION THE DISTRIBUTION OF IG USE BETWEEN IVIG AND SCIG ADMINISTRATION WILL HAVE IMPACT ON THE COSTS ASSOCIATED WITH IG ADMINISTRATION, THIS IS DETAILED FURTHER IN SECTION E.3.ESTIMATED USE AND COST PER PATIENT WHO RECEIVES IG

**Average grams per patient per year**

The annual increase in total Ig use for patients with CIDP has been around 10% for the years 2009–10 to 2019–20, except for year 2018–19 (where only a 5% increase from 2017–18 was observed). Total Ig use (in grams) was projected using linear extrapolation fitted to the observed data presented in Table 64 (Figure 15). This extrapolation will capture any trend due to changes in patient weight and/or dose that has occurred over the observed time period, in addition to the growth in patient numbers. The projected grams of total IVIg use for CIDP in Australia are presented in Table 66.

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[9] <https://www.blood.gov.au/SCIg>; accessed on 15 March 2021.
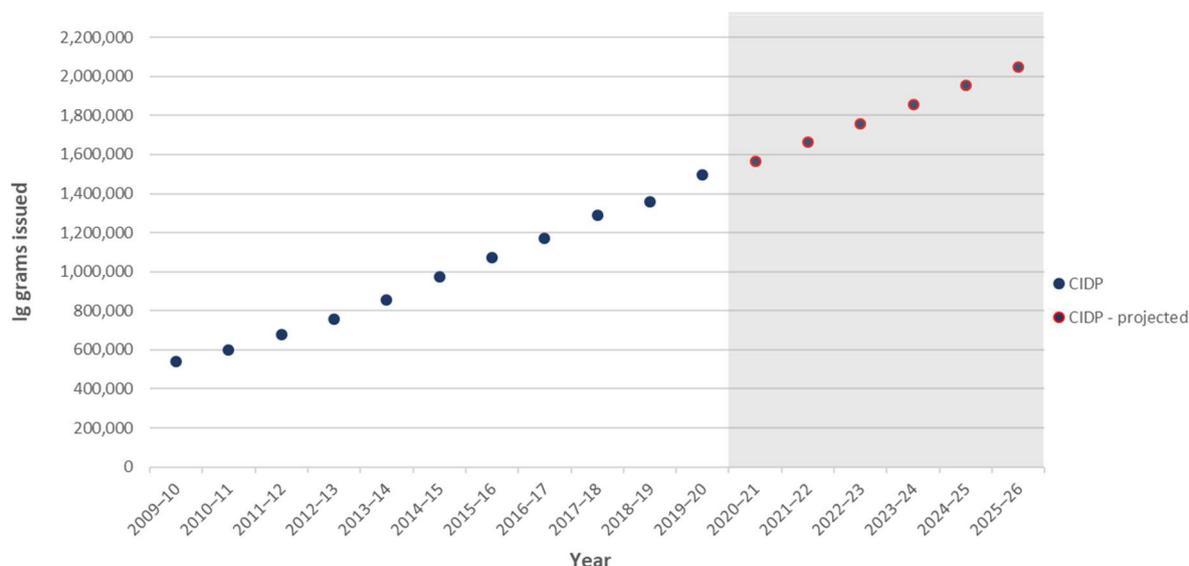
**Figure 15** **Ig for CIDP, use projections to 2025–2026**

CIDP = chronic inflammatory demyelinating polyneuropathy; Ig =immunoglobulin.
Source: 'Estimated grams issued' worksheet in 'MSAC 1564.1 Financials.xlsx' workbook.

**Table 66** **Projected number of Ig grams issued for CIDP, 2021–22 to 2025–26**

|  | 2021–22 | 2022–23 | 2023–24 | 2024–25 | 2025–26 |
|---|---|---|---|---|---|
| **Projected Ig grams issued** | 1,661,542 | 1,758,705 | 1,855,868 | 1,953,031 | 2,050,194 |

CIDP = chronic inflammatory demyelinating polyneuropathy; Ig =immunoglobulin.
Source: 'Estimated grams issued' worksheet in 'MSAC 1564.1 Financials.xlsx' workbook.

The average Ig use (g) per Australian CIDP patient annually has increased from 437 g in 2011–12 to 551 g in 2019–20; the overall trend showing rising doses. The estimated average number of grams of Ig issued per patient for CIDP using the independently extrapolated number of grams issued and projected patient numbers, equates to a projection of higher use per patient than the projection of the single variable 'use per patient', (Table 67).

**Table 67** **Average Ig use (grams) per patient per year**

|  | Av 2011–20* [observed] | 2021–22 | 2022–23 | 2023–24 | 2024–25 | 2025–26 |
|---|---|---|---|---|---|---|
| Ig use (g per patient), projected trend | 437–551 | 559 | 572 | 585 | 599 | 612 |
| Ig use (g) per patient, calculated using independent extrapolations of patient numbers and total grams used (in Tables 65 and 66)* | - | 566 | 586 | 607 | 630 | 654 |

*Ig use calculated by dividing projected Ig grams issued (Table 66) by projected number of patients (Table 65).
Av = Average; CIDP = chronic inflammatory demyelinating polyneuropathy; Ig =immunoglobulin.
Source: 'Average dose projections' worksheet in 'MSAC 1564.1 Financials.xlsx' workbook

**For the purposes of estimating financial impact in this Assessment, the estimated total Ig use in Australia is based on the projection of total Ig use, reflecting the ongoing expectation of increasing**

**average Ig use per patient. This approach is most likely to capture any impact of increasing Ig use associated with SCIg.**

**Average cost per gram of Ig**

The base case financial estimates will assume the cost per gram of Ig of $60.41 (see Section D.4.2). As per Section D, sensitivity analyses will be conducted assuming:

i)   The highest cost of Ig per gram (i.e. domestic Ig including plasma, $140.18)

ii)  The lowest cost of Ig per gram (i.e. imported IVIg, $44.94)

iii) Average cost of Ig per gram, weighted across all indications, $94.51

iv)  The weighted average cost of Ig per gram (mixed of domestic and imported product) used for CIDP in Australia which is $71.86, based on the 'HTA Data Dec 2020.xlsx' workbook.

Prices per gram are assumed to remain constant over the projected period.

### ESTIMATED COST OF IG

Projected costs of Ig therapy for CIDP are presented in Table 68.

Table 68      Projected cost of Ig for CIDP, 2021–22 to 2025–26

|  | 2021–22 | 2022–23 | 2023–24 | 2024–25 | 2025–26 |
|---|---|---|---|---|---|
| Cost per gram of Ig | $60.41 | $60.41 | $60.41 | $60.41 | $60.41 |
| Total number of patients | 2,934 | 3,003 | 3,059 | 3,102 | 3,133 |
| Total number of Ig grams issued | 1,661,542 | 1,758,705 | 1,855,868 | 1,953,031 | 2,050,194 |
| Total cost of Ig | $100,373,758 | $106,243,380 | $112,113,002 | $117,982,625 | $123,852,247 |
| Cost of Ig to the Commonwealth [a] | $63,235,467 | $66,933,329 | $70,631,191 | $74,329,054 | $78,026,916 |
| Cost of Ig to the States [a] | $37,138,290 | $39,310,051 | $41,481,811 | $43,653,571 | $45,825,331 |

CIDP = chronic inflammatory demyelinating polyneuropathy; Ig =immunoglobulin
[a] Under the National Blood Agreement, products are funded 63% by the Commonwealth and 37% by the states and territories.

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

### ADDITIONAL COSTS DUE TO IG ADMINISTRATION

Patients utilising IVIg require hospitalisation outpatient/day stay services for IVIg administration and this is a direct additional cost associated with therapy. As in Section D.4, IVIg administration costs are estimated assuming the infusion is provided in a hospital outpatient setting, under the service category of 10.13 (minor medical procedures), which includes infusions. The NWAU calculator 2020-

21 (IHPA)[10] estimated cost of this service is $693 per episode. Although SCIg is home-based program (after appropriate patient training) weekly SCIg infusions, in contrast to monthly IVIg, is associated with increased consumable costs such as syringes, lines and an infusion pump (Windegger et al. 2019, 2020). Under national blood arrangements, participating hospital are required to provide access to all resources and takes full accountability for the management and use of the SCIg product, at no additional cost to patients.

The base-case financial assumes that the SCIg uptake in patients with CIDP will increase from 5% in 2021-2022 to 15% in 2025–26. Resource use for SCIg was sourced from an Australian cost-utility study (Windegger et al. 2019) comparing IVIg versus SCIg replacement therapy in Australia in patients with secondary immunodeficiency. According to this study most patients use the Springfusor® SCIg infusion pump (Go Medical Industries Pty Ltd, Subiaco, WA, Australia) ($100 for approximately 100 infusions; equating to $1 per infusion). An average of three training sessions (approximately 2.5 hours each) is required for patients to reach competency at SCIg self-administration, which accrues direct and indirect outpatient/ward costs. The cost of consumables (syringes, needles, cannula, infusion lines, alcohol wipes) was estimated at $90.48/month on SCIg (Windegger et al. 2019). In addition, approximately 15 minutes of nursing staff time each week (or around an hour visit once a month) is required for review and the product pick up for SCIg. Resource use and costs associated with SCIg are summarised in Table 69. The total SCIg administration cost per patient per year is estimated at $6,703.

**Table 69**      **Resource use and costs associated with SCIg administration per patient per year**

| Resource | Unit cost | Cost | Source |
|---|---|---|---|
| Springfusor® pump | $1 | $52 | $100 for pump that gives approximately 100 infusions ($1 per infusion). Cost estimated for 52 weekly infusions. |
| Initial training cost of SCIg | $371 | $1,113 | 3 mean ward/nursing sessions required for patients to reach competency at SCIg self-administration (Tier 2; Clinical Nurse Specialist Interventions Classes 40.48) |
| Consumables (syringe, needle, lines, etc) | $90.48 | $1,086 | $90.48 per month for 12 months (Windegger et al. 2019) |
| Monthly review and product pick up | $371 | $4,452 | 12 reviews a year (Tier 2; Clinical Nurse Specialist Interventions Classes 40.48 (IHPA 2021)) |
| Total administration cost per year | | **$6,703** | |

SCIg = subcutaneous immunoglobulin
Source: (IHPA 2021; Windegger et al. 2019)

The average number of Ig treatment episodes per year has been derived from data provided by the NBA (Table 70). It is unclear how the weekly SCIg treatment episodes are accounted for in these data (partial year 2019–20 only), it is assumed that these data do not account for the SCIg treatment

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[10] National weighted activity unit (NWAU) calculators, available at < https://www.ihpa.gov.au/what-we-do/pricing/national-weighted-activity-unit-nwau-calculators/nwau-calculators-2020-21>

episodes. The average of data from three years is used to approximate the average number of IVIg infusions per year (13.89) to estimate the additional cost associated with IVIg administration.

**Table 70     Average number of treatment episodes per year**

|  | Average number of treatment episodes per year |
|---|---|
| 2017–18 | 13.22 |
| 2018–19 | 13.79 |
| 2019–20 | 14.64 |
| Average | **13.89** |

CIDP = chronic inflammatory demyelinating polyneuropathy; Ig =immunoglobulin
Source: 'NBA Ig use' worksheet in 'MSAC 1564.1 Financials.xlsx' workbook.

The additional healthcare costs associated with IVIg administration are estimated in Table 71. The estimated additional costs due to administration increase from $27.8 million in 2021-22 to $28.8 million in 2025-26. Administration costs are all assumed to be incurred by the States and Territories.

**Table 71     Additional costs due to Ig administration**

|  | 2021–22 | 2022–23 | 2023–24 | 2024–25 | 2025–26 |
|---|---|---|---|---|---|
| Total number of patients expected to use Ig (Table 65) | 2,934 | 3,003 | 3,059 | 3,102 | 3,133 |
| **SCIg** | | | | | |
| Number of patients switching to SCIg (5–15%) [a] | 147 | 225 | 306 | 388 | 470 |
| Cost associated with SCIg administration ($6,703 per patient per year) | $983,405 | $1,509,727 | $2,050,527 | $2,599,353 | $3,149,753 |
| **IVIg** | | | | | |
| Number of patients receiving IVIg | 2,788 | 2,778 | 2,753 | 2,715 | 2,663 |
| Cost associated with IVIg due to infusion administration ($9,623 per patient per year) [b] | $26,824,338 | $26,731,409 | $26,494,204 | $26,121,984 | $25,624,011 |
| **Total Ig administration costs (State Hospital Budgets)** | **$27,807,744** | **$28,241,137** | **$28,544,731** | **$28,721,337** | **$28,773,765** |

[a] SCIg uptake assumed at 5% in the base year; increasing 2.5% each year to reach 15% share in 2025–26
[b] Cost calculated as a product of the cost per IVIg administration ($693) and number of infusions per patient per year (13.89).
Ig = immunoglobulin; IVIg = intravenous immunoglobulin; SCIg = subcutaneous immunoglobulin.

