Immunoglobulin therapy for Myasthenia Gravis

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

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

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EXECUTIVE SUMMARY

Main issues for MSAC consideration

- *Overall the evidence was of poor quality. Several relevant RCTs were identified but they were generally in small populations. Lower level evidence was likely to be confounded by the preference to use PE over IVIg in patients who were sicker, and other baseline patient characteristics.*

- *IVIg is usually given when other treatments (including PE) are no longer effective. By denying IVIg for MG patients, access to another treatment option is denied, which may be a matter of life and death.*

- *Access to PE is limited for patients in Australia, particularly those outside major metropolitan hospitals and in some cases IVIg may be given instead of PE due to access issues.*

- *Pending RCTs comparing IVIg with placebo in patients also using other medications may provide evidence on the incremental safety and effectiveness of IVIg (NCT02473952 Indication 3 and NCT02413580 Iindication 1)*

Indication 1

- *There are adverse events associated with both PE and IVIg, although there was evidence that the frequency of events is lower with IVIg for patients in crisis (*Criteria V3 *Indication 1).*

- *The economic implications of the 'adverse events avoided' in patients who receive IVIg for MG crisis (*Criteria V3 *Indication 1) are based on a small comparative study; it is unknown whether the estimates accurately represent what would occur across a large population where a broader adverse event profile may be expected.*

- *The cost-effectiveness of IVIg for Indication 1 is dependent on the modelling of PE-associated sepsis with long-term outcomes (mortality and morbidity); this reduces the ICER from over $7 million/QALY to $45,776/QALY.*

Indication 2

- *For patients preparing for surgery (*Criteria V3 *Indication 2) the evidence was underpowered or too low quality to determine any differences between IVIg and PE on safety or effectiveness.*

Main issues for MSAC consideration

- *The cost analysis of surgery or pharmaceutical treatments as comparators to IVIg (*Criteria V3 *Indication 3) cannot be interpreted with an assumption of equivalent safety or effectiveness.*

Indication 3

- *For patients requiring a change in maintenance therapy (*Criteria V3 *Indication 3) there was no evidence comparing IVIg with oral steroids, cholinesterase inhibitors (anticholinesterases), immunosuppressants, immunomodulatory drugs or thymectomy.*
- *There was inconclusive evidence suggesting that adults given PE had greater symptom improvement than those given IVIg. For indication 3, improvement declined over four weeks for both treatments. Studies with longer term follow-up data may give further insight into effectiveness.*
- *The cost difference between IVIg and PE for maintenance therapy is dependent on the doses used; the use of immunoglobulin per person at average doses is more expensive than low intensity (4 weekly) PE, but less expensive than high intensity (weekly) PE. Where low doses or high doses of each therapy are compared, immunoglobulin is less expensive than plasma exchange.*
- *The financial analysis does not include cost-offsets associated with reductions in PE, surgery or pharmaceuticals which may be reduced in (Criteria V3 Indication 3) patients.*

Immunoglobulin therapy for Myasthenia Gravis

This contracted assessment (CA) examines the evidence to support funding of immunoglobulin therapy (Ig) by the National Blood Authority (NBA). The service is used in the hospital setting (and potentially the home setting) for the treatment or management of people with myasthenia gravis (MG). The target population are people with MG who: 1. are at risk of or are in myasthenic crisis; 2. have advanced MG and are to undergo surgery; or 3. have moderate or severe MG and other maintenance treatments have failed or have intolerable side effects. The NBA's intention for the review is to ensure that Ig is directed to those who need it most.

ALIGNMENT WITH AGREED PICO CONFIRMATION

This contracted assessment of Ig for MG (CA 1566) addresses most of the PICO[1] elements that were pre-specified in the PICO Confirmation ratified by the Ig Review Reference Group, which performed the function of the PICO Advisory Sub-Committee (PASC). This application followed a fit-for-purpose pathway, in which the PICO Confirmation was presented to and approved by the Ig Review Reference Group, which was convened for the purpose of reviewing the usage of Ig in Australia.

The MGC score was specified as an outcome measure in the PICO as it is the score used by the NBA to assess patients for Ig eligibility. However, it was rarely used in the literature identified in the systematic literature search. Studies using other assessment scores and scales were therefore included, and a comparison to the MGC score made to make the data relevant to the Australian setting. See *Section B.5 Outcome measures and analysis* for a full comparison of relevant MG tools.

Small sub-populations of MG - muscle Tyrosine kinase (MuSK) antibody positive MG, MG in pregnancy and MG in juvenile patients - were not well represented in the literature. These populations are discussed briefly in *Section F Other relevant considerations*. Evidence was not found comparing IVIg for MG to all of the comparators listed for Indication 3. The majority of patients with moderate to severe MG were taking oral steroids or immunosuppressant therapy including when participating in trials of IVIg and/or PE, but results were not reported separately.

PROPOSAL FOR PUBLIC FUNDING

The application for this CA has followed a fit-for-purpose pathway. An MBS item descriptor is not required as recommended therapies will be supplied through the National Blood Agreement and accessed through the NBA Criteria for MG (*Criteria V3*).

POPULATION

MG is a debilitating autoimmune disease associated in the majority of patients (85%) with the presence of antibodies to the acetylcholine receptors of the neuromuscular junction affecting the nervous system and causing muscle weakness. In a smaller proportion of cases, MG is associated with other antibodies, or patients may be seronegative.

Symptoms of muscle weakness are a typical pattern in MG, most commonly causing unilateral or bilateral drooping of the eyelid (ptosis), double vision (diplopia), difficulty swallowing (dysphagia), and weakness of the proximal muscles and respiratory system. Severity worsens over 1 to 3 years to its maximum degree. In some cases MG is driven by a thymic tumour or hyperplastic thymus. Disease onset is on average earlier in women at 28 years, compared to 42 years in men. Prevalence is 50%

[1] Population, Intervention, Comparator, Outcomes

greater in women than men, as women tend to be affected earlier and their cumulative years of disease are greater. For a summary of patient number and IVIg usage in Australia, see Table 8.

There are three indications for which patients with MG may be eligible for IVIg therapy under the NBA regulations. Full criteria can be seen in *Appendix F*, but in summary MG patients may be eligible if:

1. The patient is in myasthenic crisis with respiratory insufficiency requiring intubation and assisted ventilation OR at risk of myasthenic crisis displaying symptoms of respiratory insufficiency such as persistent difficulty with speech, difficulty chewing or swallowing and/or shortness of breath on minimal activity AND clinical assessment confirms severe disability as measured by a Myasthenia Gravis Composite (MGC) score of at least four points.

2. Surgery is planned AND the patient has advanced MG disease, bulbar symptoms and/or respiratory involvement.

3. The patient has moderate to severe MG as assessed by a Myasthenia Gravis Composite (MGC) score of at least four points AND at least two other treatments are ineffective, are contraindicated, unavailable or caused intolerable side effects.

It was noted from clinical input, that patients are likely to be on two other therapeutics when they receive Ig therapy. When starting a different therapy (other than IVIg and PE) immunosupression can take a considerable time to reach its full effect, with latency periods often as long as 12 to 18 months in patients with MG.

For Indications 1 and 3, a clinical assessment must confirm a moderate to severe disability, using the Myasthenia Gravis Composite (MGC) score, of at least four points. The MGC score is calculated from a 10 question clinical assessment questionnaire (seen Appendix F).

For access to ongoing Ig treatment for patients using it as maintenance therapy (Indication 3), there are further criteria (listed in Appendix F).

PROPOSED MEDICAL SERVICE

Ig delivered intravenously (IVIg) has become an alternative therapy option for MG over the last 10 to 15 years. It is currently accessed and funded through the NBA. Although the exact mechanism of action that IVIg has on MG patients is not known, it acts as an immune modulator, reducing the abnormal immune response and the neuromuscular symptoms. It is useful for patients who need urgent treatment due to myasthenic crisis or impending crisis, or have worsening symptoms on other therapies, and need a change in treatment (Alabdali et al. 2014). Due to its high cost, IVIg is usually given as a short term therapy, although some patients remain on IVIg maintenance therapy longer term.

MG patients are primarily in the care of a neurologist, although ongoing care may be additionally provided by a general medicine physician, immunologist or rheumatologist if access is limited. Access to IVIg requires an Australian Health Practitioner Regulation Agency (AHPRA) registered neurologist to diagnose MG in the patient initially, and to carry out patient reviews.

Intravenous administration of Ig requires a treating doctor to determine the dose. The intravenous infusion is overseen by the hospital medical staff with overarching responsibility held by the treating clinician. Normally, an IV infusion of Ig would be delivered by a registered nurse in a hospital in-patient or outpatient setting. Patients or their carers can deliver SCIg in an out of hospital setting, where clinically appropriate.

SCIg is not currently available for MG under the arrangements described above. The Applicant anticipates that a Schedule 4 submission is likely to be made in the near future for the use of SCIg in MG. On this basis, SCIg has been included in this assessment, for Indication 3. IVIg and SCIg are noted as intervention subgroups in the PICO due to likely differences in response to treatment. **COMPARATOR DETAILS**

The comparator for Indications 1 and 2 is plasma exchange (PE). Plasma is a blood product which is supplied through the NBA, not through the MBS. According to the Applicant, both IVIg and PE are preferentially used as short term therapies to stabilise a patient whilst waiting for other therapies to become effective (MSAC 2019). Apart from the choice of IVIg or PE, other treatments are expected to be the same for both intervention and comparator recipients.

The safety and effectiveness of PE are likely to differ based on how it is delivered (via central or peripheral venous access). In particular, access lines in central venous delivery can be a source of infection, when they are not handled with care (Vucic & Davies 1998).

Expert advice from the Ig Review Reference Group indicated that PE should be a comparator for Indication 3, despite PE usually only being provided in hospital (not outpatients). The NBA lists PE as an alternative therapy for this indication in *Criteria V3*.

For Indication 3, other standard treatments used at the same time as Ig include drugs in the categories of corticosteroids, anticholinesterases, immunosuppressants (IS) and immunomodulators (IM), as listed in Table 9 (provided by the Applicant). The majority of those listed are available through the Pharmaceutical Benefits Scheme for MG, the exceptions being mycophenolate mofetil, and rituximab. In cases where MG is driven by a thymic tumour or hyperplastic thymus, thymectomy may be an appropriate comparator treatment. To be eligible for Ig for maintenance therapeutics, at least two other treatments must have been ineffective, be contraindicated, be unavailable or have caused intolerable side effects. It should be noted that inaccessibility for patients to facilities that enable safe delivery of PE (that is major hospitals with specialised apheresis equipment and adequate facilities), can lead to the pragmatic choice of IVIg over PE as treatment.

Evidence of effectiveness is required for ongoing Ig therapy and other indicated treatments should be trialled concurrently. The incremental benefit of IVIg over these standard therapies could be shown

by comparing the effectiveness of IVIg with placebo, if patients in both arms of the comparison are taking similar standard therapies.

CLINICAL MANAGEMENT ALGORITHM(S)

The clinical management algorithms for MG Indications 1 to 3 can be seen in *Section A.6*, Figure 1 to Figure 3.

To be eligible for Ig for all MG indications covered by NBA *Criteria V3* a neurologist must make the diagnosis. Detailed criteria for eligibility are given in Appendix F.

To meet criteria for Indication 1 a patient must have respiratory insufficiency requiring intubation and assisted ventilation, or have symptoms to show they are at risk of life-threatening myasthenic crisis. Patients are often already receiving IS or CS therapy or a combination of therapies. In these circumstances, the neurologist may consider IVIg or PE treatment.

Thymectomy may be considered in MG patients to reduce the autoimmune response. Patients at an advanced stage in MG disease may require stabilization prior to surgery, through treatment with IVIg if patients meet the criteria for Indication 2. The patient should be monitored for stabilization post-surgery.

To qualify for IVIg for Indication 3, a patient with non-life-threatening moderate to severe MG symptoms must have already tried and failed at least two standard therapies, either CS, IS or a combination of the two. Alternatively, patients may have developed side effects to or become contraindicated for alternative therapies by development of comorbidities

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

IVIg and PE are two IV treatments used to reduce immune response and subsequent morbidity in patients with MG. Both IVIg and PE use blood products sourced both through collection of local blood donations, or purchased from overseas. The main differences between the two are in their patient delivery and accessibility.

IVIg is generally delivered via a peripheral vein over a shorter timeframe than PE, and commonly uses a dose of 1 or 2 g/kg per infusion for Indication 1. The infusion method for IVIg is usually delivery on consecutive days until the complete dose is administered (for example 2 to 5 days).

In comparison PE involves the infusion of larger volumes than IVIg, and is delivered on alternate days to achieve the number of plasma volume exchanges desired (for example five plasma volume exchanges over 10 days). If peripheral venous access breaks down PE may require delivery via a central vein which may carry greater risk of infection.

The Ig Review Reference Group has acknowledged that access to PE is limited in Australia, and there are factors restricting the use of this service for both clinicians and patients. The time taken to access

PE therapy may be considerably longer than the time it takes to access IVIg (days for PE, compared with hours for IVIg) if patients need to be transferred between hospitals and referred to other medical specialists for PE. It is necessary for PE to be delivered in hospital centres with both specialised equipment and central vein delivery cababilities, in the event that peripheral venous access breaks down, therefore limiting the number of hospitals that can provide PE. Recommendation or choice of treatment method by clinicians may therefore be pragmatic, based on the differing accessibility of PE and IVIg.

Ig also has the potential to be delivered subcutaneously for patients on maintenance therapy, using a lower dose of Ig than for IV therapy, and may require infusion twice weekly.