**CHANGES IN COSTS ASSOCIATED WITH IG DUE TO A REDUCTION IN COMPARATOR SERVICES**

It is highly uncertain to what extent existing Ig availability for use for CIDP replaces the nominated comparator therapies and associated cost off-sets. There are a broad range of comparator therapies patients would utilise in the absence of Ig, and in many cases at least some of these are used concurrently with Ig. No evidence was found that could be used as a basis to project the extent to which patterns of use of these would change if Ig was not available. Therefore, the cost-offsets associated with reduction in comparator services are not quantified but no significant change in current comparator resource use is anticipated with ongoing Ig use.

### E.4. FINANCIAL IMPLICATIONS FOR GOVERNMENT HEALTH BUDGETS

The net financial implications for government budgets associated with the funding of Ig for CIDP are presented in Table 72.

**Table 72    Net financial implications to government associated with Ig for CIDP**

|  | 2021–22 | 2022–23 | 2023–24 | 2024–25 | 2025–26 |
|---|---|---|---|---|---|
| **Cost of Ig** | **$100,373,758** | **$106,243,380** | **$112,113,002** | **$117,982,625** | **$123,852,247** |
| Cost of Ig to the Commonwealth | $63,235,467 | $66,933,329 | $70,631,191 | $74,329,054 | $78,026,916 |
| Cost of Ig to the States | $37,138,290 | $39,310,051 | $41,481,811 | $43,653,571 | $45,825,331 |
| Cost of Ig administration to the States | $27,807,744 | $28,241,137 | $28,544,731 | $28,721,337 | $28,773,765 |
| **Total cost** | **$128,181,501** | **$134,484,517** | **$140,657,733** | **$146,703,962** | **$152,626,012** |
| Net cost to the Commonwealth | $63,235,467 | $66,933,329 | $70,631,191 | $74,329,054 | $78,026,916 |
| Net cost to States | $64,946,034 | $67,551,187 | $70,026,542 | $72,374,908 | $74,599,096 |

CIDP = chronic inflammatory demyelinating polyneuropathy; Ig = immunoglobulin.

### E.5. IDENTIFICATION, ESTIMATION AND REDUCTION OF UNCERTAINTY

Sensitivity analyses exploring uncertainty in the assumptions used to determine the financial implications are presented in Table 73. As expected, the cost of Ig is the main driver in the financial analysis; higher cost per gram of Ig results in higher budget impact and the lower cost of Ig per gram reduces the net cost to the Government.

**Table 73    Sensitivity analyses around the financial implication estimates**

|  | 2021–22 | 2022–23 | 2023–24 | 2024–25 | 2025–26 |
|---|---|---|---|---|---|
| **Base case financial implications** | **$128,181,501** | **$134,484,517** | **$140,657,733** | **$146,703,962** | **$152,626,012** |
| Cost of Ig (base case: $60.41 per gram) |  |  |  |  |  |
| High cost of Ig, $140.18 | $260,722,714 | $274,776,429 | $288,700,345 | $302,497,273 | $316,170,024 |
| Low cost of Ig, $44.94 | $102,477,445 | $107,277,348 | $111,947,451 | $116,490,566 | $120,909,504 |
| Weighted average of Ig across all indications, $94.51 | $184,834,531 | $194,450,483 | $203,936,636 | $213,295,801 | $222,530,788 |
| Weighted average across the CIDP, $71.86 a | $147,210,848 | $154,626,655 | $161,912,663 | $169,071,683 | $176,106,525 |
| Growth rate of Ig use (base case: average 5.4%) |  |  |  |  |  |
| 5% | $127,341,007 | $132,751,063 | $138,280,153 | $143,943,530 | $149,757,068 |
| 6% | $129,245,906 | $135,765,589 | $142,520,651 | $149,535,812 | $156,837,108 |
| 8% | $133,109,873 | $141,967,437 | $151,369,135 | $161,371,693 | $172,036,150 |
| Administration cost per IV infusion (base-case: $693) |  |  |  |  |  |
| $214 per infusion b | $109,646,774 | $116,014,000 | $122,351,118 | $128,654,537 | $134,920,670 |
| Number of patients receiving Ig (base-case: projections assuming curved growth) |  |  |  |  |  |
| Numbers projected using linear growth | $129,965,580 | $137,039,285 | $144,090,757 | $151,119,996 | $158,127,003 |
| Switch to SCIg (base-case: 2.5% increase every year) |  |  |  |  |  |
| Flat 5% SCIg use | $128,181,501 | $134,703,745 | $141,104,370 | $147,383,377 | $153,540,766 |

|  | 2021–22 | 2022–23 | 2023–24 | 2024–25 | 2025–26 |
|---|---|---|---|---|---|
| **Base case financial implications** | **$128,181,501** | **$134,484,517** | **$140,657,733** | **$146,703,962** | **$152,626,012** |
| 5% increase every year | $128,181,501 | $134,265,289 | $140,211,096 | $146,024,546 | $151,711,258 |

[a] For estimation of the average weighted price per gram within the CIDP indications see Table 89, Appendix H.

[b] Windegger et al reported $53.54 per week for IVIg ward costs (Windegger et al. 2019), that is $214 for infusions every 4 weeks.

Ig = immunoglobulin; IVIg = intravenous immunoglobulin; SCIg = subcutaneous immunoglobulin.

# APPENDIX A   CLINICAL EXPERTS AND ASSESSMENT GROUP

## ASSESSMENT GROUP

**Adelaide Health Technology Assessment (AHTA)**

| Name | Position |
|---|---|
| Ruchi Mittal | Senior Health Economist |
| Joanne Milverton | Senior Health Technology Assessment Analyst |
| Camille Schubert | Team Leader – Health Economics |
| Jacqueline Parsons | Team Leader - Special Projects |

## Noted conflicts of interest

There were no conflicts of interest.

# APPENDIX B SEARCH STRATEGIES

**Table 74** **Bibliographic databases used in the literature search**

| Electronic database | Time period searched |
|---|---|
| Embase | Inception to 07 October 2020 |
| PubMed | Inception to 07 October 2020 |
| clinicaltrials.gov | Inception to 07 October 2020 |

**Table 75** **Study selection criteria**

| Selection criteria | Inclusion criteria | Exclusion criteria |
|---|---|---|
| Population | Any patients with CIDP or IgA and IgG paraprotein neuropathies | Other related immunological conditions (GBS, MS, IgM paraprotein neuropathy)<br>Studies reporting on more than one type of immune condition where CIDP results were not reported separately. |
| Intervention | Any Ig treatment for CIDP | Nil |
| Comparator | Active comparators:<br>• plasma exchange<br>• corticosteroids<br>• immunosuppressants including autologous transfer)<br>• any combination of these.<br>No treatment:<br>• no active treatment<br>• placebo | Etanercept, Interferons, Fc receptor inhibitors, Ig capture columns.<br>Note: studies comparing these excluded comparators to either Ig or another active comparator were selected for possible inclusion in the network meta-analysis. |
| Outcomes | Any treatment effect measured<br>Any safety outcomes | Outcomes not related to effectiveness or safety. |
| Study type | Comparative safety and effectiveness:<br>Any RCT on the intervention or any comparators<br>Extended assessment of harms:<br>Any non-randomised comparative study or case series study on the intervention and/or any comparators | Case reports (<10 patients)<br>Narrative reviews<br>Opinion pieces<br>Letters |

Abbreviations: CIDP = Chronic inflammatory demyelinating polyneuropathy, Ig = immunoglobulin, GBS = Guillain-Barre Syndrome, MS = Multiple sclerosis, RCT = randomised controlled trial.

# APPENDIX C STUDIES INCLUDED IN THE SYSTEMATIC REVIEW

**Table 76 Key features of the randomised controlled trials included for comparative safety and effectiveness of Ig for CIDP**

| Study ID Location | Study design Level of evidence ROB | Eligibility criteria | Baseline characteristics | Intervention details | Comparator details | Outcomes assessed | Follow-up period Funding source |
|---|---|---|---|---|---|---|---|
| PATH study, (NCT01545076) Germany<br><br>(Hartung et al. 2019)<br><br>(van Schaik, Ivo N. et al. 2018) | MC DB RCT II Low | *Inclusion*<br>PATH subjects; relapse during the Ig dependency period; successful stabilisation using 10% IVIg solution (2 g/kg followed by 1g/kg every 3 weeks) | N = 172<br>Mean age (SD) y: Placebo 55.9 (12.6); SCIg 0.2g/kg 57.5 (12.0); SCIg 0.4 g/kg 56.6 (12.7)<br>Gender (% male): placebo 64.9; SCIg 0.2 g/kg 73.7; SCIg 0.4 g/kg 53.4<br>Definite EFNS/PNS CIDP diagnosis (%): placebo 93.0; SCIg 0.2 g/kg 89.5; SCIg 0.4 g/kg 91.4<br>Mean baseline INCAT (SD): placebo 2.2 (1.7); SCIg 0.2 g/kg 2.3 (1.6); SCIg 0.4 g/kg 2.5 (1.8) | 1. SCIg (IgPro 20, Hizentra)0.4 g/kg<br>2. SCIg (IgPro 20, Hizentra)0.2 g/kg | Placebo | QoL using PROs (EQ-VAS, EQ-5D) Treatment satisfaction (TQSM) Work impact (WPAI-GH)<br><br>Relapse rate Withdrawal rate INCAT score Mean grip strength MRC sum score IRODS AEs | Follow-up: weeks 9 & 25 Funding: CSL Behring |
| (Kuitwaard et al. 2020a) Netherlands | CO DB RCT II Moderate | *Inclusion*<br>Adults with CIDP based on EFNS/PNS criteria; stable dose and interval of 10% liquid IVIg maintenance therapy; deterioration based on Martin Vigorimeter following dose reduction or interval lengthening within 9 mo prior to randomisation<br>*Exclusion*<br>Concomitant immunosuppressants unless dose was stable in 8 wks | N = 25<br>Mean age y (range): 67 (27-81)<br>Gender (% male): 73<br>Mean duration of IVIg treatment y (range): 4 (0-31)<br>IVIg dose range g: 20-80 g<br>Dose interval range days: 14-35 | IVIg half dose & interval (individualised to patient) | IVIg full dose & interval (individualised to patient) | Hand grip strength (Martin Vigorimeter) Health related QoL (SF-36) Disability (IRODS) Fatigue (RFSS) SAEs | Follow-up varied per patient: 1 baseline infusion, 2x 4 blind infusions separated by 2 wash-out infusions Fundong: Shire International GmbH, Takeda |

| Study ID Location | Study design Level of evidence ROB | Eligibility criteria | Baseline characteristics | Intervention details | Comparat or details | Outcomes assessed | Follow-up period Funding source |
|---|---|---|---|---|---|---|---|
| | | before trial start; prednisone dose ≤ 20 g daily | | | | | |

Abbreviations: AEs = adverse events; CIDP = chronic; CO = crossover; DB = double blind; EFNS/PNS = The European Federation of Neurological Societies/Peripheral Nerve Society; EQ-5D = EuroQoL 5-Dimension tool; EQ-VAS = EuroQoL Visual Analogue scale tool; INCAT = Infammatory Neuropathy Cause and Treatment disability scale; IVIg = intravenous immunoglobulin therapy; MC = multicentre; PATH = Polyneuropathy and Treament with Hizentra study; PRO = patient-reported outcome; QoL = quality of life; RCT = randomised controlled trial; ROB = risk of bias; SAEs = serious adverse events; SCIg = subcutaneous immunoglobulin therapy;.TSQM = treatment Satisfactrion Questionnaire for Medicine tool; WPAI-GH = Work Productivityand Activity Impairment Questionnaire for General Health tool

**Table 77        Studies included for the extended assessment of harms, key characteristics and safety data**

| Study ID Country | Study design level of evidence ROB | Inclusion criteria (simplified) Population description | Intervention Comparator (if relevant) | Observation period Comments regarding safety analyses | Outcomes |
|---|---|---|---|---|---|
| Safety data for Plasma Exchange | | | | | |
| (Ortiz-Salas et al. 2016) Multinational | SR & MA of RCTs and O I Moderate | RCTs or analytical OS in patients with neurological diseases (GBS or MG); studies comparing IVIg with PE; studies published up to 2014 Studies: k = 15 (reporting AEs) Patients: n= 5,642 | IVIg: n = 732 patients PE: n = 1656 patients | Not reported – go to individual studies | AEs per patient (%) |
| (Mörtzell Henriksson et al. 2016) Multinational | R MC O IV Moderate | Data from the WAA apheresis registry (www.waa-registry.org) Median age (range): 55 (0 – 94) y Diagnosis groups n (%) Malignancy 2,950 (41.8) Neurology 990 (14.0) Haematology 681 (9.6) Transplant and donors 576 (8.2) Rheumatology 501 (7.1) Endocrinology 446 (6.3) Other 958 (13.4) | PE: replacement with stored liquid plasma, fresh frozen plasma, cryoprecipitate poor plasma, solvent detergent plasma – Octoplas and Octoplas LG, and hydroxyethyl starch; rate of plasma exchange??; filtration or centrifugation methods Patients n 7,142 Procedures n = 50,846 | Variable Up to 3 AEs were recorded per event, and listed in order of severity (mild, moderate, severe) | Mild AEs per 10,000 procedures (n) Moderate AEs per 10,000 procedures (n) Severe AEs per 10,000 procedures (n) AEs for Filtration vs centrifugation Change of AEs over time Anticoagulant AEs Access AEs |
| (Basic-Jukic et al. 2005) Croatia | R O SC IV Moderate | Data on PE procedures collected between 1982 and 2003 in a single dialysis centre Diagnoses n MG 247 TTP/HUS 19 | PE: 1-2 plasma volume exchange with 5% human albumin, or fresh frozen plasma Peripheral access where possible in the antecubital veins. Central access if | Not stated | AEs n (% of treatments) Complications associated with vascular access Complications associated with PE procedure |

| | | | | | |
|---|---|---|---|---|---|
| | | SLE 34<br>GBS 60<br>Rapidly progressive glomerulonephritis 16<br>Plasmacytoma 6<br>CDIP 13<br>ABO-incompatible bone marrow transplant 23<br>Poisoning 10<br>Hyperlipoproteinaemia 5<br>Hyperthyreosis 7<br>Pemphigus vulgaris 4<br>Vasculitis 4<br>Other 42 | necessary via central venous dual lumen catheters; membrane filtration method<br>Patients n = 509<br>Procedures n = 4857 | | |
| (Nieto-Aristizábal, Vivas Á, et al. 2020)<br>Columbia | R O SC<br>IV<br>Moderate | Patients receiving PE between 2011 and 2018, as prescribed by a neurologist<br>Mean age (IQR): 50(32-64) y<br>Diagnoses:<br>MG 70 (37.4%)<br>GBS 53 (28.3%)<br>NMOSD 35 (18.7%)<br>CIDP 23 (12.3%)<br>AE 6 (3.2%) | PE: anticoagulation with citrate and replacement solutions were administered in the proportions of 1:12 to 1: to 16; replacement solutions were albumin (131 patients), fresh frozen plasma (1 patient), and succinylated gelatin (45 patients); PE was by centrifugation method; catheter placement was the jugular (n = 166; 88.7%), femoral (n = 19; 9.6%) or subclavian (n = 3; 1.6%) arteries.<br>Patients n = 187<br>Cycles per patient n = 5 | Not stated | Complications in all patients n patients (%)<br>Complications per disease group |
| **Long-term safety data for steroids** | | | | | |
| (Rice et al. 2017)<br>The Netherlands | SR<br>I<br>Moderate | Articles published between 2007 and 2016<br>K = 32<br>Studies og > 40 Patients<br>Diagnoses:<br>Autoimmun diseases 31%<br>Asthma 25%<br>COPD & Lung diseases 19%<br>Multiple disease areas 10%<br>GC-induce osteoporosis 6%<br>Alcoholic hepatitis 3%<br>Allergic rhinitis 3%<br>Kidney disease 3% | Systemic corticosteroids | Long-term corticosteroid use as described in individual studies | Summary of AEs<br>Economic burden of Long-term GC |
| (Huscher et al. 2009)<br>Germany | R O SC<br>IV<br>Moderate | Data from a RA patient database; patients taking ongoing GC > 6 mo; patients with RA in the osteoporosis module<br>N = 1066<br>N = 472 patients taking GC for > 6 months | Dose categorisation:<br>< 5mg/day<br>5-7.5 mg/day<br>>7.5 mg/day | GC treatment for > 6 months | AEs<br>Dose comparison |

| | | | | | |
|---|---|---|---|---|---|
| (van Lieverloo et al. 2018) Serbia The Netherlands Italy Moderate | R MC IV Moderate | Data on from 3 large CIDP centres; Patients with treatment naïve CIDP; patients who underwent first-line treatment with corticosteroids; definite, probable or possible CIDP according to EFNS/PNS criteria. N = 125 Mean age (SD): 53.4 (16) y Median MRC cum score (range): 53 (34-60) CIDP subtype: Typical 98 (78%) Atypical 27 (22%) | Prednisone or prednisolone n = 67 (54%) Pulsed dexamethasone n = 37 (30%) Pulsed IV MP 21 (17%) | 5 years Median duration of treatment for responders (range): 6 (2-60) months | Moderate AEs SAEs |
| (Wilson, J. C. et al. 2017b) (Wilson, J. C. et al. 2017b) UK | R O SC NCC IV Moderate | Data from a UK database CPRD on all patients 50 y and older who had GCA diagnosis and at least one prednisolone prescription within 1 month of diagnosis, 3 years medical history on the CPRD | GCA n = 5011 Controls (random matched comparison group) n = 5011 | 5 years Median duration of treatment for responders (range): 6 (2-60) mo ≥ 3 years Median prednisolone duration (IQR): cases 0.8 (1.9) y; controls 1.2 (2.1) y | AEs Incidence rates per age group |
| **Long-term safety data for intravenous immunoglobulin** | | | | | |
| (Waheed et al. 2019) US | R O MC IV Moderate | Database provided by a infusion provider company; infusions provided in homes or pharmaceutical centres (outpatient setting); patients with neuromuscular disorders All patients : n = 438 CIDP = 221 Infusions all: 5867 Infusions CIDP: 3256 | IVIg | Dose analysis Number of treatment analysis Median follow-up (IQR): 21 (7-27) weeks | AEs SAEs |

Abbreviations: AE = adverse event; CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; CPRD = Clinical Practice Research Datalink; EFNS/PNS: European Federation of Neurological Societies/Peripheral Nerve Society; GC = glucocorticoids; GCA = giant cell arteritis; GBS = Guillain Barre syndrome; IQR = interquartile range; IVIg = intravenous immunoglobulin; IVMP = intravenous methyl prednisolone; MC = mulitcentre;  MG = myasthenia gravis; MRC = medical Research Council sum score; NCC = nested case-control study; O = observational study; PE = plasma exchange; R = retrospective study; SAE = serious adverse event; SC = single centre; SD = standard deviation; SLE = systemic lupus erythematosus; TTP/HUS = thrombotic thrombocytopenic purpura/haemolytic uremic syndrome;

# APPENDIX D        EXCLUDED STUDIES

**STUDIES ASSESSING THE SAFETY AND EFFECTIVENESS OF IG FOR CIDP EXCLUDED:**

## Randomised controlled trials excluded due to population not meeting inclusion criteria, outcomes not of interest, or data duplicated elsewhere

Breiner, A, Barnett Tapia, C, Lovblom, LE, Perkins, BA, Katzberg, HD & Bril, V 2019, 'Randomized, controlled crossover study of IVIg for demyelinating polyneuropathy and diabetes', Neurol Neuroimmunol Neuroinflamm, vol. 6, no. 5, Sep.

Keller, CW, Quast, I, Dalakas, MC & Lünemann, JD 2019, 'IVIG efficacy in CIDP patients is not associated with terminal complement inhibition', Journal of Neuroimmunology, vol. 330, pp. 23-27.

Lamb, YN, Syed, YY & Dhillon, S 2019, 'Immune Globulin Subcutaneous (Human) 20% (Hizentra®): A Review in Chronic Inflammatory Demyelinating Polyneuropathy', CNS Drugs, vol. 33, no. 8, pp. 831-838.

Merkies, ISJ, van Schaik, IN, Léger, JM, Bril, V, van Geloven, N, Hartung, HP, Lewis, RA, Sobue, G, Lawo, JP, Durn, BL, Cornblath, DR, De Bleecker, JL, Sommer, C, Robberecht, W, Saarela, M, Kamienowski, J, Stelmasiak, Z, Tackenberg, B & Mielke, O 2019, 'Efficacy and safety of IVIG in CIDP: Combined data of the PRIMA and PATH studies', J Peripher Nerv Syst, vol. 24, no. 1, Mar, pp. 48-55.

## Systematic Reviews excluded due to outcomes outside the scope of this review, or were included in the original DCAR 1564 Review

Michaelides, A, Hadden, RDM, Sarrigiannis, PG, Hadjivassiliou, M & Zis, P 2019, 'Pain in Chronic Inflammatory Demyelinating Polyradiculoneuropathy: A Systematic Review and Meta-Analysis', *Pain and Therapy*, vol. 8, no. 2, pp. 177-185.

Oaklander, AL & Gimigliano, F 2019, 'Are the treatments for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) effective and safe?-A Cochrane Overview summary with commentary', *NeuroRehabilitation*, vol. 44, no. 4, pp. 609-612.

Querol, L, Crabtree, M, Herepath, M, Priedane, E, Viejo Viejo, I, Agush, S & Sommerer, P 2020, 'Systematic literature review of burden of illness in chronic inflammatory demyelinating polyneuropathy (CIDP)', *Journal of Neurology*.

# APPENDIX E            DIAGNOSTIC CRITERIA FOR CIDP

## VERSION 3 CRITERIA FOR IG MANAGEMENT OF CIDP

Source: BloodStar https://www.criteria.blood.gov.au/MedicalCondition/View/2605

| Diagnosis Requirements | A diagnosis must be made by a Neurologist. |
| --- | --- |
| Qualifying Criteria for Ig Therapy | **Treatment of chronic inflammatory demyelinating polyneuropathy (CIDP) for patients in whom walking is compromised or there is significant disability**

This indication should be used to cover first line (prior to trial off) treatment of CIDP patients. For patients who have trialled off Ig therapy and subsequently relapse within six months, please use the indication **Relapse of chronic inflammatory demyelinating polyneuropathy (CIDP) patients within six months of commencement of trial off Ig therapy**

In adults or children 10 years or older

- Significant disability or compromised walking in an adult or child 10 years or older as objectively measured by an Overall Neuropathy Limitations Scale (ONLS) score of at least two points and the Medical Research Council (MRC) sum score

OR

In children less than 10 years

- Significant disability or compromised walking in a child less than 10 years as measured by the Six Minute Walk Test (6MWT) and/or a Modified Rankin Scale (MRS) score of at least two points

Review by a neurologist is required after four months of Ig therapy to determine whether the patient has responded. If there is no benefit after this period of treatment, IVIg therapy should be abandoned.

Where treatment is continued, a review by a neurologist or general physician is required each 12 months.

A trial of cessation should be considered each 12 months in patients in remission on maintenance therapy.

Once a patient has relapsed in the first six months of a trial off therapy, a further trial might be considered after at least two years.

Documentation of clinical efficacy is necessary for continuation of IVIg therapy. |
| | **Relapse of chronic inflammatory demyelinating polyneuropathy (CIDP) patients within six months of commencement of trial off Ig therapy**

This indication should be used for patients who have previously trialled off Ig therapy and subsequently relapsed within six months. For patients requiring first line therapy (i.e. prior to trial off please use the indication: **Treatment of chronic inflammatory demyelinating polyneuropathy (CIDP) for patients in whom walking is compromised or there is significant disability**

- In a previously stable adult or child (10 years or older), deterioration in disability as measured by an increase of at least one point in the Adjusted Overall Neuropathy Limitations Scale (ONLS) or a reduction in the Medical Research Council (MRC) sum score of at least three points, when compared to the review score before stopping previous treatment

  OR

- In a previously stable child (less than 10 years), deterioration in disability as measured by a reduction in the Six Minute Walk Test (6MWT) or an increase of at least one point in the Modified Rankin Scale (MRS) compared to the review score before stopping previous treatment

AND

- Relapse has occurred within six months of the last immunoglobulin dose

IVIg should be used for a maximum period of four months (induction plus three maintenance cycles) before determining whether the patient has responded. If there is no benefit after this treatment, IVIg therapy should be abandoned.