CLINICAL CLAIM

A **non-inferiority** claim was proposed by the Applicant for *Criteria V3* Indications 1 and 2 (where Ig is intended to be used for a limited time frame to manage a patient through a crisis or surgery, and has a direct comparator in plasma exchange).

For Indication 3, where Ig may be used as an adjunct therapy to immunotherapy or other standard therapeutics (not PE), there would need to be an additional benefit from the Ig therapy to justify its use i.e., a **superiority** claim (MSAC 2019).

APPROACH TAKEN TO THE EVIDENCE ASSESSMENT

A systematic search and review of published and unpublished literature was undertaken. The medical literature was searched on 13 March 2019 to identify relevant studies and systematic reviews (SRs) published during or after Jan 1980. The search was performed in the major literature databases (sources listed in Appendix B), using search term strings that did not restrict for comparator or outcome criteria. Additional grey literature sources were searched.

Studies were selected against the eligibility criteria independently by two reviewers with a random sample independently assessed for consistency. Disagreements regarding study selection were resolved by consensus between two reviewers. Case series of three or more case reports were included for subpopulations for which there was no higher level literature identified.

Appraisal of the evidence was conducted in four stages: appraisal of the risk of bias within individual studies (or SRs); extraction of the pre-specified outcomes and synthesis of the data to determine an estimate of effect per outcome; rating the overall quality of the evidence per outcome across studies, based on the study limitations; and integration of the evidence for conclusions about the net clinical benefit of the intervention in the context of Australian clinical practice.

A profile of each included study is given in Appendix C. Study characteristics are also summarised in a shorter format in *Section B.4,* Table 11 andTable 12.

CHARACTERISTICS OF THE EVIDENCE BASE

From an initial 5918 articles identified and screened, 198 were identified for full text review, and a final number of 29 individual articles were included (for details see the PRISMA flowchart in Figure 4). Table 11 and Table 12 summarise the characteristics of the SRs and primary articles included for evidence.

Three relevant SRs were included for evidence, and were also pearled for individual studies. The majority of evidence was drawn from the individual studies, rather than any synthesis of results. The primary studies included in the SR were inconsistent in population definition and outcome measurement, so that very little meta-analysis could be performed. Eight RCTs met the inclusion criteria and provided evidence across the three *Criteria V3* indications. They were mostly assessed as moderate for risk of bias using a standard appraisal tool, although two were found to be low risk and one cross-over design RCT had a high risk of bias. In general the RCTs were small in patient number and lacked power.

The majority of the remaining studies were retrospective comparative cohort studies. Selection bias could not be ruled out in these studies, and there is a possibility that PE was used preferentially over IVIg in some cases due to its faster action, particularly for patients in crisis. Data from case series with before and after treatment results were included for the use of SCIg in patients with Indication 3 MG as there was no higher level evidence for this group. Case series data were also included from an Australian juvenile population with Indication 3 MG treated with IVIg.

RESULTS

Overall, evidence for all three indications was of poor quality. The relevant RCTs were mostly small and underpowered, and one large retrospective cohort study was likely to be confounded for outcomes of interest to this assessment.

Safety

Indication 1: patients in or at risk of myasthenic crisis

Six comparative studies reporting adverse events (AEs) for Indication 1 found there were more AEs associated with PE than IVIg treatment. In addition, a greater proportion of patients experienced AEs when given PE compared to those given IVIg. This difference reached significance in one RCT and a large cohort study but not in the lower level studies. Some particular events were more common to PE or IVIg. Hypotension was a common AE in the PE group, while headaches and nausea were more common in those treated with IVIg, but these were all considered minor symptoms.

Of concern was the large number of systemic infections occurring in association with PE treatment reported by one cohort study. This was likely caused by the larger proportion of crisis patients who experienced acute respiratory failure and endotracheal intubation in the PE group compared to the IVIg group ($p < 0.0001$ for both). This indicates that the PE group may have been sicker to begin with, and this influenced the selection of their treatment, leading to selection bias. In the literature there was evidence that PE is given in preference to IVIg in life-threatening crises because it is thought to be faster acting (Barth et al. 2011; Liu et al. 2010; Qureshi et al. 1999). Some treatment guidelines for MG also indicate the longer action time of IVIg compared to PE in crisis patients (Bird SJ 2019).

Indication 2: patients preparing for surgery

The rate of post-operative intubation and myasthenic crises were the outcomes reported for patients treated with IVIg in preparation for surgery. The patients in the three studies included for this indication were all patients listed for thymectomy. Results from one RCT found that intubation was required significantly more frequently in the PE group ($p = 0.01$). In two other studies post-operative frequency of crisis was also more frequent in patients given PE than those given IVIg or IS alone, but these differences were not significant. As for Indication 1, results may be confounded by the preference for PE treatment for patients in crisis or at higher risk of crisis.

Indication 3: patients undergoing maintenance therapy

There was no evidence comparing IVIg with oral steroids, anticholinesterases, or IS that met the inclusion criteria. Data entered on clinicaltrials.gov for the RCT NCT02473952, found no statistical differences in serious or non-serious AEs when IVIg was compared with placebo in 62 patients on standard maintenance therapeutics. The maintenance therapeutics were not specified, and there was no published article for this trial.

The majority of evidence identified compared IVIg with PE for maintenance therapy of MG. One moderate quality RCT in adults found significantly more headaches and vomiting in the IVIg population, and more venous access problems (citrate reaction, restricted venous access so as to delay treatment and vasospasm) in the PE group. Serious events (cardiac failure, vasoreaction) were infrequent but all occurred in the PE group. Two other studies reporting AEs for IVIg and PE in adults found no difference between treatment groups.

One study in juvenile MG patients reported cases of pyrexia and rigors and central line sepsis for patients receiving IVIg or PE treatments and found no significant differences (Liew et al. 2014).

In two case series with pre and post-treatment results for patients on SCIg maintenance therapy the most frequent events were headaches (77.3%), injection site reaction (63.6%) and nausea (27.3%). It is likely that the populations had milder MG than that described by the *Criteria V3* for Indication 3.

A literature review not meeting the inclusion criteria but reported here due to lack of data, assessed the frequency of side effects for a number of MG therapies, including IVIg, PE and other standard

therapies (Alderson, Homer & Dierick 2018). The outcomes were reported in a conference poster. Amongst MG treatments, the highest frequency of AEs occurred with corticosteroids (29%), while the frequency was lower for IVIg (18%). The authors reported a frequency of 6% for PE from a global registry of 16,942 PE procedures, although the registry was not limited to MG PE procedures.

Effectiveness

Indication 1

In one large retrospective cohort analysis comparing IVIg and PE in patients in crisis, mortality was significantly more frequent in the patients receiving PE (P = 0.002) (Mandawat et al. 2010), however it is likely that this result was confounded by the preference for PE treatment for patients in crisis and requiring intubation. Mortality rates may also be impacted by the quality of services provided in intensive care units (ICU), as the survival of patients in crisis can be dependent on treatment in ICU until PE becomes effective (Vucic & Davies 1998). Two other smaller studies did not find any difference in mortality between the treatment groups (Murthy et al. 2005; Qureshi et al. 1999).

The MGC was not used in any comparative studies to measure change in symptoms for the MG crisis population. For other symptom measures (MMS and MSS) there was an improvement from baseline for patients given either IVIg or PE but no conclusive differences between groups. In addition, treatment response defined as an increase in MMS of 20 points, reported by one RCT, (Gajdos et al 1997) was found to be similar in both treatment groups 15 days from the start of IVIg or PE.

Indication 2

Evidence from two small comparative studies found that there was no difference in symptom change (change in Osserman grade) between patients treated with IVIg or PE. Symptoms improved in both groups following surgery.

Indication 3

There was very little literature comparing IVIg with standard maintenance therapies other than PE (including corticosteroids, cholinesterase inhibitors, IS, IM, and thymectomy). Griffin et al published early data on clinicaltrials.gov for patients on standard maintenance therapies and randomised to either IVIg or placebo. There were no statistically significant differences between them, although the one death that occurred was in the IVIg-C group (Griffin et al. 2017b). Further data on the change in symptoms (change in QMGS) from this trial and a second trial comparing IVIg and placebo in corticosteroid dependent MG patients, for which there is not yet any published data, will be of interest (Griffin et al. 2017a).

Patients on IVIg and PE had similar improvement in symptoms measured using the QMGS at 28 days (Barth et al. 2011) and 16 weeks (Rønager et al. 2001) from start of treatment. Strongest improvement in symptoms was seen in the first 2 weeks in a third study (p = 0.01, (Liu et al. 2010)). Only a small degree of improvement appeared to be sustained for up to 16 weeks for either IVIg or PE. Longer term

comparative studies may be more informative on the degree of sustained symptom improvement. The degree of improvement may be influenced by the severity of symptoms at baseline.

There was no difference in the rate of infection between patients receiving IVIg (n = 171) or PE (n = 737) reported in a retrospective cohort study (Mandawat et al. 2010). Although it was specified that the participants in this arm of the study were not in crisis, it was difficult to tell if they met the criteria for moderate to severe MG requiring a change in maintenance therapy (*Criteria V3* for Indication 3) as there was a lack of baseline data.

Effectiveness evidence for IVIg in children, and for SCIg, was too poor to make reliable conclusions.

Summary of findings Table 48 toTable 51 summarise the clinical benefits and harms for IVIg against its comparators for critical outcomes in Indications 1, 2 and 3.

On the basis of the benefits and harms reported in the evidence base (summarised above), **it is suggested that for patients in crisis or at risk of crisis (*Criteria V3* Indication 1), relative to PE, IVIg has superior safety and non-inferior effectiveness.**

Due to the low level of evidence **it is suggested that for patients preparing for surgery (*Criteria V3* Indication 2), relative to PE, IVIg has uncertain safety and uncertain effectiveness.**

It is suggested that for patients on maintenance therapy (*Criteria V3* Indication 3), relative to other therapies (including corticosteroids, cholinesterase inhibitors, immunosuppressants, immunomodulators, and thymectomy), no conclusions can be made regarding the relative safety and effectiveness of IVIg, with the exception of a comparison against PE where IVIg appears to have non-inferior safety and non-inferior effectiveness.

TRANSLATION ISSUES

The translation issues of relevance to the economic analysis are associated with estimation of resource use applicable to the Australian setting. Consideration to the circumstances of use of IVIg and PE and other comparators in the clinical studies was compared to available evidence describing resource use patterns in the Australian setting.

With respect to Indications 1 and 2, applicability assessments identified minor adjustments to IVIg doses were required to represent Australian usage. Australian practices with regard to PE (fluid exchange volume, composition and the number of exchanges) also varied slightly from the clinical trial informing Indication 1. Estimates of the resource implications associated with adverse events in Indication 1; and for Indication 2 the implications of identified differences in surgery time and intubation times, are described as they apply to the Australian setting.

With respect to Indication 3, the ongoing nature of maintenance treatment is detailed and an approach to compare cost estimates over both shorter and longer time horizons is considered

appropriate. Assessment of the circumstances of ongoing use of maintenance therapies is made to enable extrapolation of a pattern of associated resource use for each comparator.

The translation of the difference in adverse event profiles into an estimate of a quality-adjusted life year decrement is quite uncertain. Few studies are adequately powered to provide precise estimates of adverse event differences, at the event-type level. The comparative data which forms the basis of the economic analysis presents a limited adverse event profile comparison given it has small numbers, therefore it may not be representative of the differential adverse event profile that would be observed across a population. For example; infection was not an observed adverse event in the RCT, yet this is observed in other studies of PE, and additional external literature identifies significant mortality and morbidity consequences associated with sepsis in the ICU setting. The Ig Review Reference group considered that further modelling should be attempted to include sepsis and sepsis-related consequences, however the quantative inputs around sepsis were required to be based on non-comparative data sources. These become significant drivers in the model, but are highly uncertain. Furthermore the utility values applied to the observed adverse events could only be sourced from multiple external studies and the contexts of these estimates varies such that their applicability and consistency is uncertain.

ECONOMIC EVALUATION

For Indication 1, based on the clinical conclusions and the decision algorithm (Table 59), with the limited information available on the clinical significance of the safety differences identified, a cost-utility analysis is presented.

For Indication 2, based on the decision algorithm, Table 59, a cost-analysis is appropriate.

For Indication 3, based on the decision algorithm, a cost-minimisation analysis is appropriate vs PE. However at the request of the Ig Review Reference Group an exploratory cost-utility analysis was conducted based on a reduced infection rate using IVIg compared to PE. Caution should be taken interpreting the results of this analysis as this is highly uncertain.

For the remainder of comparators, no directly comparative economic analyses are appropriate and only a non-comparative cost-analysis can be provided, noting that it is not appropriate to assume equivalence between treatments.