Review by a neurologist is required within four months and annually thereafter (neurologist or general physician).

Documentation of clinical efficacy is necessary for continuation of IVIg therapy.

Once a patient has relapsed when trialled off Ig treatment, a second line immunomodulatory agent should be strongly considered as additional therapy. |

## EFNS/PNS CRITERIA FOR CIDP DIAGNOSIS

Source: EFNS/PNS CIDP Guidelines. *Journal of the Peripheral Nervous System* 15:1-9. 2010 (Van den Bergh, PY et al. 2010)

**Table 1.** Electrodiagnostic criteria.

(1) Definite: at least one of the following
  (a) Motor distal latency prolongation ≥50% above ULN in two nerves (excluding median neuropathy at the wrist from carpal tunnel syndrome), or
  (b) Reduction of motor conduction velocity ≥30% below LLN in two nerves, or
  (c) Prolongation of F-wave latency ≥30% above ULN in two nerves (≥50% if amplitude of distal negative peak CMAP <80% of LLN values), or
  (d) Absence of F-waves in two nerves if these nerves have distal negative peak CMAP amplitudes ≥20% of LLN + ≥1 other demyelinating parameter[a] in ≥1 other nerve, or
  (e) Partial motor conduction block: ≥50% amplitude reduction of the proximal negative peak CMAP relative to distal, if distal negative peak CMAP ≥ 20% of LLN, in two nerves, or in one nerve + ≥1 other demyelinating parameter[a] in ≥1 other nerve, or
  (f) Abnormal temporal dispersion (>30% duration increase between the proximal and distal negative peak CMAP) in ≥2 nerves, or
  (g) Distal CMAP duration (interval between onset of the first negative peak and return to baseline of the last negative peak) increase in ≥1 nerve (median ≥ 6.6 ms, ulnar ≥ 6.7 ms, peroneal ≥ 7.6 ms, tibial ≥ 8.8 ms)[b] + ≥1 other demyelinating parameter[a] in ≥1 other nerve
(2) Probable
  ≥30% amplitude reduction of the proximal negative peak CMAP relative to distal, excluding the posterior tibial nerve, if distal negative peak CMAP ≥ 20% of LLN, in two nerves, or in one nerve + ≥1 other demyelinating parameter[a] in ≥1 other nerve
(3) Possible
  As in (1) but in only one nerve
  To apply these criteria, the median, ulnar (stimulated below the elbow), peroneal (stimulated below the fibular head), and tibial nerves on one side are tested. If criteria are not fulfilled, the same nerves are tested at the other side, and/or the ulnar and median nerves are stimulated bilaterally at the axilla and at Erb's point. Motor conduction block is not considered in the ulnar nerve across the elbow and at least 50% amplitude reduction between Erb's point and the wrist is required for probable conduction block. Temperatures should be maintained to at least 33°C at the palm and 30°C at the external malleolus (good practice points).
  CMAP, compound muscle action potential; ULN, upper limit of normal values; LLN, lower limit of normal values.

[a]Any nerve meeting any of the criteria (a–g).
[b]Isose S. *et al. (Isose et al., 2009).*

**Table 4.** Clinical diagnostic criteria.

(1) Inclusion criteria
  (a) Typical CIDP
      Chronically progressive, stepwise, or recurrent symmetric proximal and distal weakness and sensory dysfunction of all extremities, developing over at least 2 months; cranial nerves may be affected; and
      Absent or reduced tendon reflexes in all extremities
  (b) Atypical CIDP (still considered CIDP but with different features) One of the following, but otherwise as in (a) (tendon reflexes may be normal in unaffected limbs):
      Predominantly distal (distal acquired demyelinating symmetric, DADS) or
      Asymmetric [multifocal acquired demyelinating sensory and motor neuropathy (MADSAM), Lewis-Sumner syndrome] or
      Focal (e.g., involvement of the brachial or lumbosacral plexus or of one or more peripheral nerves in one upper or lower limb)
      Pure motor or
      Pure sensory (including chronic immune sensory polyradiculopathy affecting the central process of the primary sensory neuron)
(2) Exclusion criteria
  Borrelia burgdorferi infection (Lyme disease), diphtheria, drug or toxin exposure probably to have caused the neuropathy
  Hereditary demyelinating neuropathy
  Prominent sphincter disturbance
  Diagnosis of multifocal motor neuropathy
  IgM monoclonal gammopathy with high titre antibodies to myelin-associated glycoprotein
  Other causes for a demyelinating neuropathy including POEMS syndrome, osteosclerotic myeloma, diabetic and non-diabetic lumbosacral radiculoplexus neuropathy. PNS lymphoma and amyloidosis may occasionally have demyelinating features

**Table 5.** Supportive criteria.

1. Elevated CSF protein with leukocyte count <10/mm$^3$ (level A recommendation)
2. MRI showing gadolinium enhancement and/or hypertrophy of the cauda equina, lumbosacral or cervical nerve roots, or the brachial or lumbosacral plexuses (level C recommendation)
3. Abnormal sensory electrophysiology in at least one nerve (Good Practice Points):
   a. Normal sural with abnormal median (excluding median neuropathy at the wrist from carpal tunnel syndrome) or radial sensory nerve action potential (SNAP) amplitudes; or
   b. Conduction velocity <80% of lower limit of normal (<70% if SNAP amplitude <80% of lower limit of normal); or
   c. Delayed somatosensory evoked potentials without central nervous system disease
4. Objective clinical improvement following immunomodulatory treatment (level A recommendation)
5. Nerve biopsy showing unequivocal evidence of demyelination and/or remyelination by electron microscopy or teased fibre analysis (Good Practice Points)

# APPENDIX F    CLINICAL MANAGEMENT ALGORITHMS
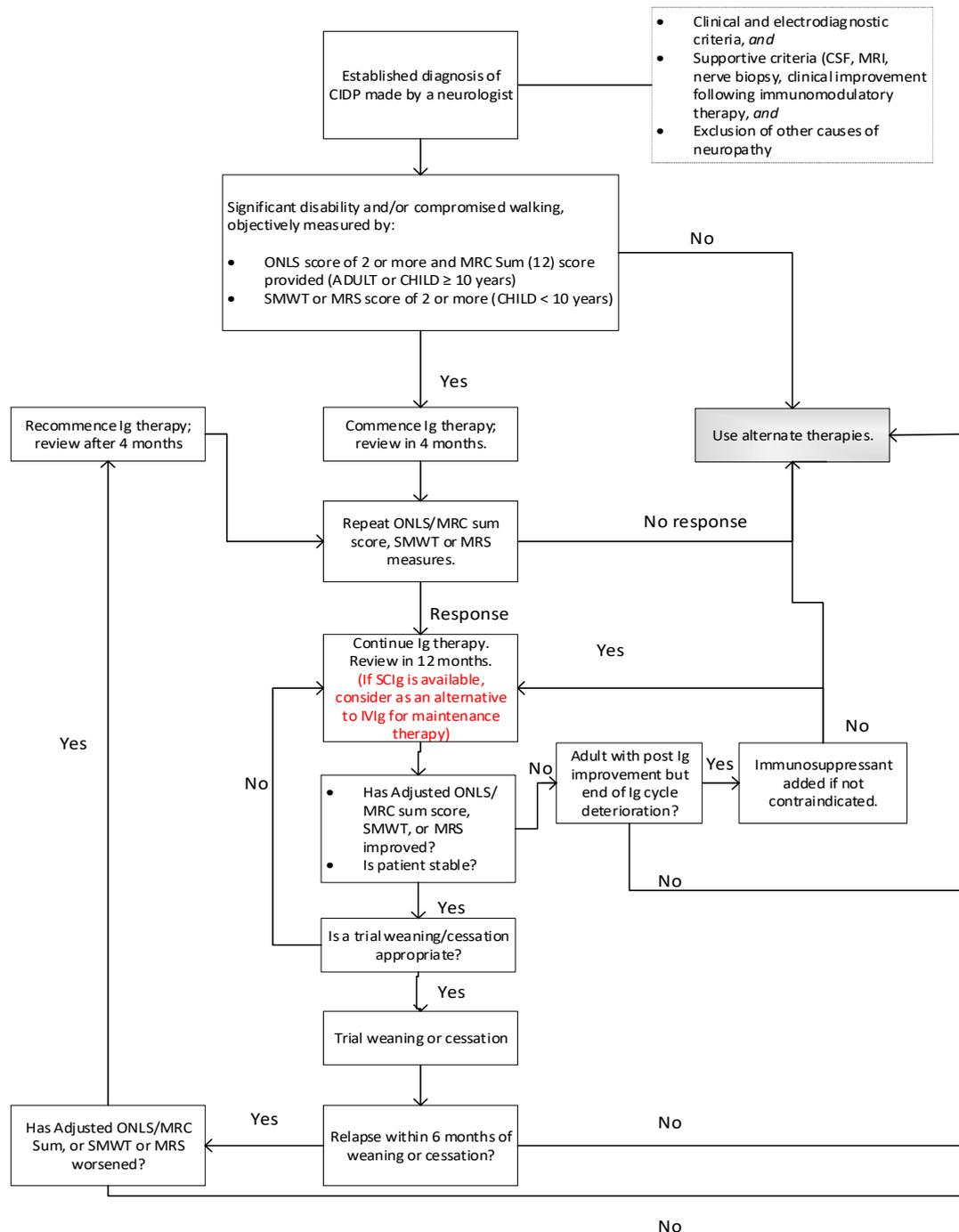


**Figure 16    Current management algorithm for CIDP patients eligible for Ig therapy**

Source: reproduced from Figure 1, page 28 and Figure 2, page 36 of the Referral Form.
Abbreviations: ONLS = Overall Neuropathy Limitations Scale, MRC = Medical Research Council, SMWT = Six-minute walking test, MRS = Modified Rankin Scale, Ig = Immunoglobulin, CIDP = Chronic inflammatory demyelinating polyneuropathy, SCIg = subcutaneous immunoglobulin.
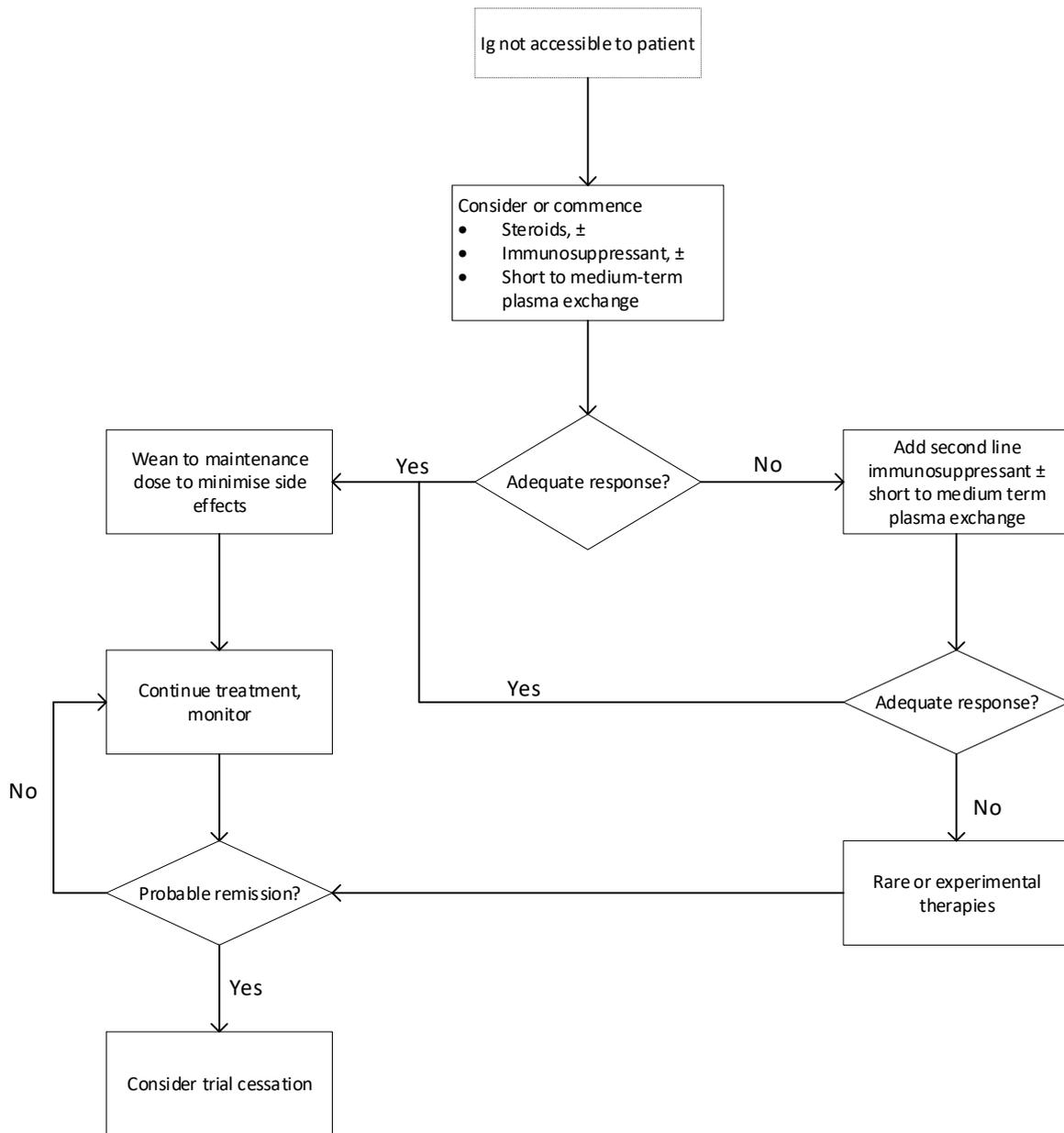
**Figure 17       Proposed algorithm for treatment of patients in the absence (or failure) of Ig.**

Source: reproduced from Figure 3 page 42 of the Referral Form.
Abbreviations: Ig = Immunoglobulin
Note: this algorithm may also be applicable for any patient not/no longer eligible for Ig under Version 3 of 'the Criteria' (i.e. reach 'use alternate therapies' stage on Figure 1), or for patients in whom Ig is contraindicated.

# APPENDIX G    ADDITIONAL INFORMATION FOR ECONOMIC EVALUATION

## DATA UPDATE FROM THE DEPARTMENT OF HEALTH

Table 78 summarises Ig use between first and second clinical review of Ig for CIDP excluding patients who switched from IVIg to SCIg, as provided by the Department of Health on 31st March 2021.

**Table 78    IVIg dose (g) supplied between first and second clinical review of Ig for CIDP, excluding patients who switched to SCIg**

| Description | N | Mean | Maximum | Minimum | Mode | Median |
|---|---|---|---|---|---|---|
| Not treated between first and second clinical review, but received treatment again more than 16 months after initiation | 4 | - | - | - | - | - |
| Ceased Ig treatment between first and second clinical review and had no treatment break | 48 | 317.58 | 1,440 | 30 | 60 | 215 |
| Ceased Ig treatment between first and second clinical review and had a treatment break | 6 | 248.7 | 380 | 140 | - | 245 |
| Received Ig after first and second clinical review without any treatment break | 89 | 773.5 | 2,400 | 190 | 455 | 635 |
| Continued beyond second clinical review (> 16 months) but had a break during this time | 37 | 525.4 | 1,820 | 75 | 200 | 420 |
| Total | 184 | | | | | |

CIDP = chronic inflammatory demyelinating polyneuropathy; Ig = immunoglobulin; IV = intravenous; N= number of patients; SCIg = subcutaneous

## DATA EXTRACTED FROM OBSERVATIONAL STUDIES

**Table 79    Summary of data extracted from the randomised controlled trials and observational studies in CIDP patients**

| Study | N | Treatment duration | Follow-up duration | Response | Remission | Relapse |
|---|---|---|---|---|---|---|
| **Immunoglobulin** | | | | | | |
| (Lopate, Pestronk & Al-Lozi 2005) | 7 | 2 g/kg over 2 days repeated every 1–6 months | Mean: 3.6 years | 6/7 (86%) | NR | NR |

| Study | N | Treatment duration | Follow-up duration | Response | Remission | Relapse |
|---|---|---|---|---|---|---|
| (Gorson et al. 2010) | 106 | IVIg and others | 6.4 years | 82% response rate<br>51% stable on treatment | 11% at least 5 years<br>31% cured/remission | NR |
| (Viala et al. 2010) | 58 | 2g/kg over 3–5 days every 4 weeks for 2 months; then the interval between two courses progressively increased by 1 week | Median follow-up of 2.9 years (1.5–16 years) | 38/58 (66%)<br>21/38 (55%) continued treatment | 18% of treated patients stopped treatment (<6 months) with no relapse during the follow-up.<br>29% of treated patients stopped treatment after mean of 15 months. (treatment not specified) | NR |
| (Hughes et al. 2008) ICE Trial | 59 | 2-g/kg loading dose followed by a 1-g/kg maintenance dose every 3 weeks, for up to 24 weeks<br>24 weeks extension phase | 24 weeks after stopping treatment | 32/59 (54.2%)<br>Response conditional cross-over period: 26/45 (57.8%) | 56% of patients who were treated with IVIg in the first 24 weeks and were re-randomised to placebo remained in remission in an extension phase of 24 weeks | 4/31 (13%) treated with IVIg in the extension phase deteriorated.<br>35% of the patients re-randomised to placebo in the extension phase had a relapse. |
| (Nobile-Orazio et al. 2012) (IMC trial) | 24 | 2g/kg every 4 weeks for 24 weeks | 24 weeks of treatment + 24 weeks of follow-up | 21/24 (88%) had response to treatment | All responders were in remission after 24 weeks treatment. 62% remained in remission for 24 weeks. | 8/21 (38%) |
| IMC extension study (Nobile-Orazio et al. 2015) | 32 | No treatment | Median of 42 months no treatment | 28/32 (87.5%) from the IMC trial | 14% | 24/28 (85.7%)<br>Median time to relapse 4.5 (1–24) months |
| (Querol et al. 2013) | 86 | 2g/kg or 1g/kg loading dose over 5 days. The IVIg dose was subsequently tailored according to patient features and clinical responses.<br>Short-term: 6 weeks<br>Mid-term: 24 weeks<br>Long-term: 48 weeks | Mean: 3.9 years | 60.5% responded at short term, 54.6% at midterm.<br>36% received only 1 course until mid-term, 23.3% did not receive additional IVIg during the study period (60% of these were in remission, 30% on other treatment, and 10% non-responders). | At long term, 22/86 (25.6%) patients were in remission, 65.1% were stable, and 9.3% were non-responders. | NR |

| Study | N | Treatment duration | Follow-up duration | Response | Remission | Relapse |
|---|---|---|---|---|---|---|
| (Kuitwaard et al. 2015) | 281 | At least one full course of IVIg (2g/kg) | Mean: 5.2 years Median 3.8 years (20 days–28 years) | Response rate: 76% (214/281). | 86/214 (40%) achieved remission (16% only needed one IVIg course) | NR |
| Kuwabara 2017 (Kuwabara et al. 2017) | 49 | Induction IVIg therapy (0.4 g/kg/day for 5 consecutive days), maintenance dose IVIg (1.0 g/kg) every 3 weeks for up to 52 weeks. | 52 weeks | At week 28, the responder rate was 77.6% (38/49 patients; 95% CI 63% to 88%), and the 38 responders continued the maintenance therapy from 28–49 weeks. | During 52 weeks, 34 (69.4%) of the 49 enrolled patients had a maintained improvement. *All of these patients were receiving treatment and therefore are not considered in remission for the purpose of this assessment.* | At week 52, 4 of the 38 (10.5%) had a relapse (95% CI 3% to 25%). |
| (Rajabally, Yusuf A. & Afzal 2019) | 47 | 2g/kg body weight for loading dose Variable maintenance dose using algorithm | 4 years | 39/47 (83%) 29/39 long-term IVIg dependent | 10/39 (25.6%) | NR |
| **Corticosteroids** | | | | | | |
| (Lopate, Pestronk & Al-Lozi 2005) | 16 | initial dose of 1g/day IVMP for 3–5 consecutive days, followed by IVMP every 2–12 weeks for up to 10 years. | Mean: 4.6 years | 13/16 (81%) | NR | NR |
| (Viala et al. 2010) | 46 | Prednisone 1 mg/kg/day for 4 weeks, followed by slowly tapered dosages | Median follow-up of 2.9 years (1.5–16 years) | 27/46 (59%) 5/27 (19%) continued treatment | 18% of treated patients stopped treatment (<6 months) with no relapse during the follow-up. 29% of treated patients stopped treatment after mean of 15 months. (Tx not specified) | NR |
| PREDICT trial (van Schaik, I. N. et al. 2010) | 40 | Dexamethasone 40 mg × 4 for 6 cycles or daily prednisolone for 32 weeks starting with 60 mg per day for 5 weeks and tapering ultimately to zero | Treatment period (weeks 1–32) and a follow-up period (weeks 33–52). | 20/40 (50%) | 16/40 (40%) Median time to remission was 20 weeks in patients treated with dexamethasone and 39 | - |

| Study | N | Treatment duration | Follow-up duration | Response | Remission | Relapse |
|-------|---|---------------------|---------------------|----------|-----------|---------|
| | | | | | weeks in those receiving prednisolone. | |
| PREDICT extension study (Eftimov et al. 2012) | 39 | Off treatment | Median (range) follow-up of 54 (9–100) months | - | 10/39 (26%) in remission | 8/16 (50%): 5/8 relapsed within a year after ceasing therapy. median time to relapse: 17.5 months for dexamethasone, 11 months for prednisolone |
| (Nobile-Orazio et al. 2012) | 21 | 2g every 4 weeks for 24 weeks | 24 weeks of treatment + 24 weeks of follow-up | 10/21 (48%) | 10/10 (100%) *Only during short-term follow-up. Most of these patients relapsed after a median follow-up of 43 months.* | 0/10 (0%) |
| (Nobile-Orazio et al. 2015) | 24 | Off treatment | Median follow-up 43 months | 13/24 (54.2%) | 23% | 10/13 (76.9%) Median time to relapse 14 (1–31) months |
| (Börü Ü et al. 2014) | 20 | 1000 mg/day for 10 days and then 1000 mg monthly for five years. | 5 years on treatment + 5 years after ceasing treatment | 15 had treatment for 5 years | - | 6/15 |
| (van Lieverloo et al. 2018) | 125 | Prednisolone, pulse dexamethasone, pulse intravenous methylprednisolone | Mean 4.5 years | 60% (95% CI 51–69%) | 61% (the probability of responders reaching 5-year remission was 55% (95% CI 44–70%), with no difference between the three groups). | 20/29 (69%) who experienced a relapse, did so in the first 6 months after treatment |
| **Plasma exchange** | | | | | | |
| (Dyck et al. 1994) | 20 | PE twice a week for 3 weeks then once a week for 3 weeks | 6 weeks | 17/20 (85%) | NR | NR |
| (Choudhary & Hughes 1995) | 33 | Most required only one course. 7 patients Seven patients received repeated courses of PE for 8.1-59.7 months | Retrospective analysis of case series | 23/33 (70%) responded well 7/23 (30%) had repeated courses | - | - |

| Study | N | Treatment duration | Follow-up duration | Response | Remission | Relapse |
|---|---|---|---|---|---|---|
| (Hahn, Bolton, Pillay, et al. 1996) | 18 | 10 PE treatments over 4 weeks | Long-term follow-up of 33.9±3.5 months available for 16 patients | 3/18 did not complete trial due to venous access or AE. 12/18 (67%) responded | All but two patients required long-term immunosuppressive drug therapy for stabilization. After 6 months, 10 patients had almost completely recovered. | 8/12 (66%) relapsed within 7–14 days after stopping PE. Long-term: 3/16 patients had relapsed |
| (Viala et al. 2010) | 21 | 6 PEs during the first month, followed by a progressive increase in the interval between two PEs | Median follow-up of 3 years (1.5–16 years) | 13/21 (62%) 3/13 (23%) continued treatment | 18% of treated patients stopped treatment (<6 months) with no relapse during the follow-up. 29% of treated patients stopped treatment after mean of 15 months. (treatment not specified) | NR |
| (Codron et al. 2017) | 11 | PE every other day for 1 week, twice a week for 2 weeks, once a week for 4 weeks, every 2 weeks for 3 weeks, and was then progressively spaced depending on the patients' response. | PE sessions per patient, median (range): 28 (10–73) | 8/11 (72.7%) responders 6/11 (54.5%) treatment dependent | 2/11 (18.2%) recovered | |
| (Lieker et al. 2017) | 10 | 6 sessions of PE in 12 days (51 sessions in total for 9 patients) | Four weeks after treatment | 4/9 (44.4%) | 4/4 (100%) stable after 4 weeks of ceasing treatment | - |