Table 1 Summary of the economic evaluations

	Indication 1 MG crisis	**Indication 2** MG patients pre-surgery	**Indication 3** Maintenance in refractory MG disease
Perspective	Healthcare system	Healthcare system	Healthcare system
Comparator	PE	PE	Various pharmacological treatments (anticholinesterases,

			immunomodulation), surgery or PE
Type of economic evaluation	Cost-utility analysis. Cost-consequences analysis	Cost-analysis	Individual non-comparative cost-analyses. Exploratory cost-utility analysis IVIg vs PE.
Sources of evidence	Gajdos 1997 is the basis of the clinical outcomes (single RCT detailed in *Section B*). Additional references for utility values and to inform resource requirements (see C.4, D.4)	Alipour-Faz et al. 2017 is the basis of the clinical outcomes (single RCT identified in Systematic Review in *Section B*).	Various sources (no RCTs for most comparators in Systematic Review, *Section B*). Sources detailed in D.4
Time horizon	Base case: 3 months (Exploratory analysis including QALY loss due to fatal AE: 10 years)	4 weeks	1 year to 10 years
Outcomes	$ per QALY, $ per adverse event avoided	Cost difference	Costs (including discounted costs)
Methods used to generate results	Trial-based analysis, with stepped analysis incorporating NBA IVIg usage data: cohort expected value analysis.	Trial-based analysis, with stepped analysis incorporating NBA IVIg usage data	Expected value analysis
Discount rate	NA (5% pa to costs and outcomes in exploratory analysis)	NA	5% pa to costs and outcomes
Software packages used	Excel	Excel	Excel

IVIg = intravenous immunoglobulin; MG = myasthenia gravis; NA = not applicable; NBA = National Blood Authority; PE = plasma exchange; QALY = quality adjusted life year; RCT = randomised controlled trial

Assumptions in the economic analyses are:

- For Indication 1: There are no differences in MG crisis-related health outcomes associated with treatment effectiveness for IVIg compared to PE, but there are safety outcome differences which can be modelled because PE is associated with more adverse events. Also; because the patient is already in an ICU setting, differences in minor adverse events that do not necessitate treatment discontinuation have minimal economic consequences. However potential highly serious adverse events associated with PE (retroperitoneal haematoma, thrombois and sepsis) are clinically significant and have both resource use and quality of life implications;

- For Indication 2: A statistically significant difference in average operation time that was observed in the RCT is assumed to be associated with the pre-surgery treatments in the base case (but an alternative assumption; that this is a chance finding, is also tested as a scenario analysis).

- For Indication 3: The various analyses assume that, aside from induction doses, maintenance doses of IVIg, PE and pharmaceuticals would be constant and follow a regular treatment pattern (however in clinical practice these may fluctuate). Monitoring costs are included, but

costs associated with treatment of adverse events are not included in the base case analyses. Additionally, it is assumed that only 5% of PE patients utilise fistula-based IV access, and non-fistula IV access devices require replacement approximately every three years, on average.

The overall costs and incremental costs and consequences for IVIg and PE in the Indication 1 analysis, using the base case assumptions, are shown in the table below.

Table 2 Indication 1: Selected results from a stepped cost consequences and cost utility analysis

	IVIg	PE	Increment
Step 4: RCT evidence base adapted to Australian resource use patterns			
Total Costs	$58,895	$50,998	$7,898
Health outcome (safety) consequences			
Patients with adverse events	2.2%	19.5%	-17.3%
Patients with clinically significant adverse events	0%	4.9%	-4.9%
QALY decrement due to AEs		-0.001100	0.001100
ICER ($/QALY)			**$7,177,933**
Step 7: Modelling sepsis morbidity/mortality over 15 years			
Total Costs	$58,895	$52,388	$6,558
QALY decrement due to AEs		-0.143261	0.143261
ICER ($/QALY)			**$45,776**

AE = adverse event; IVIg = intravenous immunoglobulin; FFP = fresh frozen plasma; PE = plasma exchange; QALY = quality adjusted life years; RCT = randomised controlled trial.

At Step 4, the economic implications of the adverse events are not well defined with respect to their patient relevance and resource implications, therefore this will disfavour IVIg in the comparison.

The overall costs and incremental costs for IVIg and PE in the Indication 2 analysis, using the base case assumptions, are shown in the Table 3.

Table 3 Indication 2: Cost-minimisation analysis

	IVIg	PE	Incremental cost
Resources (disaggregated)	Total Cost	Total Cost	
IVIg product (156g)	$9,424	$0	$9,424
PE replacement fluid (Albumin 4%)	$0	$685	-$685
All outpatient Tx administration costs (pre-admission)	$922	$7,231	-$6,309
Thymectomy Operating Theatre	$9,393	$11,317	-$1,924
Other hospitalisation (for surgery) costs	$27,518	$27,518	$0
Total	**$47,257**	**$46,751**	**$506**

IVIg = intravenous immunoglobulin; FFP = fresh frozen plasma; PE = plasma exchange

Overall, the cost-minimisation analysis suggests PE may be marginally less expensive than IVIg for pre-treatment prior to surgery in MG patients, however the difference is small in the broader context of the surgery cost.

The cost-minimisation for IVIg and PE in the Indication 3 analysis, using the base case assumptions, are shown in Table 4 (additional time horizons are presented in Section D.5).

Table 4 Indication 3: Cost analysis over varying time horizons, discounted at 5% pa

	Total discounted costs over varying time horizons		
	1 year	**5 years**	**10 years**
IVIg			
NBA data derived average annual dose	$34,516	$156,164	$277,001
PE			
low intensity (every 4 weeks)	$33,362	$120,554	$207,165
high intensity (every 1 week)	$100,219	$442,675	$782,848
Cost Difference IVIg vs PE			
IVIg base case – low intensity PE	$1,154	$35,610	$69,836
IVIg base case – high intensity PE	-$65,703	-$286,511	-$505,847

IVIg = intravenous immunoglobulin; PE = plasma exchange; NBA = National Blood Authority

Where IVIg is costed at the estimated average maintenance dose used in Australia, it is more expensive than a low intensity PE regimen (e.g. 4 weekly), but less expensive than intensive weekly plasma exchange. Low dose IVIg also appears less expensive than low intensity PE, and high dose IVIg monthly appears less expensive than high intensity PE.

There is some evidence of an infection risk associated with PE, however the applicability of the estimates to the current setting, and any comparable risk in IVIg is unknown. Exploratory analysis of ICERs allowing for a sepsis cost and QALY decrement yielded ICERs ranging between 'dominant' (in all cases where the comparison is vs high intensity PE or low dose IVIg is compared to low dose PE), through to $18 million per QALY (Table 87, Section D5.3). The broad range of ICERs is consistent with the findings of the cost comparison where cost-savings were demonstrated in all comparisons except average IVIg dosing vs low dose PE.

Additional cost analyses of other therapies used in Indication 3 analysis are presented, using the base case assumptions, are shown in Table 5.

Table 5 Indication 3: Non-comparative cost analysis of other Indication 3 therapies over varying time horizons, discounted at 5% pa (equivalent effectiveness cannot be assumed).

	Total discounted costs over varying time horizons		
	1 year	**5 years**	**10 years**
Surgery (thymectomy)	$47,335	$47,335	$47,335
Other Pharmaceuticals			
Prednisolone + Pyridostigmine (P+P)	$1,241	$5,615	$9,959
Mycophenolate mofetil added to (P+P)	$3,308	$14,965	$26,545
Azathioprine added to (P+P)	$1,964	$8,884	$15,758
Methotrexate (+ folic acid) added to (P+P)	$1,574	$7,119	$12,628
Cyclophosphamide IV then Azathioprine (and P+P)	$7,283	$14,205	$21,081

	Total discounted costs over varying time horizons		
Ciclosporin 100mg added to (P+P)	$9,111	$41,222	$73,118
Rituximab added to (P+P)	$8,341	$18,810	$28,119

P+P = prednisolone + pyridostigmine

Surgery and pharmaceuticals (with the exception of long-term ciclosporin) are all considerably less expensive therapies than IVIg, however equivalent effectiveness cannot be assumed.

Sensitivity analyses showed an increased cost associated with IVIg in all analyses except where the IVIg price was the lowest price suggested for analysis, in which case it became a less expensive option than PE in Indication 2 and less expensive than high intensity PE in Indication 3. The sensitivity analyses across all IVIg prices, for all indications are presented in *Section D.6*.

ESTIMATED EXTENT OF USE AND FINANCIAL IMPLICATIONS

A market-based approach was used to estimate the financial implications of Ig in MG, based on current utilisation of Ig products in Australian patients with MG.

The financial implications associated with funding Ig for MG are summarised in Table 6.

Table 6 Total costs to government associated with Ig for MG

	2019-20	2020-21	2021-22	2022-23	2023-24
Total cost of Ig	$36,181,120	$39,060,321	$41,939,401	$44,818,602	$47,697,742
Cost of Ig to the Commonwealth	$22,794,105	$24,608,002	$26,421,823	$28,235,719	$30,049,578
Cost of Ig to the States	$13,387,014	$14,452,319	$15,517,578	$16,582,883	$17,648,165
Additional cost to states (administration)	$5,338,380	$5,756,046	$6,179,705	$6,598,293	$7,021,952
Total cost offsets due to a reduction in PE	$781,695	$836,982	$897,993	$961,196	$1,024,399
Offsets to the Commonwealth	$323,921	$349,642	$374,413	$400,565	$426,717
Offsets to the States	$457,774	$487,341	$523,581	$560,632	$597,683
Net cost	**$40,737,805**	**$43,979,384**	**$47,221,113**	**$50,455,699**	**$53,695,295**
Net cost to the Commonwealth	$22,470,184	$24,258,360	$26,047,410	$27,835,154	$29,622,861
Net cost to States	$18,267,621	$19,721,024	$21,173,703	$22,620,544	$24,072,434

Ig = immunoglobulin; MG = myasthenia gravis

These estimates do not include likely cost offsets associated with reduced comparator therapy use in Indication 3 patients, therefore these costs are likely to overestimate net costs.

CONSUMER IMPACT SUMMARY

Targeted feedback on the PICO Confirmation was received from a medical device company and a neurologist. There was general agreement with the population, intervention and comparator descriptions in the PICO Confirmation. The company, which supplies a device used in PE practice provided alternative clinical algorithms as they disagree with the placement of PE in the clinical pathway provided in the PICO Confirmation.

Sponsor feedback to the PICO Confirmation relevant to Ig for MG was received from two companies. One company noted approval of Ig products for specific indications only was contrary to the purpose of the NBA *Criteria V3* which is intended to support funding for IVIg as a class of products (not specific indications). Restricted approval has the potential for limiting access to all IVIg products, and to exacerbate product shortages

There was disagreement from a second company regarding the validity of the comparators and the management algorithm for Indication 3. IVIg should be considered a subsequent line of therapy, and the majority of comparators are first-line therapies. It was noted that it will be difficult to assess IVIg against PE or first line therapies considering the low level and small volume of evidence. Usage of the comparator therapies (including PE) is largely based on clinical experience rather than good quality trial data.

OTHER RELEVANT CONSIDERATIONS

A discussion of three clinical scenarios of MG is included in *Section F*: rituximab for patients with MG; IVIg compared with PE in patients with MuSK antibody positive MG (MuSK-MG); and IVIg for MG in pregnancy.

Safety and effectiveness of rituximab for patients with MG

Evidence has shown rituximab to be effective for patients meeting *Criteria V3* for Indication 3 but it has not been compared to IVIg in trials. In particular rituximab has been used in clinical settings for refractory MG cases which have not responded to standard therapies, PE or IVIg. Rituximab appears to have a stronger treatment effect in patients with MuSK-MG compared to those with AChRAb-MG.

An article published Australian data on 38 MG patients from South East Queensland receiving rituximab for reasons of refractory disease, side effects with standard IS therapies or contraindication to IS. The majority of patients were of moderate to severe disease status according to their MGFA score and met eligibility criteria for IVIg under *Criteria V3* Indication 3.

The overall response to rituximab was clinical improvements for 28 out of 38 patients (74%). Five patients were unchanged or worse symptoms, and five were deceased. Five patients were able to cease IVIg treatment, and two patients ceased PE. In addition, of those receiving rituximab and IVIg, six were able to reduce their dose of IVIg, and one patient was commenced on IVIg. Treatment response is summarised in Figure 11.

Safety and effectiveness of IVIg compared with PE in patients with MuSK-MG

In the evidence provided on the safety and effectiveness of IVIg for MG, the majority of patients were AChRAb positive, and those that were not (either MuSK antibody positive or seronegative) were rarely analysed separately.

Two retrospective cohort studies, which represented the best evidence identified in the literature search, provided data in MuSK-MG patients comparing the effectiveness of IVIg and PE (Guptill, Sanders & Evoli 2011; Pasnoor et al. 2010). Both studies found response was greater in the patients receiving PE.

IVIg for MG in pregnancy

Pregnancy is a known trigger of MG exacerbation (Statland & Ciafaloni 2013), but there were very limited data on the use of IVIg during pregnancy in MG patients. In two studies a total of eight patients were treated with IVIg during pregnancy or in the post-partum period. The patient numbers were too small to make conclusions from the data.

ACRONYMS AND ABBREVIATIONS

Acronym/abbreviation	Meaning
AChRAb	Acetylcholine receptor antibodies
ARTG	Australian Register of Therapeutic Goods
CI	Confidence interval
CS	Corticosteroid therapy
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IM	Immunomodulation therapy
IS	Immunosuppression therapy
IVIg	Intravenous immunoglobulin therapy
MBS	Medicare Benefits Schedule
MD	Mean difference
MG	Myasthenia gravis
MG-ADL	Myasthenia gravis activities of daily living tool
MGAS	Myasthenia gravis absolute score
MGC	Myasthenia gravis composite score
MGFA	Myasthenia Gravis Foundation America
MGFA-PIS	Myasthenia Gravis Foundation America post-intervention status
MG-QoL	Myasthenia gravis quality of life questionnaire
MMS	Myasthenia muscle score
MMT	Manual muscle test
MPN	Methylprednisolone therapy
mRS	Modified Rankin scale
MSAC	Medical Services Advisory Committee
MSS	Myasthenia severity scale
MuSK	Muscle specific kinase
NHMRC	National Health and Medical Research Council
PASC	PICO Confirmation Advisory Sub-Committee of the MSAC
PE	Plasma exchange
PN	Prednisone therapy

Acronym/abbreviation	Meaning
QALY	Quality adjusted life year
QMGS	Quantitative myasthenia gravis score
QoL	Quality of Life
TGA	Therapeutic Goods Administration
VAS	Visual analogue scale

SECTION A CONTEXT

This contracted assessment (CA) of immunoglobulin (Ig) for the treatment of myasthenia gravis (MG) is intended for the Medical Services Advisory Committee (MSAC). MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Schedule (MBS) in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

Adelaide Health Technology Assessment (AHTA) has been commissioned by the Australian Government Department of Health to conduct a systematic literature review and economic evaluation of CA 1566 – Ig for MG. This assessment has been undertaken as part of the review of immunoglobulin (Ig) use funded under the National Blood Agreement.