Ig = immunoglobulin; PE = plasma exchange;

**IMMUNOGLOBULIN (IG) COSTS**

**Table 80        Estimation of Ig costs***

| 2017/18 Ig Report | Price in $(million) | Grams (weight,%) | Price/gram in $ | Reference to Ig report (Milverton et al. 2019) section |
|---|---|---|---|---|
| Domestic IVIg including plasma fractionation (excluding hyperimmune plasma) Intragam P* Intragam 10 | 443.2 | 3,161,673 (51.6%) | 140.18 | Calculation required for cost: Plasma fractionation costs of $252.2M (expenditure section) + total domestic product cost of $195M (Table 6) – Evogam product cost of $4M (Table 6) = $443.2M<br><br>Calculation for grams: Total domestic grams 3,225,722 (Table 6) – Evogam grams 64,049 = 3,161,673 |
| Domestic IVIg excluding plasma fractionation Intragam P* Intragam 10 | 191 | 3,161,673 (51.6%) | 60.41 | Table 6:<br>Calculation for price: Total domestic price – Evogam price<br>Calculation for grams: Total domestic grams – Evogam grams |
| Imported IVIg Flebogamma Privigen | 124 | 2,759,266 (45.0%) | 44.94 | Table 6:<br>Calculation for price: Total imported price – Hizentra price<br>Calculation for grams: Total imported grams – Hizentra grams |
| SCIg domestic Evogam | 4 | 64,049 (1.0%) | 62.45 | Table 6 |
| SCIg imported Hizentra | 8 | 143,729 (2.3%) | 55.66 | Table 6 |
| Total domestic Ig grams | | 3,225,722 | | Expenditure |
| Total imported Ig grams | | 2,902,995 | | Expenditure |

Ig = immunoglobulin; IVIg = intravenous immunoglobulin; SCIg = subcutaneous immunoglobulin.
Source: *This table is adapted from MSAC 1566 report (Milverton et al. 2019) as advised by the Department, data were provided by NBA (NBA 2018)

**RESOURCE USE AND COSTS ASSOCIATED WITH LONG-TERM VASCULAR ACCESS**

**Table 81        Resource use and costs associated with vascular access**

| Resource | Unit price | Source |
|---|---|---|
| Placement/replacement of an AV fistulae | $10,508 | Weighted cost of AR-DRG F14B and F14C (IHPA 2021) |
| Placement/replacement of an apheresis compatible port-a-cath or CVC for long-term use | | |
| Port-a-cath | $267.00 | November 2020 Prostheses List A,a 10.09.03, TX054 + |
| PICC line | $183.00 | November 2020 Prostheses List A,a 10.09.02, TX035 |
| Medical fee | $231.00 | MBS 13318 (CVC/PICC insertion) + |
| Day surgery | $497.20 | same-day surgery facility accommodation (PR420) + |
| Operating theatre cost | $479.80 | Theatre fees (PRT01) |

| Resource | Unit price | Source |
|---|---|---|
| Placement/replacement, Port-a-cath | $1,475.00 | Sum of costs for port-a-cath, medical fee, day surgery and operating theatre cost |
| Placement/replacement, PICC line | $1,391.00 | Sum of costs for PICC line, medical fee, day surgery and operating theatre cost |

Source: Resource required for vascular access were sourced from MSAC 1566 report (Milverton et al. 2019).
AR-DRG = Australian Refined Diagnosis Related Groups; AV = arteriovenous; CVC = central venous catheter; MBS = Medicare Benefits Schedule; PICC= peripherally inserted central catheter

**Table 82     Estimated vascular access use and associated costs in patients treated with IVIg or PE**

| Delivery mode | IVIg | PE |
|---|---|---|
| *Initial access in first 4–6 months of treatment* | | |
| Peripheral IV access | 90% | 50% |
| PICC line ($1,391 per placement) | 1% | 50% |
| Port-a-cath ($1,475 per placement) | 9% | 0 |
| AV fistulae ($10,508 per placement) | 0% | 0% |
| **Total cost per patient** | $146.66 | $737.50 |
| *Chronic vascular access >6 months on treatment* | | |
| Peripheral IV access | 80% | 70% |
| PICC line ($1,391 per placement) | 1% | 19% |
| Port-a-cath ($1,475 per placement) | 19% | 1% |
| AV fistulae ($10,508 per placement) | 0 | 10% |
| **Total cost per patient** | $294.16 | $1,345.84 |

Source: Estimates provided by clinical expert (Department of Health 2021a); Costs estimated in Table 81 for each delivery mode.
Peripheral access has no additional surgery or device costs associated.
AV = arteriovenous; CVC = central venous catheter; PE = plasma exchange; PICC= peripherally inserted central catheter

## COSTS ASSOCIATED WITH MANAGING ADVERSE EVENTS

### OSTEOPOROSIS

**Table 83     Estimated costs for managing osteoporosis**

| Description | Cost | Source | Units per year | Cost per item |
|---|---|---|---|---|
| GP visits | $38.75 | MBS 23 | 2.5 | $96.88 |
| Pathology tests - liver and renal function | $17.70 | MBS 66512 | 2 | $35.40 |
| Pathology tests - Blood examination | $16.95 | MBS 65070 | 2 | $33.90 |
| Vitamin D | $30.05 | MBS 66833 | 1 | $30.05 |
| DXA scan | $105.60 | MBS 12312 (once every three years) | 0.33 | $34.85 |
| Denosumab + Calcium + Vitamin D | $641.79 | PBS 5457F, 11726E, Vit D | 1 | $641.79 |

| Description | Cost | Source | Units per year | Cost per item |
|---|---|---|---|---|
| Denosumab | $277.58 | PBS 5457F (denosumab 60 mg/mL injection, 1 mL syringe, once every 6 months) | 2 | $555.16 |
| Calcium supplement | $27.88 | PBS 11726E (calcium carbonate 1.25g, calcium 500mg, 240 tablets; 2 tablets /day | 3.04 | $84.80 |
| Vitamin D | $10.99 | https://www.chemistwarehouse.com.au/buy/51650/ostelin-vitamin-d3-1000iu---vitamin-d---60-capsules; 1 tablet/day | 6 | $1.83 |
| Total cost | | | | $872.87 |

DXA = dual-energy X-ray absorptiometry; GP = General Practitioner; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Schedule

## SEVERE INFECTIONS

**Table 84       Estimated costs for managing severe infections**

| Code | AR-DRG description | Separations | Cost | Weight |
|---|---|---|---|---|
| E62A | Respiratory Infections and Inflammations, Major Complexity | 41,621 | $9,144 | 0.328 |
| E62B | Respiratory Infections and Inflammations, Minor Complexity | 44,435 | $3,866 | 0.350 |
| I64A | Osteomyelitis, Major Complexity | 1,851 | $18,314 | 0.015 |
| I64B | Osteomyelitis, Minor Complexity | 3,048 | $6,340 | 0.024 |
| T60A | Septicaemia, Major Complexity | 5,687 | $27,828 | 0.045 |
| T60B | Septicaemia, Intermediate Complexity | 11,928 | $13,010 | 0.094 |
| T60C | Septicaemia, Minor Complexity | 13,810 | $6,516 | 0.109 |
| B72A | Nervous System Infection Except Viral Meningitis, Major Complexity | 1,938 | $21,353 | 0.015 |
| B72B | Nervous System Infection Except Viral Meningitis, Minor Complexity | 2,486 | $4,802 | 0.020 |
| | Weighted cost per event of severe infection | | $8,378 | |

AR-DRG = Australian Refined Diagnosis Related Groups

## COSTS ASSOCIATED WITH ADVERSE EVENTS PER PROCEDURE FOR PLASMA EXCHANGE

**Table 85       Costs associated with adverse events per procedure for Plasma Exchange**

| Adverse event | Number of events per procedure | Unit price | AE cost per procedure | Source (AR-DRG codes) |
|---|---|---|---|---|
| Hypotension, Syncope | 0.11% | $3,121 | $3.43 | F73, Syncope |
| Urticaria | 0.06% | $1,214 | $0.73 | X61, Allergic reactions |
| Fever, chills | 0.03% | $4,369 | $1.31 | T62, fever of unknown origin |
| Nausea vomiting | 0.02% | - | $0.00 | Not costed |
| Access problem | 0.02% | $5,268 | $1.05 | F65, Peripheral vascular disorders |
| Flush | 0.02% | - | $0.00 | Not costed |
| Tingling, stitching | 0.02% | | $0.00 | Not costed |
| Arrhythmia | 0.02% | $3,379 | $0.68 | F76, Arrhythmia |
| Bronchospasm | 0.01% | $6,419 | $0.64 | E62, Respiratory infections and inflammations |
| Quincke oedema | 0.01% | $1,214 | $0.12 | X61, Allergic reactions |
| Anaphylactic reaction | 0.002% | $1,214 | $0.02 | X61, Allergic reactions |
| TRALI chest pain, chest pain | 0.004% | $1,066 | $0.04 | F74, chest pain |

| Adverse event | Number of events per procedure | Unit price | AE cost per procedure | Source (AR-DRG codes) |
|---|---|---|---|---|
| GI bleeding | 0.002% | $5,698 | $0.11 | G61 GI Haemorrhage |
| Hypertension | 0.004% | $2,655 | $0.11 | F67, Hypertension |
| AE to drug | 0.002% | $1,214 | $0.02 | X61, Allergic reactions |
| **Total** | | | **$8.28** | **Sum of all AE costs per procedure** |

Source: Table 18 and (Mörtzell Henriksson et al. 2016). Costs sourced from IHPA cost reports (IHPA 2021)
AE = adverse event; AR-DRG = Australian Refined Diagnosis Related Groups; IHPA = the Independent Hospital Pricing Authority

## MARKOV TRACES FOR MODELLED ANALYSES

**Figure 18      Markov model traces, Ig arm**
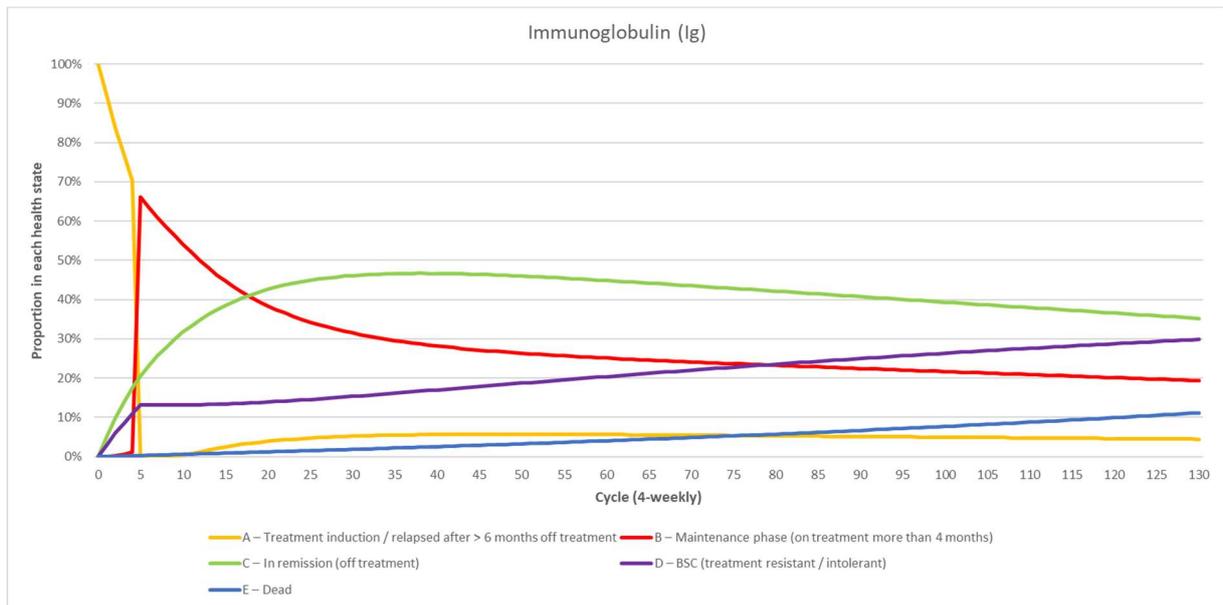
**Figure 19        Markov model traces, corticosteroids arm**



Figure: Corticosteroids — Markov model trace. X-axis: Cycle (4-weekly), 0 to 130. Y-axis: Proportion in each health state, 0% to 100%.