Appendix A provides a list of the people involved in the development of this assessment report, including clinical expertise provided by the NBA.

The National Blood Authority (NBA) is a statutory authority forming part of the Commonwealth of Australia, established in the *National Blood Authority Act 2003* (*NBA Act*). There are three frameworks defining the supply of publicly funded Ig products established under the *NBA Act*: a) Therapeutic Goods Authority regulation; b) policy decisions of all Australian Governments described in Version 3 of the Criteria for the clinical use of immunoglobulin in Australia (*Criteria V3*); and c) supply arrangements implemented under national contracts established by the NBA.

The Ig Review Reference Group was convened to review the use of Ig products in Australia including usage for chronic inflammatory demyelinating polyneuropathy (CA 1564), acquired hypogammaglobulinaemias (CA 1565) and MG (CA 1566). This application is following a fit-for-purpose pathway, in which the PICO Confirmation outlining the proposed use of Ig for MG in Australian clinical practice was presented to and approved by the Ig Review Reference Group.

A.1. ITEMS IN THE AGREED PICO CONFIRMATION

This CA of Ig for MG (1566) addresses most of the PICO elements that were pre-specified in the PICO Confirmation that was ratified and approved by the Ig Review Reference Group.

Only one study that met the inclusion criteria used the myasthenia gravis composite (MGC) score to assess symptom severity. The MGC score was specified in the PICO and is the score used to by the NBA to assess patients for Ig eligibility. To overcome this deficit in evidence, studies using other assessment scores and scales were included, and a comparison to the MGC score made to make the data relevant to the Australian setting. A full comparison of scores and tools used in the clinical assessment of MG can be seen in *Section B.5 Outcome measures and analysis*.

The presence of acetylcholine receptor antibodies (AChRAb) is a diagnostic factor in the most common form of MG and the majority of the evidence is conducted in this population. However other forms also exist. Evidence for Ig use in muscle specific tyrosine kinase antibody positive MG (MuSK-MG) is discussed in *Section F Other Relevant Considerations* as this sub-population is less common, requires special consideration and was additional to the PICO (MSAC 2019). For the same reasons MG in pregnancy is also discussed briefly in *Section F*. The evidence on Ig for MG in juvenile patients was more substantial and has been presented in *Section B Clinical evaluation*. Patients with MG who underwent thymectomy, or patients with ocular symptoms were included in Indication 3 if they were patients undergoing maintenance treatment or Indication 1 if they were crisis patients, as thymectomy is often used to treat these groups. If patients were given IVIg when preparing for thymectomy they were included in Indication 2. Patients with purely ocular symptoms were not included in this assessment as under the *Criteria V3* they are not eligible to receive Ig.

Evidence was not found comparing IVIg for MG to all of the comparators listed for Indication 3. Because the treatments listed as comparators were given as primary therapies or adjuncts to IVIg or plasma exchange therapy (PE) they were usually very similar in both population arms of study trials. The majority of patients with moderate to severe MG were receiving oral steroids or immunosuppressants on inclusion in trials of IVIg and/or PE.

Although the PICO Confirmation indicated that subgroup analysis of peripheral and central line access safety in PE delivery in comparison with IVIg would be helpful, studies did not separate data in this way and the analysis was not possible.

A.2. PROPOSED MEDICAL SERVICE

Ig delivered intravenously (IVIg) has become an alternative therapy for MG over the last 10 to 15 years. It is a therapy now commonly used for immune deficiency diseases. Ig products are made from the plasma of healthy donors, which is pooled and purified to remove red cells and filtered to produce an immunoglobulin rich product, containing a wide variety of antibodies (ASCIA 2019). Although the exact mechanism of action that IVIg has on MG patients is not fully understood, it acts as an immune modulator, reducing the abnormal immune response and the neuromuscular symptoms. It is particularly useful for patients who need urgent treatment due to myasthenic crisis, or have worsening symptoms on other therapies, and need a change in treatment (Alabdali et al. 2014). Due to its high cost, IVIg is usually given as a short term therapy, although some patients remain on IVIg maintenance therapy longer term.

Ig therapy is delivered by intravenous (IV) infusion and requires that patients attend hospital for a day procedure to be infused. Depending on the dose, which may be split over several days, they may (or may not) be required to attend hospital on a number of days (usually consecutive) each month. For patients in myasthenic crisis, they are likely to already be inpatients at the time of receiving IVIg.

Neurologists primarily care for patients with MG. If patients live in regional or rural areas, they may have ongoing care provided by a general medicine physician and/or neurologist. To be eligible to

access IVIg under governance arrangements initially, an Australian Health Practitioner Regulation Agency (AHPRA) registered neurologist must diagnose MG in the patient. The reviewing medical officer must also be an AHPRA registered neurologist.

IV administration of Ig requires a treating doctor to determine the dose. The administration of intravenously delivered Ig is undertaken by nursing staff and cannot be delegated. The IV infusion is overseen by the hospital medical staff with overarching responsibility held by the treating clinician. Normally, an IV infusion of Ig would be delivered by a registered nurse in a hospital in-patient or outpatient setting. Some facilities may allow an enrolled nurse under the supervision of a registered nurse. Local hospital policies will vary. All sites that administer blood or blood products should be accredited under the National Safety and Quality Health Service Standard for Blood Management.[2] Patients or their carers can deliver SCIg in an out of hospital setting, where clinically appropriate.

IV infusion involves:

- Identification check to ensure the right patient is receiving the right product at the right dose and at the right time. This check is done by two health professionals – usually one must be a doctor or a registered nurse and the other can be either a doctor, registered nurse or an enrolled nurse
- preparation of equipment (Ig vial/bottle, vented line, aseptic dressing pack, cannula)
- the procedure is explained to the patient and consent is obtained
- cannula is inserted using aseptic technique by a credentialed nurse or doctor
- the IV line is inserted directly into the Ig vial/bottle and the IV line is primed with Ig product (without dilution) and hung in accordance with the local hospital's protocol
- the patient is monitored for any reactions and the infusion is slowed or stopped depending on the patient's response.

Subcutaneous administration of Ig (SCIg) means that the patient themselves or their carer can administer the treatment at home. The patient or carer requires education and training on how to administer the product at home. They will undertake more frequent subcutaneous (SC) infusions (usually twice weekly) at home. This requires:

- storing the product in accordance with the manufacturer's advice
- insertion of a butterfly SC cannula using aseptic techniques into SC layer just under the skin of the abdomen or thigh
- drawing up the required dose into a syringe
- connection of the syringe to the SC line

[2] http://nationalstandards.safetyandquality.gov.au/7.-blood-management

- pushing the dose into the abdomen at the required rate which will vary depending on the dose size and the patient's response.

SCIg is not currently available for MG under the arrangements described above. The Applicant reports that current clinical trials indicate that SCIg may be considered for use in MG in the future. Due to the advanced stage of phase 3 trials, it is anticipated that a Schedule 4 submission is likely to be made in the near future for the use of SCIg in MG. On this basis, SCIg has been included in this assessment, for Indication 3 (MSAC 2019). It would not be used in Indications 1 and 2 as these patients are already likely to be inpatients of hospital given their advanced and serious health states, and would therefore not be suitable to receive SCIg at home. As there could be differences in response rates between IVIg and SCIg for some of the selected outcomes (adverse events, disability, venous damage), and differences in health service consumption (e.g. outpatient day- admission hospital care v self-care), IVIg and SCIg are noted as intervention subgroups in the PICO.

MARKETING STATUS OF DEVICE / TECHNOLOGY

All therapeutic products marketed in Australia require listing on the Australian Register of Therapeutic Goods (ARTG). MSAC will not consider a therapeutic product for reimbursement if the device is not listed on the ARTG. Items on the ARTG that are relevant to this application are shown in Table 7.

Two Ig products are registered on the ARTG for MG; they are highlighted green on Table 7 and are:

- Intragam 10 – can only be administered intravenously. It is a domestic product. The price excludes the cost of plasma collection. It is available under the National Blood Arrangements for MG.
- Privigen 10%. – can only be administered intravenously. It is an imported product. It is available in four different doses (5g, 10g, 20g, 40g) and is funded under the National Blood Arrangements for MG.

The NBA currently provides Ig by IV infusion for a further three products for MG: Flebogamma 5%, Flebogamma 10% and Intragam P. The latter will be removed from the Product List once current stocks expire. It has been replaced by Intragam 10. A further 12 Ig products are listed on the ARTG, either for IV or SC infusion, but are not indicated for MG.

Table 7 Ig products listed on the ARTG

ARTG no.	TGA registered indications including MG	Route of Administration	TGA indication for MG?	NBA Funded for MG*?
199979-199981, 162486-162489	Intragam 10 – CSL Behring Australia P/L	IV	Yes	Yes[a]
146273, 143337, 143368, 219160, 265147, 269689-269691, 306801,	Privigen 10% – CSL Behring Australia P/L	IV	Yes	Yes[a]
285345, 285344, 207386, 207385, 207384, 207383	Hizentra – CSL Behring Australia P/L	SC	No	No[b]
116689, 117237-117240	Gamunex 10% – Grifols Australia P/L	IV and SC	No	No
182358, 182359, 184353	Flebogamma 10% – Grifols Australia P/L	IV	No	Yes[a]
140602, 143800-143803	Flebogamma 5% – Grifols Australia P/L	IV	No	Yes[a]
219007, 171139, 171140, 158712, 154210, 66295, 66300, 68632-68635, 74356, 74540	Intragam P – CSL Behring Australia P/L	IV	No	Yes[b]
291644-291648, 291740	Panzyga – Octaphama Australia P/L	IV	No	No
235178	Hyqvia – Shire Australia P/L	SC	No	No
232077, 232078, 232084, 232085	Intratect – Pfizer Australia P/L	IV	No	No
164548-164551	Intratect 5% – Pfizer Australia P/L	IV	No	No
173315, 173323, 173324, 204954-204956	Evogam 16% – CSL Behring Australia P/L	SC	No	No
113925-113928, 155601-155604	Octagam – Octapharma P/L	IV	No	No
128703, 128705	Gammanorm – Octapharma P/L	SC and IM	No	No
131953, 131966, 131968, 131969, 131973, 198488	Kiovig – Shire Australia P/L	IV and SC	No	No
282579	Cuvitru – Shire Australia P/L	SC	No	No
61215, 61216	CSL Normal Immunoglobulin VF- CSL Behring Australia P/L	IM	No	No[c]

Source: Therapeutic Goods Administration, accessed 20 May 2019 Link to TGA.gov.au

ARTG = Australian Register of Therapeutic Goods; IV = intravenous; SC = subcutaneous; IM = intramuscular; MG = myasthenia gravis; NBA = national Blood Authority; TGA = Therapeutic Goods Administration

[a] Indicates that Ig is *currently* funded for MG. Note that tendering arrangements may change products funded in the future.
[b] Intragam P will be removed from funded access under the National Blood Arrangements once current inventory reserves have expired
[c] IMIg is not in scope for this review.

OTHER INDICATIONS

Ig is used for treating other indications in Australia, including acquired hypogammaglobulinaemia secondary to haematological malignancies or post-haemopoietic stem cell transplantation, which is being assessed in CA 1565, and chronic inflammatory demyelinating polyneuropathy, which is being assessed in CA 1564.

CURRENT FUNDING ARRANGEMENTS

Ig is currently supplied and funded through the National Blood Agreement and the NBA. MG patients must be approved by meeting the criteria for Indication 1, 2 or 3 (NBA *Criteria V3*) by an APHRA accredited neurologist to access the products.

A.3. PROPOSAL FOR PUBLIC FUNDING

The application for this CA has followed a fit-for-purpose pathway and a MBS item descriptor has not been provided. Recommended therapies will be supplied through the National Blood Agreement and accessed through the NBA *Criteria V3* for MG.

A.4. PROPOSED POPULATION

MG is a debilitating autoimmune disease affecting the nervous system and causing muscle weakness. MG is associated in the majority of patients (85%) with the presence of a higher than normal AChRAb titre. In a smaller proportion of cases, MG is associated with antibodies to muscle specific tyrosine kinase (MuSK), a protein found at the neuromuscular junction which has a role in acetylcholine receptor function. A very small number of MG patients are seronegative, that is, they do not have antibodies to either of these two proteins.

Symptoms of muscle weakness are have a common pattern in MG, most commonly causing unilateral or bilateral drooping of the eyelid (ptosis), double vision (diplopia), difficulty swallowing (dysphagia), weakness of the proximal muscles and respiratory system. Disease onset is on average earlier in women at 28 years, compared to 42 years in men, this difference contributing to women being affected 50% more often than men. Symptoms can appear at any age however, and 10% of cases begin in childhood. Severity worsens over 1 to 3 years to its maximum degree. (Muscular Dystrophy Foundation Australia 2012).

MG affects two to seven out of every 10,000 people in Western countries. Quality of life is severely impacted by MG with everyday activities made difficult due to the weakness in muscles, especially in the limbs. Over 30% of patients experience very severe symptoms requiring hospitalisation and/or intensive care.