Legend:
A – Treatment induction / relapsed after > 6 months off treatment
B – Maintenance phase (on treatment more than 4 months)
C – In remission (off treatment)
D – BSC (treatment resistant / intolerant)
E – Dead
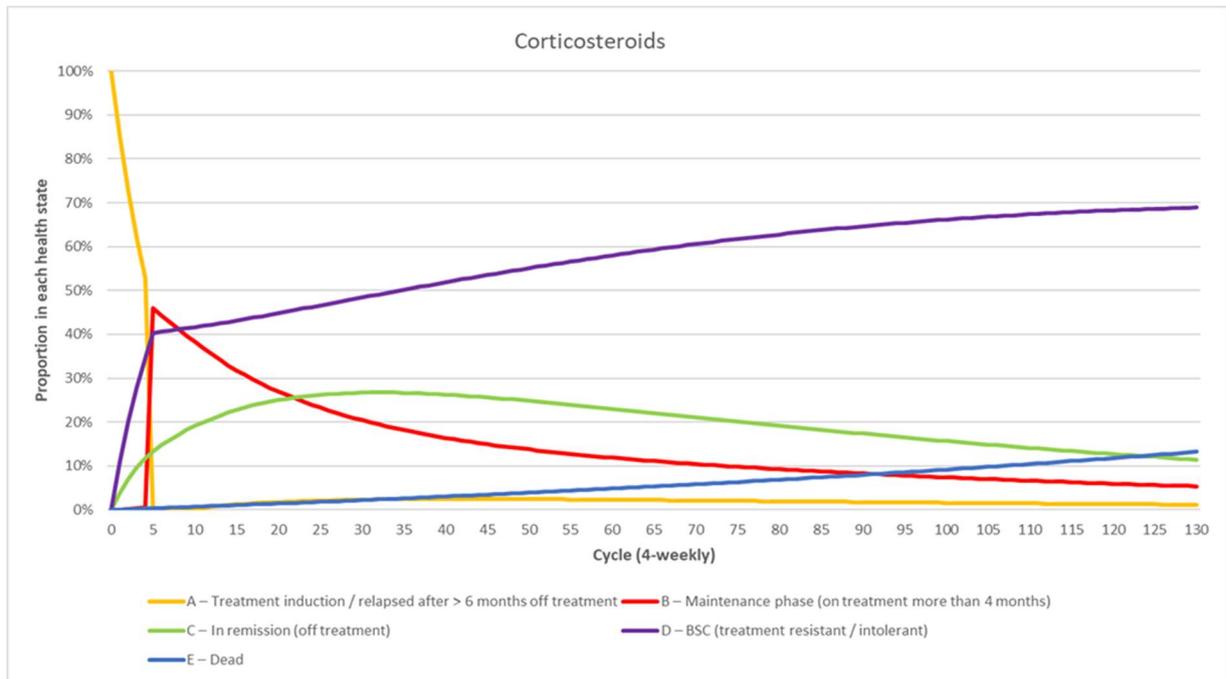
**Figure 20        Markov model traces, plasma exchange arm**



Figure: Plasma exchange therapy (PE) — Markov model trace. X-axis: Cycle (4-weekly), 0 to 130. Y-axis: Proportion in each health state, 0% to 100%.

Legend:
A – Treatment induction / relapsed after > 6 months off treatment
B – Maintenance phase (on treatment more than 4 months)
C – In remission (off treatment)
D – BSC (treatment resistant / intolerant)
E – Dead

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**Figure 21    Markov model traces, best supportive care arm**
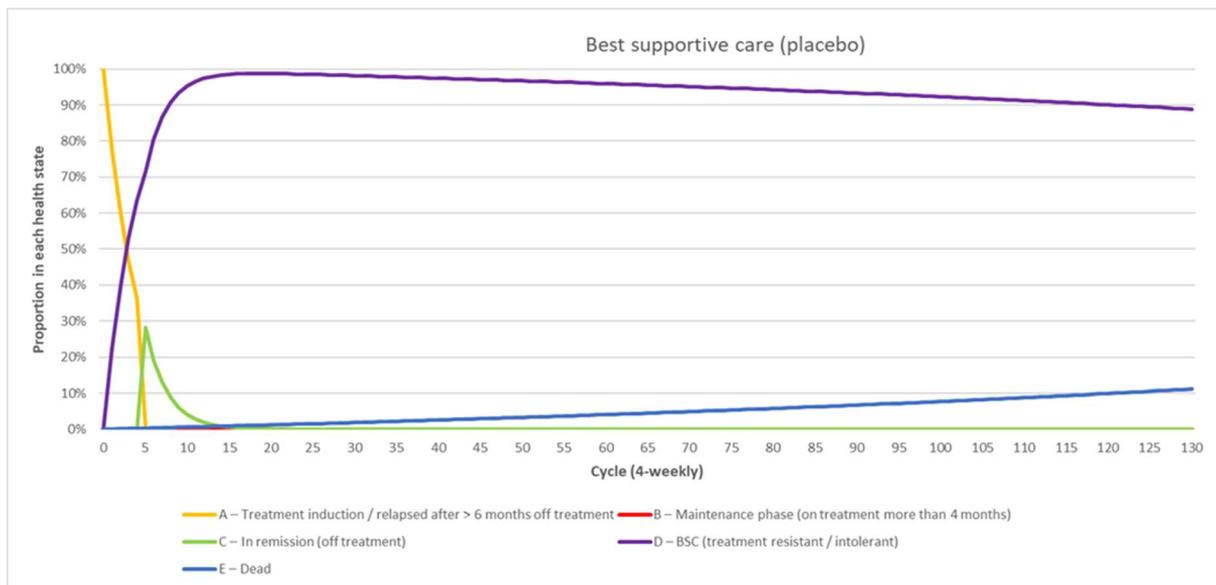


### SENSITIVITY ANALYSIS

#### IG VERSUS CORTICOSTEROIDS

**Table 86    Sensitivity analyses, Ig versus corticosteroids**

| | Inc. cost | Inc. QALYs | ICER | %Change |
|---|---|---|---|---|
| **Cost per gram of Ig** | | | | |
| **Base case (domestic IVIg, excluding cost of plasma), $60.41 per gram of Ig** | **$137,443** | **1.1840** | **$116,088** | |
| High cost (domestic IVIg, including cost of plasma), $140.18 per gram of Ig | $310,795 | 1.1840 | $262,505 | 126% |
| Low cost (imported IVIg), $44.94 per gram of Ig | $103,825 | 1.1840 | $87,693 | -24% |
| weighted average across all indications, $94.51 per gram of Ig | $211,540 | 1.1840 | $178,672 | 54% |
| **Maintenance dose intervals for Ig (base case: 4 weeks)** | | | | |
| 3 weeks | $184,329 | 1.1772 | $156,582 | 35% |
| 6 weeks | $90,558 | 1.1907 | $76,053 | -34% |
| 8 weeks | $67,115 | 1.1941 | $56,206 | -52% |
| **Maintenance IVIg dose per treatment course (base case: 0.7g/kg)** | | | | |
| 0.4 g/kg | $87,628 | 1.1840 | $74,013 | -36% |
| 1.0 g/kg | $187,259 | 1.1840 | $158,163 | 36% |
| **Weaning off trial for Ig** | | | | |
| Starting dose in maintenance phase- 1g/kg, then applying 20% dose reduction for 5 cycles | $100,559 | 1.1840 | $84,934 | -27% |
| **Utility gain with Ig (base case:0.12)** | | | | |
| 0.06 | $137,443 | 1.0139 | $135,553 | 17% |
| 0.18 | $137,443 | 1.3540 | $101,511 | -13% |
| **Discount rate (base-case: 5%)** | | | | |

| | Inc. cost | Inc. QALYs | ICER | %Change |
|---|---|---|---|---|
| 0% (undiscounted) | $167,350 | 1.4894 | $112,361 | -3% |
| 3% | $148,162 | 1.2930 | $114,592 | -1% |
| **Modelled time horizon (base case: 10 years)** | | | | |
| 1 year | $31,109 | 0.1616 | $192,522 | 66% |
| 3 years | $64,521 | 0.4355 | $148,140 | 28% |
| 5 years | $90,108 | 0.6766 | $133,184 | 15% |
| 7 years | $111,571 | 0.8960 | $124,520 | 7% |
| **Demographics** | | | | |
| Mean patient weight, base-case 78 Kg | | | | |
| Mean patient weight - 83.62 Kg (BloodStar summary data) | $146,902 | 1.1840 | $124,077 | 7% |
| Mean patient age (base case: 65 years) | | | | |
| 50 years | $141,071 | 1.2553 | $112,379 | -3% |
| 55 years | $140,306 | 1.2365 | $113,473 | -2% |
| 60 years | $139,154 | 1.2110 | $114,908 | -1% |
| **Administration costs per infusion (base case: $693)** | | | | |
| $371 (used in the previous DCAR) | $132,362 | 1.1840 | $111,796 | -4% |
| $200 | $129,664 | 1.1840 | $109,517 | -6% |
| $400 | $132,820 | 1.1840 | $112,183 | -3% |
| $500 | $134,398 | 1.1840 | $113,515 | -2% |
| **Health state transitions, Ig** | | | | |
| Treatment failure (base case: 3.1% per cycle in State A) | | | | |
| 8.72% per cycle in State A | $85,422 | 0.6167 | $138,524 | 19% |
| Proportion of patients relapsing in remission health state (base case: 3.8%) | | | | |
| 1.50% | $91,384 | 1.3294 | $68,740 | -41% |
| 4.12% | $143,085 | 1.1689 | $122,414 | 5% |
| Treatment to in remission - off treatment health state (base case: 5.3%) | | | | |
| 0.57% | $276,595 | 1.0566 | $261,775 | 125% |
| 1.03% | $252,055 | 1.0763 | $234,185 | 102% |
| 3.66% | $166,243 | 1.1522 | $144,284 | 24% |
| 6.12% | $125,859 | 1.1987 | $104,994 | -10% |
| Severe adverse event (base case: 1.02%) | | | | |
| 0.03% | $149,537 | 1.3136 | $113,839 | -2% |
| **Health state transitions, steroids** | | | | |
| Treatment failure (base case: 10.5% per cycle in State A) | | | | |
| 4.7% per cycle in State A | $129,407 | 0.9178 | $140,995 | 21% |
| Proportion of patients relapsing in remission health state (base case: 3.1%) | | | | |
| 4.93% | $135,423 | 1.2915 | $104,861 | -10% |
| Treatment to in remission - off treatment health state (base case: 3.85%) | | | | |

| | Inc. cost | Inc. QALYs | ICER | %Change |
|---|---|---|---|---|
| 0.56% | $127,179 | 1.4804 | $85,909 | -26% |
| 1.93% | $132,908 | 1.3236 | $100,414 | -14% |
| 5.78% | $140,060 | 1.0883 | $128,696 | 11% |
| **Relative risk of death with steroids use (base case: RR = 1.2)** | | | | |
| No excess risk with steroids use, RR = 1 | $137,273 | 1.1474 | $119,641 | 3% |
| **Induction phase loading treatment episodes (base case: 5)** | | | | |
| 7 | $136,003 | 1.1851 | $114,762 | -1% |
| **AE associated with chronic use of steroids based on cumulative dose (base case: 0.003 and 0.004)** | | | | |
| No excess risk of AE based on higher cumulative doses of steroids | $134,919 | 1.0592 | $127,378 | 10% |
| **Utility gain/loss with steroids use (base case: –0.003165)** | | | | |
| No associated disutility with steroids use | $137,443 | 1.0821 | $127,014 | 9% |
| Disutility applied only when on steroids treatment (no disutility applied after stopping treatment) | $137,443 | 1.1557 | $118,930 | 2% |
| Utility gain of 0.06 with steroids use | $137,443 | 0.9882 | $139,082 | 20% |

Ig = immunoglobulin; ICER = incremental cost-effectiveness ratio; Ig = immunoglobulin; Inc = Incremental; IV = intravenous; kg = kilograms; QALY = quality-adjusted life years