Table 8 gives an estimate of the number of patients treated for Indications 1, 2 and 3 in Australia, and the Ig usage per patient, calculated with data from NBA BloodSTAR[3]. By far the largest number of patients with MG use IVIg for maintenance therapy. In total there were 15,079 treatment episodes, in which 514,257 g of Ig were administered in the period July 2017 to June 2018. The IVIg usage per treatment episode based on this rate was 34.1 g and the usage per patient for all indications was

[3] BloodSTAR is an online system used to manage the access to the supply of government funded Ig products in Australia

438.04 g.

Table 8 Number of patients using IVIg for MG in Australia for the period of July 2017 to June 2018

Item	Patient Number
All MG patients (n)	1,174
Indication 1 (% g)	201 (17.1%)[a]
Indication 2 (% g)	33 (2.8%)[a]
Indication 3 (% g)	940 (80.11%)[a]

[a] Patient numbers for Indication 1, 2 and 3 are calculated using percentages extracted from NBA BloodSTAR data which were exclusively of NSW patients

There is evidence that the natural history of MG is characterised by exacerbations and remissions similar to those seen in other autoimmune diseases. The most striking initiating factor of exacerbation has been infection. Respiratory failure is the most common cause of death. Advanced technology in artificial ventilation has significantly contributed to a decrease in mortality, from 40% to 5%. Similarly, improved antibiotics have also reduced mortality from respiratory and other infections in patients with severe exacerbations. More recent publications have reported that most individuals with the condition have normal life expectancy.

Remission occurs in about 20% of people with MG. Usually, the remissions are temporary, with an average duration of 5 years, but some people experience more than one remission during their lifetime. Occasionally permanent remission can occur, lasting over 20 years.

Ig products are registered by the TGA for the treatment of a range of indications under two main categories: 'replacement therapy' and 'immunomodulatory effect'. Under the National Blood Agreement, the basis for access to publicly funded Ig products is specified in the *Criteria for the Clinical Use of Intravenous Immunoglobulin in Australia, Version 3*[4]*.* The *Criteria V3*, list three specific indications in MG for which Ig treatment is publicly funded through the National Blood Arrangements (see also Appendix F for *Criteria V3* on MG):

1. Patients with, or at risk of, myasthenic crisis.
2. Patients with advanced MG, bulbar symptoms or respiratory involvement, prior to surgery and/or thymectomy.
3. As maintenance therapy in patients with moderate to severe MG when other treatments have been ineffective or caused intolerable side effects.

Various criteria around each of these indications must be met for patients to qualify for treatment.

[4] National Blood Authority 2018, *Criteria for the clinical use of immunoglobulin in Australia v3.0.1*, www.criteria.blood.gov.au/MedicalCondition/View/2549.

A.5. COMPARATOR DETAILS

The comparator for Indications 1 and 2 is plasma exchange (PE). As a blood product, plasma is supplied and regulated through the NBA. Both IVIg and PE are seen as short term therapies to be used to stabilise a patient whilst waiting for other therapies to become effective. Apart from the choice of stabilising therapy (IVIg or PE), other treatments are expected to be the same for both intervention and comparator.

The Ig Review Reference Group noted that the safety and effectiveness of PE were likely to be different based on how it is delivered (via central or peripheral venous access) and thus these would be considered as subgroups of the comparator in the review if evidence were available.

The Applicant stated that PE is not usually provided on an outpatient basis and cannot be used long term in most places, however it should be noted that the *Criteria V3* for ongoing use of Ig in the maintenance population lists PE as an alternative therapy. Expert advice from the Ig Review Reference Group indicated that PE should be a comparator in this indication.

The Ig Review Reference Group has indicated that access to PE is limited in Australia, restricting the use of this service for both clinicians and patients. The time taken to access PE services is usually considerably longer than the time it takes to access IVIg (days for PE compared witih hours for IVIg). It is necessary for PE to be delivered in hospital centres with central vein delivery cababilities, in the event that peripheral venous access breaks down, therefore limiting the number of hospitals that can provide PE. It should be noted therefore, that the choice of treatment by clinicians may be pragmatic, based on the different accessibility of PE and IVIg.

For Indication 3, patients may or may not be using other treatments at the same time as Ig; these include drugs in the categories of corticosteroids, anticholinesterases, immunosuppressants (IS) and immunomodulators (IM), as listed in Table 9 (provided by the Applicant). It is likely that most patients with moderate to severe MG would be on two other therapies. The majority of those listed can be prescribed for MG through the PBS, the exceptions being mycophenolate mofetil, ciclosporin and rituximab. Future comparator therapies are eculizumab and FcRn inhibitors but these are yet to be approved for use in Australia for this indication. It was noted from clinical input that it can take a long time to induce immunosuppression with a new therapeutic in MG patients, with a latency period of up to 18 months.

To be eligible for Ig for maintenance therapy, at least two other treatments must have been ineffective, contraindicated, unavailable, or have caused intolerable side effects. Evidence of effectiveness is required for ongoing Ig therapy and other indicated treatments should be trialled concurrently. It should be noted that the NBA *Criteria V3* state that IVIg "should be regarded as a stopgap treatment while using short-term drugs such as pyridostigmine and while introducing effective immunotherapy".

Table 9 Drug comparators for patients in Indication 3

Generic Name (Brand names)	PBS subsidised for MG	PBS unrestricted, restricted or Authority Required.	PBS item numbers and presentations If available for MG See Attachment D for ARTG indications
Oral Steroids			
Prednisone (Panafcort, Sone)	Yes	Unrestricted	25mg tablet, 30) (1936X) 5mg tablet, 60 (1935W) 1mg tablet, 100 (1934T)
Prednisolone (Panafcortelone, Solone)	Yes	Unrestricted	25mg tablet, 30) (1916W) 5mg tablet, 60 (1917X) 1mg tablet, 100 (3152X)
Dexamethasone (Dexamethasone Mylan, Dexmethsone)	Yes	Unrestricted	4mg Tablet, 30 (2507Y) 500 mcg tablet, 30 (1292B)
Methylprednisolone (Solu-Medrol, Methylpred, Methylprednisolone Alphapharm)	Yes	Unrestricted	40mg/ml injection, 5x1ml vials (1928L) 40mg injection, 5 vials & inert substance diluent, 5x1ml vials (2981X) 40mg/ml injection, 5x1ml vials (5148Y) 40mg powder for injection, 5 (5263B) 1g powder for injection, 1 (5264C)
Immunosuppressant and immunomodulatory drugs			
Azathioprine (APO-Azathioprine, Azathioprine GH, Azathioprine Sandoz, Imuran)	Yes	Unrestricted	25mg tablet, 200 (2688L) 50mg tablet, 100 (2687K)
Cyclophosphamide (Cyclonex, Endoxan)	Yes	Unrestricted	50mg tablet, 50 (1266P) Injection 2,800mg (4327R) Injection 2,800mg (7226H)
Ciclosporin (Neoral, Neoral 25, Neoral 50, Neoral 100, Cyclosporin Sandoz	Yes	Unrestricted For General Schedule listings only S100 listings are 'Authority Required' and do not include MG.	10MG capsule, 60 (8657P) 25mg capsule, 30 (8659Q) 50mg capsule, 30 (8659Q) 100mg capsule, 30 (8660T) 100mg/mL oral liquid, 50mL (8661W)
Mycophenolate mofetil (Ceptolate, Myfortic, APO-Mycophenolate, CellCept, Mycophenolate Sandoz, Pharmacor Mycophenolate 250, Mycophenolate AN, Mycophenolate Sandoz, Pharmacore Mycophenolate 500,	Yes	Unrestricted in General Schedule Authority required in S100 and MG not included.	250mg capsule, 50 (1836P) 180mg enteric tablet, 120 (2150E) 360mg enteric tablet, 120 (2150E) 250mg capsule, 100 (8649F) 500mg tablet, 50 (8650G) 1g/5mL powder for oral liquid, 165 mL (8651H
Methotrexate (Methoblastin	Yes	Unrestricted in General Schedule	2.5mg tablet, 30 (1622J) 10mg tablet, 15 (2272N)
Rituximab (Mabthera)	No	Chemotherapy Items, General Schedule and S100 listings are	NA

Generic Name (Brand names)	PBS subsidised for MG	PBS unrestricted, restricted or Authority Required.	PBS item numbers and presentations If available for MG See Attachment D for ARTG indications
		'Authority Required' and MG not included	
Other drugs			
Pyridostigmine (Mestinon Timespan, Mestinon)	Yes	Unrestricted in General Schedule	180mg modified release tablet, 50 (2608G) 10mg tablet, 50 (2724J)

ARTG = Australian Therapeutic Goods Administration; MG = myasthenia gravis; NA = not available; PBS = Pharmaceutical Benefits Scheme

A.6. CLINICAL MANAGEMENT ALGORITHM(S)

Clinical questions are partly defined through the development of flow charts, which help define the place of the intervention in clinical management. This includes whether the new intervention will be used incrementally or will replace a current intervention. This assists with identifying the correct comparator for the new intervention.

The clinical management pathways for Indications 1, 2, and 3 are shown in Figure 1,

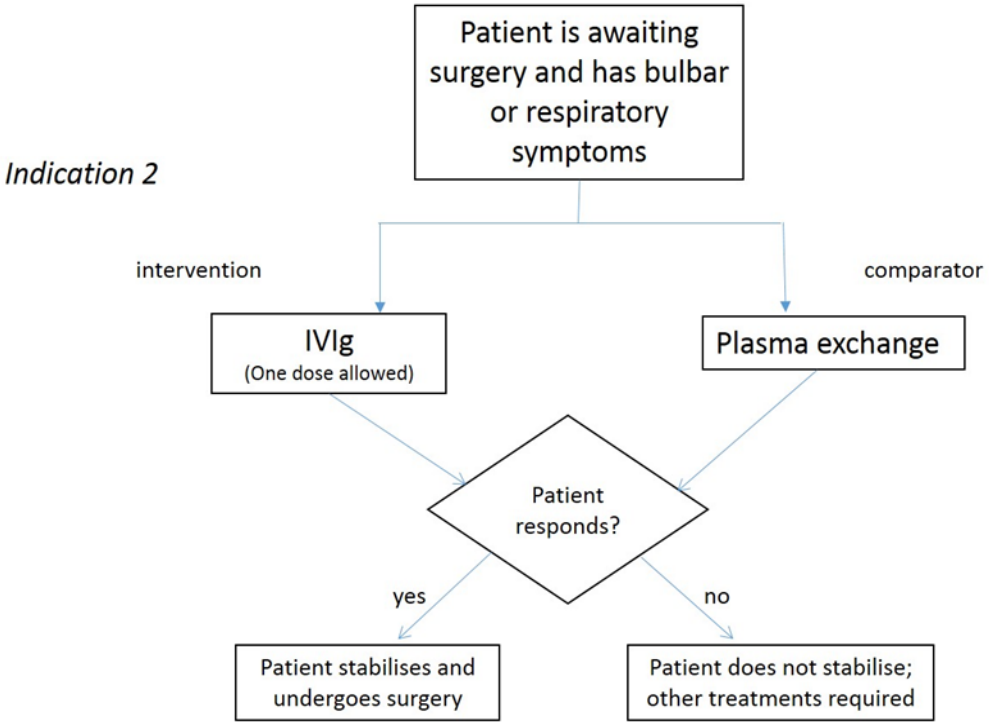

Figure 2 and Figure 3, below. Initially, patients must be diagnosed with MG by tests recommended by the Association of British Neurologist MG management guidelines. To be eligible for Ig for all indications covered by NBA *Criteria V3* a neurologist must make the diagnosis. Detailed criteria for eligibility are given in Appendix F.

To meet criteria for Indication 1 a patient must have respiratory insufficiency requiring intubation and assisted ventilation, or have symptoms to show they are at risk of life-threatening myasthenic crisis. Persistent respiratory or bulbar symptoms are considered to be life threatening. Patients are often already receiving IS or CS therapy or a combination of therapies. In these circumstances, the neurologist may consider IVIg or PE treatment. The availability of treatment, comorbidities and the type of MG (AChRAb, MuSK or seronegative) are factors to consider when choosing between IVIg and PE. If the patient is still receiving IVIg after 12 months a weaning off trial should be attempted.

Thymectomy is treatment often considered in MG patients to reduce the autoimmune response. Patients undergoing surgery can be at an advanced stage in the disease, and require stabilization prior to surgery. This may be achieved through treatment with IVIg if patients meet the criteria for Indication 2. The patient should be monitored for stabilization post-surgery.

To qualify for IVIg for Indication 3, a patient with non-life-threatening moderate to severe MG symptoms must have already tried and failed at least two standard therapies, either CS, IS or a combination of the two. Alternatively patients may have developed side effects to, or become contraindicated for, alternative therapies by development of comorbidities. Azathioprine is considered the first-line IS agent, but other non-steroidal IS therapies for use in MG include, ciclosporin, mycophenolate mofetil, methotrexate and tacrolimus. Rituximab and cyclophosphamide are considered for second-line therapies. A patient given IVIg (or PE) under Indication 3 should be using it as a stop-gap measure while he or she becomes stabilized on other standard therapies, as they cannot lead to remission of disease.

Indication 1

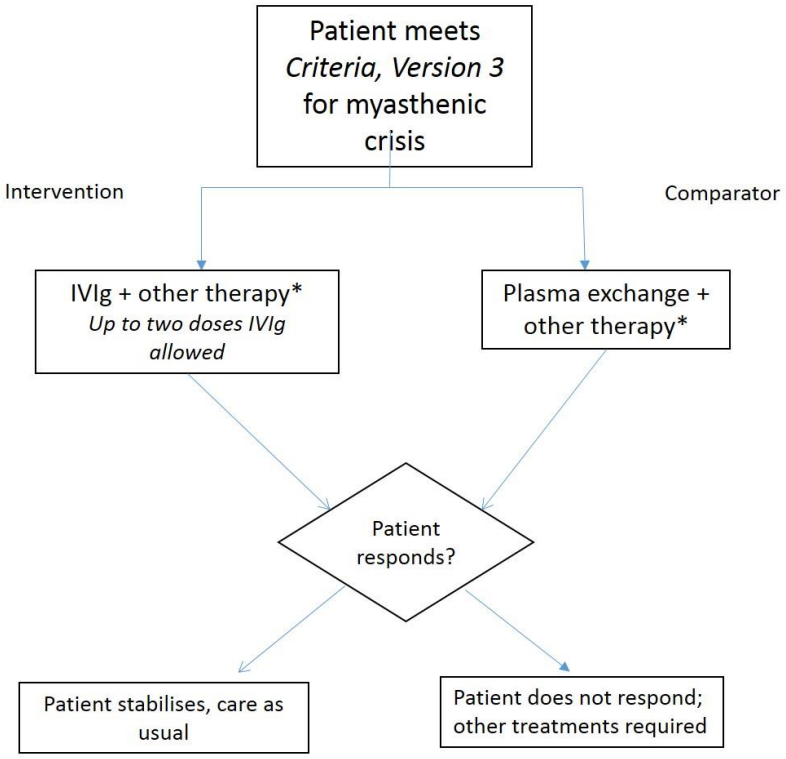

Figure 1 Clinical management pathway for patients with, or at risk of, myasthenic crisis

IVIg = intravenous immunoglobulin therapy

*Other therapies include corticosteroids, anticholinesterases, and immunotherapy; patients would not receive IVIg and plasma exchange concurrently.

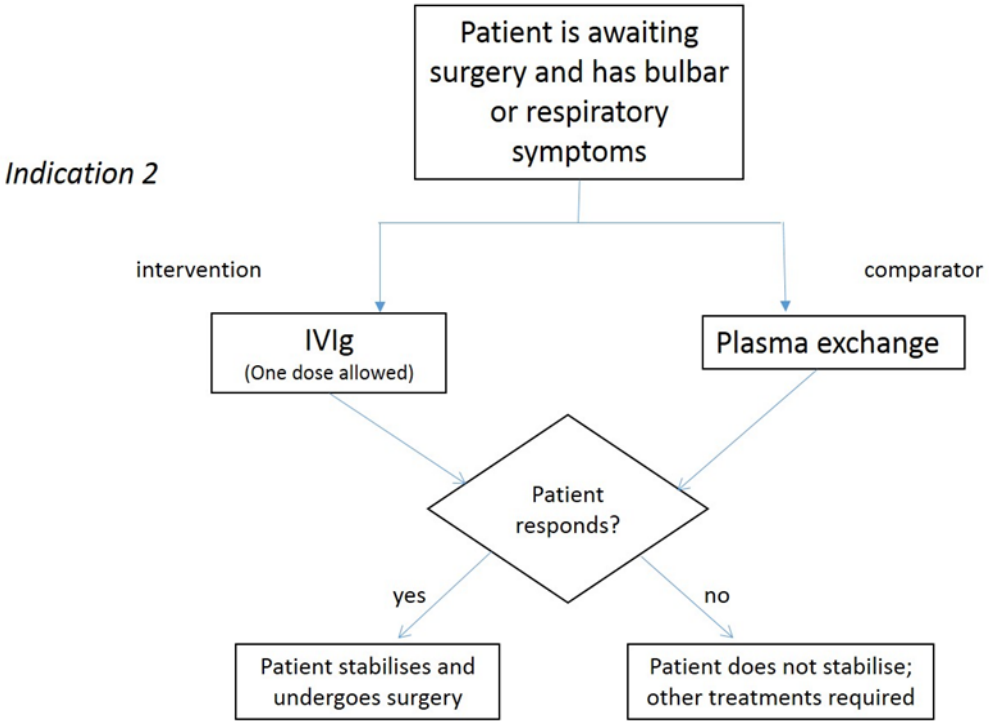

Figure 2 Clinical management pathway for patients with MG awaiting surgery and/or thymectomy

IVIg = intravenous immunoglobulin therapy; MG = myasthenia gravis

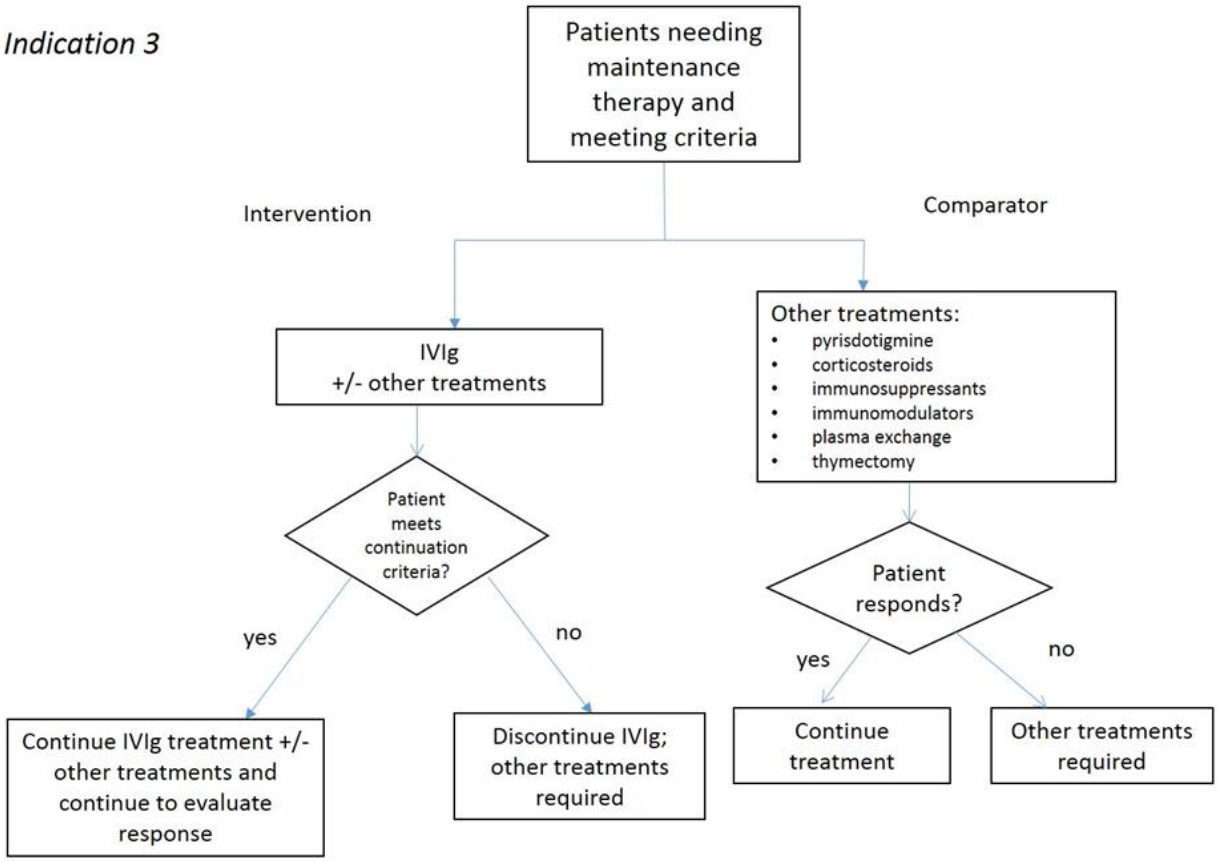

Figure 3 Clinical management pathway for patients with moderate to severe MG on maintenance therapy

IVIg = intravenous immunoglobulin therapy; MG = myasthenia gravis

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

The proposed medical service IVIg, is delivered intravenously, as is the main comparator, PE. IVIg is generally delivered over a shorter timeframe than PE, and uses a specific dosage per person. The dosage is based on a patient's weight and is usually a total of 1 or 2 g/kg. The infusion rate of IVIg is determined by the TGA's approved rate for the particular product and the hospital protocol, but is usually delivered on consecutive days until complete (for example, 2 to 5 days). If the patient experiences side effects such as headache, the infusion rate can be slowed to reduce the impact.

In comparison, PE is delivered on alternate days to achieve the number of plasma volume exchanges desired (for example, five plasma volume exchanges over 10 days). If peripheral venous access breaks down, PE may require delivery via a central vein which may carry greater risk of infection. This added risk of infection may impact on the safety profile of PE when compared to IVIg. Delivery by central vein access is only be performed in major city teaching hospitals in Australia, thereby restricting access for patients in rural areas. A large proportion of patients receiving PE long-term are likely to require central vein delivery, so those not living near to services would need to travel or temporarily move closer.

Ig also has the potential to be delivered subcutaneously for patients on maintenance therapy. In this circumstance, a patient would receive a lower dose of Ig than for IV therapy, and may require infusion twice weekly. A carer who is educated to administer the SCIg, or the patient themself, could perform this at the patient's home.

Both IVIg and PE use blood products that can be sourced both through collection and processing of blood donations from the Australian public, or through purchase from overseas. The majority of IVIg supplies are imported to meet the needs of Australians.

A.8. CLINICAL CLAIM

A **non-inferiority** claim was proposed by the Applicant for Indications 1 and 2 (where Ig is intended to be used for a limited time frame to manage a patient through a crisis or surgery, and has a direct comparator in plasma exchange).

For Indication 3, where Ig may be used as an adjunct therapy to immunotherapy or other standard therapeutics (not PE), there would need to be an additional benefit from the Ig therapy to justify its use i.e., a **superiority** claim (MSAC 2019).

A.9. SUMMARY OF THE PICO

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

The Population, Intervention, Comparator and Outcomes (PICO) that were pre-specified to guide the systematic literature review are presented in Box 1 to Box 3 (MSAC 2019).

Box 1 PICO criteria for assessing IVIg for the treatment of myasthenic crisis (Indication 1)

Component	Description
Population	Patients with, or at risk of, myasthenic crisis
Interventions	Intravenous Immunoglobulin
Comparators	Plasma exchange, delivered via central or peripheral venous access
Outcomes	**Patient-relevant outcomes** ***Safety*** adverse events associated with administration of the therapy (such as IV line insertion risks, line sepsis) side effects of the therapy (such as haemodynamic effects, inflammatory and thrombotic effects) ***Effectiveness*** mortality rates of infection improvement in symptoms (MGC score) improvement in quality of life rates of remission disease stability time to relapse need for ventilation or other life support systems **Healthcare system resources utilisation** ***Changes in health system resource utilisation associated with the intervention*** Ig products, Infusion equipment, Administrative and clinician time (e.g. resources associated with requesting, and authorising, access to Ig), Nursing time (for initiation and monitoring if IVIg) Hospitalisation (including use of hospital resources) Medication to treat of adverse events (e.g. analgesia or antihistamines) Product dispensing and disposal of any unused product Follow-up and/or monitoring visits, including regular neurology visits ***Change in health system resource utilisation associated with the comparator(s)*** Comparator products Resources to deliver the comparator (eg hospital and staff time for IV steroids and plasma exchange, dispensing for oral treatments) Hospitalisation

	Management of adverse events Follow-up and/or monitoring visits, including regular neurology visits
Study design	Randomised or non-randomised controlled trials, comparative studies with or without concurrent controls, or systematic reviews of these study designs
Search period	1981 (earliest use of Ig)-February 2019
Language	Studies in languages other than English will only be translated if they represent a higher level of evidence than that available in the English language evidence-base
1. What are the safety, effectiveness, and cost-effectiveness of IVIg for the treatment of MG compared to plasma exchange in patients experiencing or at risk of myasthenic crisis?	

Ig = immunoglobulin; IV = intravenous; MG = myasthenia gravis; MGC = myasthenia gravis composite score;

Box 2 PICO criteria for assessing IVIg treatment in patients with planned surgery or thymectomy (Indication 2)

Component	Description
Patients	Patients with advanced MG disease, bulbar symptoms or respiratory involvement, in whom surgery and/or thymectomy is planned
Intervention	Intravenous Immunoglobulin
Comparator	Plasma exchange, delivered by central or peripheral venous access
Outcomes	**<u>Patient-relevant outcomes:</u>** ***Safety*** adverse events associated with administration of the therapy (such as IV line insertion risks, line sepsis) side effects of the therapy (such as haemodynamic effects, inflammatory and thrombotic effects) ***Effectiveness*** mortality rates of infection improvement in symptoms (MGC score) improvement in quality of life rates of remission disease stability time to relapse time to surgery **<u>Healthcare system resources utilisation</u>** ***Changes in health system resource utilisation associated with the intervention*** Ig products, Infusion equipment, Administrative and clinician time (e.g. resources associated with requesting, and authorising, access to Ig), Nursing time (for initiation and monitoring if IVIg) Hospitalisation (including use of hospital resources) Medication to treat of adverse events (e.g. analgesia or antihistamines) Product dispensing and disposal of any unused product Follow-up and/or monitoring visits, including regular neurology visits ***Change in health system resource utilisation associated with the comparator(s)***

	Comparator products Resources to deliver the comparator (eg hospital and staff time for IV steroids and plasma exchange, dispensing for oral treatments) Hospitalisation Management of adverse events Follow-up and/or monitoring visits, including regular neurology visits
Study design	Randomised or non-randomised controlled trials, comparative studies with or without concurrent controls, or systematic reviews of these study designs
Search period	1981 (earliest use of Ig)-February 2019
Language	Studies in languages other than English will only be translated if they represent a higher level of evidence than that available in the English language evidence-base
2. What are the safety, effectiveness, and cost-effectiveness of IVIg for the treatment of MG compared to plasma exchange in patients with advanced MG disease in whom surgery and/or thymectomy is planned?	