## IG VERSUS PLASMA EXCHANGE

**Table 87        Sensitivity analyses, Ig versus plasma exchange**

| | Inc. cost | Inc. QALYs | ICER | %Change |
|---|---|---|---|---|
| **Cost per gram of Ig** | | | | |
| **Base case (domestic IVIg, excluding cost of plasma), $60.41 per gram of Ig** | **$49,991** | **0.5316** | **$94,038** | |
| High cost (domestic IVIg, including cost of plasma), $140.18 per gram of Ig | $223,343 | 0.5316 | $420,129 | 347% |
| Low cost (imported IVIg), $44.94 per gram of Ig | $16,373 | 0.5316 | $30,799 | -67% |
| weighted average across all indications, $94.51 per gram of Ig | $124,088 | 0.5316 | $233,422 | 148% |
| **Maintenance dose intervals for Ig (base case: 4 weeks)** | | | | |
| 3 weeks | $96,877 | 0.5249 | $184,579 | 96% |
| 6 weeks | $3,106 | 0.5384 | $5,769 | -94% |
| 8 weeks | -$20,337 | 0.5417 | Dominant (ICER: –$37,541) | Dominant (ICER: –$37,541) |
| **Maintenance IVIg dose per treatment course (base case: 0.7g/kg)** | | | | |
| 0.4 g/kg | $176 | 0.5316 | $331 | -100% |
| 1.0 g/kg | $99,807 | 0.5316 | $187,745 | 100% |
| **Weaning off trial for Ig** | | | | |
| Starting dose in maintenance phase- 1g/kg, then applying 20% dose reduction for 5 cycles | $13,107 | 0.5316 | $24,656 | -74% |
| **Utility gain with Ig (base case:0.12)** | | | | |
| 0.06 | $49,991 | 0.3616 | $138,253 | 47% |

| | Inc. cost | Inc. QALYs | ICER | %Change |
|---|---|---|---|---|
| 0.18 | $49,991 | 0.7016 | $71,251 | -24% |
| **Discount rate (base-case: 5%)** | | | | |
| 0% (undiscounted) | $65,011 | 0.7050 | $92,216 | -2% |
| 3% | $55,327 | 0.5931 | $93,291 | -1% |
| **Modelled time horizon (base case: 10 years)** | | | | |
| 1 year | $3,590 | 0.0164 | $218,409 | 132% |
| 3 years | $12,974 | 0.1025 | $126,578 | 35% |
| 5 years | $23,719 | 0.2203 | $107,657 | 14% |
| 7 years | $34,600 | 0.3472 | $99,650 | 6% |
| **Demographics** | | | | |
| Mean patient weight, base-case 78 Kg | | | | |
| Mean patient weight - 83.62 Kg (BloodStar summary data) | $57,852 | 0.5316 | $108,825 | 16% |
| Mean patient age (base case: 65 years) | | | | |
| 50 years | $51,895 | 0.5893 | $88,057 | -6% |
| 55 years | $51,492 | 0.5738 | $89,744 | -5% |
| 60 years | $50,891 | 0.5543 | $91,819 | -2% |
| **Administration costs per infusion (base case: $693)** | | | | |
| $371 (used in the previous DCAR) | $37,102 | 0.5316 | $69,792 | -26% |
| $200 | $30,257 | 0.5316 | $56,916 | -39% |
| $400 | $38,263 | 0.5316 | $71,976 | -23% |
| $500 | $42,266 | 0.5316 | $79,506 | -15% |
| **Health state transitions, Ig** | | | | |
| Treatment failure (base case: 3.1% per cycle in State A) | | | | |
| 8.72% per cycle in State A | -$2,030 | -0.0357 | Less costly, less effective (ICER: $56,869) | Less costly, less effective (ICER: $56,869) |
| Proportion of patients relapsing in remission health state (base case: 3.8%) | | | | |
| 1.50% | $3,932 | 0.6771 | $5,807 | -94% |
| 4.12% | $55,633 | 0.5165 | $107,710 | 15% |
| Treatment to in remission - off treatment health state (base case: 5.3%) | | | | |
| 0.57% | $189,143 | 0.4043 | $467,878 | 398% |
| 1.03% | $164,603 | 0.4240 | $388,257 | 313% |
| 3.66% | $78,791 | 0.4998 | $157,633 | 68% |
| 6.12% | $38,407 | 0.5464 | $70,294 | -25% |
| Severe adverse event (base case: 1.02%) | | | | |
| 0.03% | $62,085 | 0.6612 | $93,893 | 0% |
| **Health state transitions, PE** | | | | |
| Treatment failure in State A (base case: 3.77%) | | | | |

| | Inc. cost | Inc. QALYs | ICER | %Change |
|---|---|---|---|---|
| 2.73% | $42,102 | 0.4434 | $94,950 | 1% |
| 9.38% | $82,841 | 0.9031 | $91,725 | -2% |
| **AE per PE procedure (base case: 1.68%)** | | | | |
| 0.10% | -$6,561 | -0.0702 | Less costly, less effective (ICER: $93,483) | Less costly, less effective (ICER: $93,483) |
| 0.84% | $24,815 | 0.2609 | $95,119 | 1% |
| Proportion of patients relapsing in remission health state (base case: 3.8%) | | | | |
| 0.015 | $75,651 | 0.3025 | $250,127 | 166% |
| 0.0412 | $47,237 | 0.5571 | $84,795 | -10% |
| Treatment to in remission - off treatment health state (base case: 2.09%) | | | | |
| 0.57% | $6,747 | 0.9414 | $7,167 | -92% |
| 6.12% | $54,845 | 0.4826 | $113,655 | 21% |
| **Induction phase, number of exchanges for loading treatment (base case: 7)** | | | | |
| 5 | $55,150 | 0.5298 | $104,092 | 11% |
| 10 | $42,254 | 0.5343 | $79,084 | -16% |
| **Number of exchanges per maintenance treatment (base case: 1.5)** | | | | |
| 1 | $73,833 | 0.5233 | $141,078 | 50% |
| 2 | $26,150 | 0.5399 | $48,437 | -48% |
| **Plasma volume exchanged per treatment course (base case: 45 ml/kg)** | | | | |
| 40 ml/kg | $50,488 | 0.5316 | $94,973 | 1% |
| 50 ml/kg | $49,495 | 0.5316 | $93,104 | -1% |
| **Plasmapheresis administration cost (base case: $1,477)** | | | | |
| $738 | $83,317 | 0.5316 | $156,726 | 67% |
| **Utility gain with PE therapy (base case: 0.12)** | | | | |
| 0.0 | $49,991 | 0.7654 | $65,316 | -31% |
| 0.06 | $49,991 | 0.6485 | $77,089 | -18% |
| 0.18 | $49,991 | 0.6485 | $77,089 | -18% |

Ig = immunoglobulin; ICER = incremental cost-effectiveness ratio; Ig = immunoglobulin; Inc = Incremental; IV = intravenous; kg = kilograms; QALY = quality-adjusted life years

**IG VERSUS PLACEBO**

Table 88        Sensitivity analyses, Ig versus best supportive care

| | Inc. cost | Inc. QALYs | ICER | %Change |
|---|---|---|---|---|
| **Cost per gram of Ig** | | | | |

| | Inc. cost | Inc. QALYs | ICER | %Change |
|---|---|---|---|---|
| **Base case (domestic IVIg, excluding cost of plasma), $60.41 per gram of Ig** | **$159,573** | **1.7162** | **$92,983** | |
| High cost (domestic IVIg, including cost of plasma), $140.18 per gram of Ig | $332,925 | 1.7162 | $193,995 | 109% |
| Low cost (imported IVIg), $44.94 per gram of Ig | $125,954 | 1.7162 | $73,393 | -21% |
| weighted average across all indications, $94.51 per gram of Ig | $233,670 | 1.7162 | $136,159 | 46% |
| **Maintenance dose intervals for Ig (base case: 4 weeks)** | | | | |
| 3 weeks | $206,458 | 1.7094 | $120,778 | 30% |
| 6 weeks | $112,687 | 1.7229 | $65,405 | -30% |
| 8 weeks | $89,244 | 1.7263 | $51,697 | -44% |
| **Maintenance IVIg dose per treatment course (base case: 0.7g/kg)** | | | | |
| 0.4 g/kg | $109,757 | 1.7162 | $63,955 | -31% |
| 1.0 g/kg | $209,388 | 1.7162 | $122,010 | 31% |
| **Weaning off trial for Ig** | | | | |
| Starting dose in maintenance phase- 1g/kg, then applying 20% dose reduction for 5 cycles | $122,688 | 1.7162 | $71,490 | -23% |
| **Utility gain with Ig (base case:0.12)** | | | | |
| 0.06 | $159,573 | 1.5461 | $103,207 | 11% |
| 0.18 | $159,573 | 1.8862 | $84,601 | -9% |
| **Discount rate (base-case: 5%)** | | | | |
| 0% (undiscounted) | $193,257 | 2.1473 | $90,000 | -3% |
| 3% | $171,656 | 1.8706 | $91,767 | -1% |
| **Modelled time horizon (base case: 10 years)** | | | | |
| 1 year | $38,138 | 0.1878 | $203,117 | 118% |
| 3 years | $77,476 | 0.6408 | $120,906 | 30% |
| 5 years | $106,839 | 1.0259 | $104,145 | 12% |
| 7 years | $130,976 | 1.3438 | $97,465 | 5% |
| **Demographics** | | | | |
| Mean patient weight, base-case 78 Kg | | | | |
| Mean patient weight - 83.62 Kg (BloodStar summary data) | $169,031 | 1.7162 | $98,494 | 6% |
| Mean patient age (base case: 65 years) | | | | |
| 50 years | $163,800 | 1.8870 | $86,803 | -7% |
| 55 years | $162,908 | 1.8445 | $88,322 | -5% |
| 60 years | $161,564 | 1.7840 | $90,562 | -3% |
| **Administration costs per infusion (base case: $693)** | | | | |
| $371 (used in the previous DCAR) | $146,683 | 1.7162 | $85,472 | -8% |
| $200 | $139,838 | 1.7162 | $81,483 | -12% |
| $400 | $147,844 | 1.7162 | $86,148 | -7% |
| $500 | $151,847 | 1.7162 | $88,481 | -5% |
| **Health state transitions, Ig** | | | | |
| Treatment failure (base case: 3.1% per cycle in State A) | | | | |

| | Inc. cost | Inc. QALYs | ICER | %Change |
|---|---|---|---|---|
| 8.72% per cycle in State A | $107,551 | 1.1488 | $93,616 | 1% |
| Proportion of patients relapsing in remission health state (base case: 3.8%) | | | | |
| 1.50% | $113,513 | 1.8616 | $60,976 | -34% |
| 4.12% | $165,214 | 1.7011 | $97,125 | 4% |
| **Treatment to in remission - off treatment health state (base case: 5.3%)** | | | | |
| 0.57% | $298,724 | 1.5888 | $188,018 | 102% |
| 1.03% | $274,184 | 1.6085 | $170,459 | 83% |
| 3.66% | $188,373 | 1.6844 | $111,834 | 20% |
| 6.12% | $147,988 | 1.7309 | $85,497 | -8% |
| **Severe adverse event (base case: 1.02%)** | | | | |
| 0.03% | $171,666 | 1.8458 | $93,005 | 0% |

Ig = immunoglobulin; ICER = incremental cost-effectiveness ratio; Ig = immunoglobulin; Inc = Incremental; IV = intravenous; kg = kilograms; QALY = quality-adjusted life years

# APPENDIX H       FINANCIAL IMPLICATIONS APPENDIX

**IDENTIFICATION, ESTIMATION AND REDUCTION OF UNCERTAINTY**

**Table 89       Estimation of the average weighted cost per gram within the CIDP indications**

|  | Usage (grams) | Proportion of use | Cost per gram |
|---|---|---|---|
| Domestic IVIg | 418,630 | 28% | $140.18 |
| Imported IVIg | 1,041,822 | 70% | $44.94 |
| Domestic SCIg | - | 0% | $62.45 |
| Imported SCIg | 33,996 | 2% | $55.66 |
| **Weighted price** |  |  | **$71.86** |

CIDP = chronic inflammatory demyelinating polyneuropathy; Ig = immunoglobulin; IVIg = intravenous immunoglobulin; SCIg = subcutaneous immunoglobulin.
Source: 'NBA Ig use' worksheet in the 'HTA Data December 2020.xlsx' workbook.

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