Ig = immunoglobulin; IV = intravenous; MG = myasthenia gravis; MGC = myasthenia gravis composite score;

Box 3 PICO criteria for assessing IVIg treatment for maintenance therapy in patients with moderate to severe MG (Indication 3)

Component	Description
Patients	Patients with moderate to severe MG as assessed by a Myasthenia Gravis Composite score of at least four points, in whom at least two other treatments have been ineffective or caused intolerable side effects, or are contraindicated or unavailable.
Intervention	Immunoglobulin, delivered intravenously or subcutaneously
Comparators	Oral steroids (such as prednisone, prednisolone, dexamethasone, methylprednisolone) Anticholinesterases (pyridostigmine) Immunosuppressant and immunomodulatory drugs (such as azathioprine, methotrexate, cyclophosphamide, cyclosporine, mycophenolate mofetil, rituximab) Plasma exchange (via peripheral or central venous access) Thymectomy
Outcomes	**<u>Patient-relevant outcomes:</u>** ***Safety*** adverse events associated with administration of the therapy (such as IV line insertion risks, line sepsis) side effects of the therapy (such as haemodynamic effects, inflammatory and thrombotic effects) ***Effectiveness*** mortality rates of infection improvement in symptoms (MGC score) improvement in quality of life rates of remission disease stability time to relapse time to surgery

	need for ventilation or other life support systems **<u>Healthcare system resources utilisation</u>** ***Changes in health system resource utilisation associated with the intervention*** Ig products, Infusion equipment, Administrative and clinician time (e.g. resources associated with requesting, and authorising, access to Ig), Nursing time (for initiation and monitoring if IVIg) Hospitalisation (including use of hospital resources) Medication to treat of adverse events (e.g. analgesia or antihistamines) Training of patient or carer to provide infusions (SCIg only) Product dispensing and disposal of any unused product Follow-up and/or monitoring visits, including regular neurology visits ***Change in health system resource utilisation associated with the comparator(s)*** Comparator products Resources to deliver the comparator (eg hospital and staff time for IV steroids and plasma exchange, dispensing for oral treatments) Hospitalisation Management of adverse events Follow-up and/or monitoring visits, including regular neurology visits
Study design	Randomised or non-randomised controlled trials, comparative studies with or without concurrent controls, or systematic reviews of these study designs
Search period	1981 (earliest use of Ig)-February 2019
Language	Studies in languages other than English will only be translated if they represent a higher level of evidence than that available in the English language evidence-base
3. What are the safety, effectiveness, and cost-effectiveness of IVIg for the treatment of MG compared to plasma exchange, oral steroids, immunosuppressant or immunomodulatory drugs, or thymectomy in patients requiring maintenance therapy for moderate to severe MG and who have failed two previous therapies?	

Ig = immunoglobulin; IV = intravenous; MG = myasthenia gravis; MGC = myasthenia gravis composite score; SCIg = subcutaneous immunoglobulin therapy

A.10. STAKEHOLDER FEEDBACK ON THE PICO CONFIRMATION

TARGETED CONSULTATION

Feedback to the Targeted consultation Survey was received from a specialist neurologist, a manufacturer of therapeutic plasma exchange devices and a consumer.

The consumer did not provide comments specific to the referral form, but expressed that IVIg allows MG sufferers to experience a better quality of life and did not consider any disadvantages associated with IVIg treatment.

The medical device company emphasised the need for safety procedures in the administration of PE and IVIg. The New Zealand nursing IVIg guidelines were reiterated, and following of the guidelines was encouraged prior to first Ig infusion.

Overall the medical device company and neurologist agreed with the population (albeit the device company considered that MuSK-MG patients should be considered separately), intervention, and comparators described. The device company disagreed with the management algorithms, as PE was not shown as a true comparator to IVIg. The neurologist considered that the clinical scenarios in which IVIg could benefit patients was well described, and noted that IVIg is not a continuing therapy for most patients but a valuable alternative in the scenarios described.

SPONSOR COMMENTS ON THE PICO CONFIRMATION

On 21 May 2019, sponsors of Ig were contacted and given an opportunity to provide input to the development of this contracted assessment, specifically information relevant to the utilisation, efficacy, safety and cost-effectiveness of Ig.

Two sponsors provided comments on:

- The PICO, including the appropriateness of comparators and concurrent therapies
- Products that should be included/excluded from the assessment, and the interchangeability of products
- Patient benefits associated with new SCIg formulations
- Geographic inequity (related to access to plasma exchange compared to Ig)
- The treatment algorithm, treatment categories and place of Ig in therapy
- Available MG treatment guidelines
- The published data on effectiveness of Ig and comparators in MG treatment
- Estimating the utilisation of Ig for the treatment of MG, including care setting.

Sponsors also provided comments on management of the Ig supply and access to SCIg, and the process for the Ig Review. Sponsors did not provide any unpublished clinical trial data that would further inform the assessment.

SECTION B CLINICAL EVALUATION

B.1. LITERATURE SOURCES AND SEARCH STRATEGIES

The medical literature was searched on 13 March 2019 to identify relevant studies published during or after Jan 1980. Searches were conducted of the databases and sources described in Appendix B. Attempts were also made to source unpublished data or data from the Current Controlled Trials metaRegister. Search terms used for the PubMed/Medline platform are described in Table 10. It was not considered necessary to do separate searches for Indications 1, 2 and 3 as the population search terms were kept broad. Other databases were searched with similar text words and medical subject headings relevant to the database.

Table 10 Search terms used (PubMed/Medline platform)

Element of clinical question	Search terms
Population	myasthenia gravis (MeSH) OR myasthenia gravis
Intervention	immunoglobulin (MeSH) OR immunoglobulin (text) OR Ig OR IgG OR IVIg OR SCIg OR immunoglobulin G (MeSH) OR immunoglobulin G OR immune globulin OR immuneglobulin OR gamma globulin OR gammaglobulin
Comparator (if applicable)	NA
Outcomes (if applicable)	NA
Limits	Humans; published from 1980 onwards (IVIg was not used prior to 1980)

IVIg = intravenous immunoglobulin therapy; MeSH = Medical Subject Heading, based on a Medline/PubMed platform

B.2. RESULTS OF LITERATURE SEARCH

A PRISMA flowchart provides a graphic depiction of the results of the literature search and the application of the study selection criteria (listed in Box 1, Box 2 and Box 3) (Liberati et al. 2009).

The PRISMA flowchart for this assessment is provided in Figure 4. Studies were selected independently by two reviewers with a random sample independently assessed for consistency. Disagreements regarding study selection were resolved by consensus between two reviewers.

Case series were excluded except in subpopulations where little or no higher evidence was identified. Meeting presentation and poster abstracts, correspondence and non-systematic literature reviews were excluded unless there were extenuating reasons to include them such as they provided higher level evidence than was otherwise identified. Articles that were written in a language other than

English were excluded, unless the English abstract indicated that the article was of higher level evidence than identified in the other eligible articles.

Studies that could not be retrieved or that met the inclusion criteria but contained insufficient or inadequate data for inclusion are listed as Excluded Studies in Appendix D. All other studies that met the inclusion criteria are listed in Appendix C.

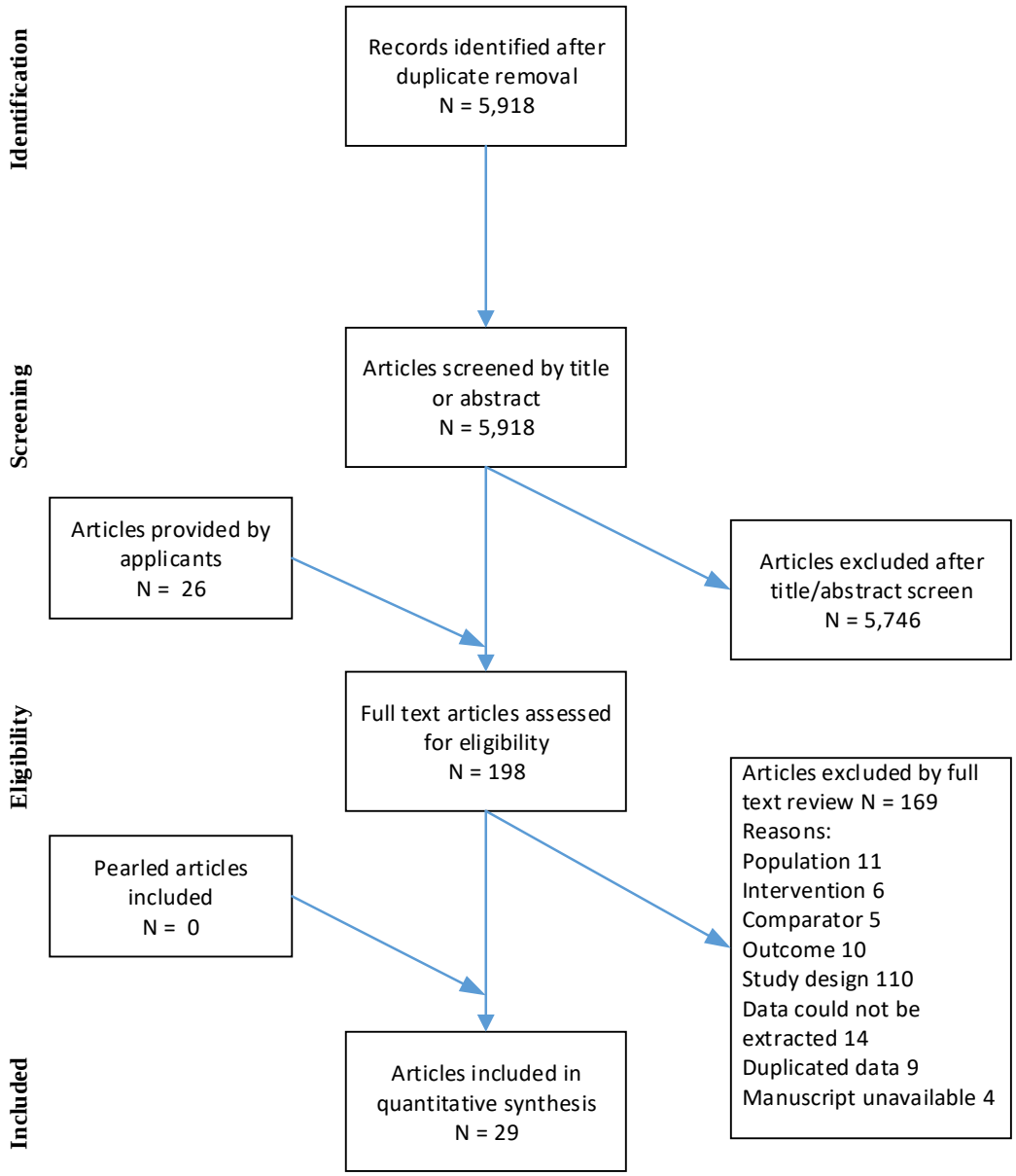

Figure 4 PRISMA flowchart: summary of the process used to identify and select studies for the assessment

A profile of each included study is given in Appendix C. This study profile describes the authors, study ID, publication year, study design and quality (level of evidence and risk of bias), study location, setting, length of follow-up of patients, study population characteristics, description of the intervention, description of the comparator, types of statistical analysis conducted, funding source

and the relevant outcomes assessed. Study characteristics are also summarised in a shorter format in *Section B.4,* Table 11 and Table 12.

APPRAISAL OF THE EVIDENCE

Appraisal of the evidence was conducted in four stages:

Stage 1: Appraisal of the risk of bias within individual studies (or SRs) included in the review. Some risk of bias items were assessed for the study as a whole, while others were assessed at the outcome level. (*Section B.3*)

Stage 2: Extraction of the pre-specified outcomes for this assessment, synthesising (meta-analysing or a narrative synthesis) to determine an estimate of effect per outcome.

Stage 3: Rating the overall quality of the evidence per outcome, across studies, based on the study limitations (risk of bias), imprecision, inconsistency of results, indirectness of evidence, and the likelihood of publication bias. This was done to provide an indication of the confidence in the estimate of effect in the context of Australian clinical practice (Evidence profile tables, Appendix D).

Stage 4: Integration of this evidence for conclusions about the net clinical benefit of the intervention in the context of Australian clinical practice. (*Sections B.6 Results of the Systematic Literature Review* and *B.7 Interpretation of the Clinical Evidence*)

B.3. RISK OF BIAS ASSESSMENT

Individual studies to be included were assessed using standard appraisal instruments appropriate for each study design. Study quality and level of bias were assessed using the AMSTAR 2 checklist for systematic reviews (Shea et al. 2017), the SIGN Methodology checklists 2 and 3 for randomised and non-randomised controlled trials and observational studies (SIGN 2014); and the Institute of Health checklist (IHE) was used to assess case series (IHE 2016).

Three SRs (level I) were identified that included studies relevant to this assessment. Two were found to be of low quality (high risk of bias) (Alabdali et al. 2014; Ortiz-Salas et al. 2016) and one high quality (low risk of bias) (Gajdos, Chevret & Toyka 2012). As only a proportion of articles from each SR fitted the eligibility criteria, all relevant studies were also appraised individually. The high quality SR included only RCTs, whereas the others included non-randomised trials as well. One SR performed a meta-analysis of adverse events reported in RCTs which had compared IVIg and PE therapies in MG patients in crisis or requiring maintenance therapy in one combined analysis (Ortiz-Salas et al. 2016). The outcome is reported in *Section B.6* and Figure 5. Three RCTs were common to all three SRs (Barth et al. 2011; Gajdos et al. 1997; Rønager et al. 2001).

In all, eight RCTs (level II) were identified that were relevant to this assessment (Alipour-Faz et al. 2017; Barth et al. 2011; Gajdos et al. 1997; Gajdos et al. 2005; Griffin et al. 2017b; Liu et al. 2010; Rønager et al. 2001; Zinman, Ng & Bril 2007). One of these was not yet published in the peer reviewed literature, but the authors had entered relevant data on clinicaltrials.gov and had published a related meeting abstract (Griffin et al. 2017b). Two further studies by Gajdos et al (Gajdos et al. 1998) and Barnett et al (Barnett et al. 2013) contributed additional data to the RCTs by Gajdos et al, 1997 and Barth et al, 2011 respectively. The published RCTs ranged in risk of bias from low to high. The high risk of bias RCTs tended not to be blinded, had poor randomisation methods, or did not reach their participant quotas and so lacked power. One RCT with high risk of bias used a cross-over design and included only 12 patients who received both treatments with an observation period between them (Rønager et al. 2001).

Nine comparative cohort studies (level III-2) were included for evidence (Jensen & Bril 2008; Leuzzi et al. 2014; Liew et al. 2014; Mandawat et al. 2010; Murthy et al. 2005; Panda et al. 2004; Pittayanon, Treeprasertsuk & Phanthumchinda 2009; Qureshi et al. 1999; Wang et al. 2016). The majority were retrospective in design. These studies were rated as moderate or high risk of bias. The studies tended to be very small, and it was not possible to rule out selection bias within some of them. One exception was a moderate quality study which included data from 1,606 MG patients, however some study characteristics were not well described and selection bias was a likely confounder (Mandawat et al. 2010). In most of the cohort studies the populations could be identified as Indication 1, 2 or 3 according to *Criteria V3,* which enabled most of the outcomes listed in the PICO Confirmation to be assessed.

Seven case series were included where there was a lack of evidence in a population of interest (for example patients receiving SCIg). The case series reported before and after IVIg treatment data and were well conducted and reported, however the case numbers were small (n = 9 to 52). They were all rated low for risk of bias (Beecher, Anderson & Siddiqi 2017; Bourque et al. 2016; Eienbröker et al. 2014; Hellmann et al. 2014; Nosadini et al. 2016; Selcen et al. 2000; VanderPluym et al. 2013).

B.4. CHARACTERISTICS OF THE EVIDENCE BASE

A summary of the key features of the included SRs is provided in Table 11 and for included primary studies in Table 12.

See Appendix C for full details on the individual studies included in the evidence base.

Table 11 Key features of the systematic reviews comparing IVIg with PE and other comparators in MG patients

Systematic review	K studies	Risk of bias	Intervention	Comparator	Patient population	Key outcome(s)	Used in economic model
(Alabdali et al. 2014)	K = 8	High	IVIg	PE Placebo IVIg (dose comparison)	Patients with acute or severe MG disease flare ups (myasthenic crisis) Worsening moderate to severe disease or on therapy for chronic disease	Change in MG status AEs	no
(Gajdos, Chevret & Toyka 2012)	K = 7	Low	IVIg	PE Oral MPN Placebo IVIg (dose comparison)	Patients with worsening MG or exacerbation Patients with severe but stable MG	Change in symptoms AEs	no
(Ortiz-Salas et al. 2016)	K = 10	High	IVIg	PE	RCT or observational studies of more than 10 cases that compared management with PE vs IVIg for MG	Patients improved AEs	no

AE = adverse event; IVIg = intravenous immunoglobulin therapy; K = number of studies; MG = myasthenia gravis; MPN = methylprednisolone therapy; PE plasma exchange therapy

Table 12 Key features of the primary comparative studies comparing IVIg with PE and other comparators in MG patients meeting *Criteria V3* Indication 1, 2 and 3

Trial/Study	N	Design	Risk of bias	Patient population	Comparison	Key outcome(s)	Used in econ model
Indication 1							
(Gajdos et al. 1997) (Gajdos et al. 1998)	47	RCT MC, DB Level II	moderate	Consecutive MG patients with exacerbation	IVIg v PE	AEs Change in MMS	yes
(Gajdos et al. 2005)	168	RCT MC,DB Level II	low	Consecutive MG patients with exacerbation	IVIg 1 g/kg v IVIg 2 g/kg	AEs Change in MMS	no
(Mandawat et al. 2010)	698	Ret Coh Level III-2	moderate	ICD-9-CM codes for primary diagnoses of MG (358.0) and MG crisis (358.01)	IVIg v PE	AEs Mortality Infection rate	yes
(Murthy et al. 2005)	21	Ret Coh Level III-2	high	All patients with episodes of MG crisis identified from the case records of the patients with MG seen by the senior author	IVIg v PE	AEs Mortality	no
(Panda et al. 2004)	11	Ret Coh Level III-2	high	Patients admitted to a neurology ward and ICU with MG crisis	IVIg v PE	AEs	no
(Pittayanon, Treeprasertsuk & Phanthumchinda 2009)	33	Ret Coh Level III-2	moderate-high	Patients with episodes of MG crisis recruited retrospectively using the hospital database	IVIg v PE	AEs Infection rate	yes
(Qureshi et al. 1999)	54	Ret Coh Level III-2	moderate	All patients with MG crisis who were treated with PE or IVIg in 4 US university-affiliated hospitals	IVIg v PE	AEs Mortality Infection rate Change in MSS	no
Indication 2							
(Alipour-Faz et al. 2017)	24	RCT SC, OL Level II	moderate	Adults with generalised MG & thymoma, positive AChRAb, undergoing thymectomy	IVIg v PE	AEs Ventilation needs	yes
(Jensen & Bril 2008)	18	Ret CC Level III-2	low	MG patients who underwent thymectomy	IVIg v PE	AEs Infection rate Change in OG	no
(Leuzzi et al. 2014)	177	Ret Coh Level III-2	moderate	MG patients who underwent thymectomy	IVIg v PE	Post-operative crisis	no

Trial/Study	N	Design	Risk of bias	Patient population	Comparison	Key outcome(s)	Used in econ model
Indication 3							
(Barth et al. 2011) (Barnett et al. 2013)	84	RCT SC, SB Level II	low	Adults (>18 y) with moderate to severe MG with QMGS >10.5 and worsening weakness sufficient to warrant change in treatment	IVIg v PE	AEs Change in QMGS Change in QoL	no
(Liu et al. 2010)	40	RCT SC, SB Level II	moderate	Patients with late-onset MG attending a Chinese hospital	IVIg v PE	AEs Change in QMGS	no
(Rønager et al. 2001)	12	RCT (cross-over) Level II	high	Generalised moderate to severe MG on IS treatment for at least 12 months, in Osserman Classes 3-5 and with functional status 4-5	IVIg v PE	AEs Infection rate	no
(Zinman, Ng & Bril 2007)	51	RCT SC, DB Level II	low	Adults with worsening weakness	IVIg v placebo	Change in QMGS	no
NCT02473952 (Griffin et al. 2017b)	62	RCT Level II	NA	MG patients who are symptomatic on standard of care treatment with a QMGS > 10 points at screening.	IVIg v placebo	AEs Mortality	no
(Mandawat et al. 2010)	908	Ret Coh Level III-2	moderate	ICD-9-CM codes for primary diagnoses of MG (358.0) and MG crisis (358.01)	IVIg v PE	AEs Infection rate	no
(Liew et al. 2014)	33	Ret Coh Level III-2	moderate	Children and adolescents with a diagnosis of juvenile MG who were seen in 3 Boston clinics	IVIg v PE	AEs Response to treatment	no
(Wang et al. 2016)	70	Ret CC Level III-2	high	Children with MG, pathological fatigue and daily unstable manifestation of myasthenia, positive neostigmine test result	IVIg + MPN v MPN	AEs Change in symptoms	no
(Nosadini et al. 2016)	12	CS Level IV	moderate	Children who received IVIg for MG at a single Australian hospital	IVIg	Change in severity (mRS)	no
(Selcen et al. 2000)	9	CS Level IV	moderate	Juvenile MG patients refractory to other treatments	IVIg	Change in functional status[a]	no
(VanderPluym et al. 2013)	34	CS Level IV	moderate	Cases of PM identified through the Canadian paediatric Surveillance Program	IVIg	Improvement	no
(Eienbröker et al. 2014)	16	CS Level IV	moderate	Incomplete response to standard long-term, high-dose IS therapy	IVIg	Change in QMGS	no
(Hellmann et al. 2014)	52	CS Level IV	low	Patients of any MG class attending a medical centre who failed to respond or were contraindicated to other therapies and offered maintenance IVIg	IVIg	AEs Change in MGFA class	no

(Beecher, Anderson & Siddiqi 2017)	22	CS Level IV	low	18 y or older, mild to moderate MG, worsening symptoms (MGFA class I to II/III or class II to III)	SCIg	AEs Change in symptoms (MGC, MMT QMGS) Change in QoL	no
(Bourque et al. 2016)	9	CS Level IV	low	Consecutive cases identified on a hospital Neuromuscular Disease Database	SCIg	AEs Change in QoL	no

AChRAb = acetylcholine receptor antibodies; AE = adverse event; CS = case series; DB = double blind; ICU = intensive care unit; IS = immunosuppressive therapy; IVIg = intravenous immunoglobulin therapy; MC = multi-centre; MG = myasthenia gravis; MGC = myasthenia gravis composite score; MGFA = Myasthenia gravis Foundation America; MMS = myasthenia muscle score; MMT = manual muscle test; MPN = methylprednisolone therapy; mRS = modified Rankin Scale; MSS = myasthenia severity scale; NA = not applicable; OG = Osserman grade; OL=open label (unblinded); PE = plasma exchange therapy; QMGS = quantitative myasthenia gravis score; QoL=quality of life; RCT=randomised controlled trial; Ret CC = retrospective case control; Ret Coh = retrospective cohort; SB=single blind; SC = single centre; SCIg = subcutaneous immunoglobulin therapy

[a] Functional status measured by the University of Virginia modification of Osserman classification

B.5. OUTCOME MEASURES AND ANALYSIS

The clinical effectiveness outcomes of interest reported by the included studies were:

- mortality
- change in symptoms (change in disability and muscle strength by various scales, described below)
- change in quality of life (by various scales described below)
- rate of remission
- disease stability
- time to relapse
- need for ventilation or other life support systems
- adverse events (AEs) associated with administration of the therapy or side effects of therapy (such as IV line insertion risks, line sepsis, haemodynamic effects, inflammatory and thrombotic effects)

The included studies used different classification scales to determine the change in muscle strength (or MG severity) in response to treatment. These measures fell into four broad categories: 1) functional categorical scales that divided patients into four or five classes or grades depending on their physical abilities; 2) categorical scales that measured the effectiveness of treatments according to the relative degree of physical improvement or detriment of patients after treatment; 3) subjective clinical and/or patient-reported questionnaires based on functional, clinical and QOL aspects of the disease, and 4) diagnostic tests such as antibody testing for AChRAb and MuSK titres or electrophysiology studies. Outcomes for category 4) diagnostic tests were not included in this assessment. See Appendix C for details on the outcome measures used in each included study, along with the statistical methods used to analyse the results.

FUNCTIONAL OR CLINICAL CATEGORICAL SCALES

Functional or clinical scales are designed to identify subgroups of patients with MG who share distinct clinical features or severity of disease. This may indicate different prognoses or responses to therapy (Jaretzki et al. 2000). Statistical evaluation of changes in these scales must treat variables as categorical/ordinal values and not as linear variables, or the results would be unreliable (Alabdali et al. 2014). The scales that were used are listed in Table 13. All of these scales were based on the historical Osserman clinical scales (Osserman & Genkins 1971), the most recognised being the Myasthenia Gravis Foundation of America (MGFA) classification (Jaretzki et al. 2000).

TREATMENT EFFECTIVENESS SCALES

Two studies discussed in *Section F Other Relevant Considerations* used the MGFA-ratified post-treatment status classifications scales (MGFA-PIS) to determine the effectiveness of the treatment, rating patients according to response to treatment from complete remission to death (Jaretzki et al. 2000). One study used the relative difference in pre-and post-treatment scores of the Myasthenia Gravis absolute score (MGAS; scored 0−60) to classify patients as recovered, improved or unchanged (Wang et al. 2016). The details of these two scales are summarised in Table 14.

MG SEVERITY AND/OR QOL LINEAR SCALES

These scales provide a score based on questions about muscle function or coping with daily living. To assess the effect of treatment, the scales should compare measurements at appropriate intervals with a baseline measurement. The effectiveness of a treatment can be assessed according to whether or not the change in score effects a minimal clinically important difference (MCID). The scales used by the included studies are listed in Table 15, with a summary of what the scales measure provided in the footnotes.

Only one study (Beecher, Anderson & Siddiqi 2017) used the MGC scale to measure the change in muscle strength after treatment, as outlined above. The most commonly used scale was the quantitative myasthenia gravis score (QMGS), and its use in clinical trials has been recommended by the MGFA (Jaretzki et al. 2000). The QMGS is a quantitative assessment of sentinel muscle groups that measures the severity of any loss of strength to the eyelids, throat, hands, arms and legs. It provides an objective evaluation of therapy for MG.

The MGC score is used for eligibility in *Criteria V3* and is considered a condensed and less time consuming assessment compared to the QMGS. It uses items routinely measured at a clinical examination. An improvement of ≥ 3 points on the MGC has been shown to have clinical significance (National Blood Authority).

The MG activities of daily living (MG-ADL) scale is also a validated scale (Wolfe et al. 1999) that was used in several studies. Most of the other scales used by studies to evaluate muscle strength were validated against either the QMGS or MG-ADL scales.

The Myasthenia Gravis Quality-of-Life (MG-QoL-60) 60-question scale was used to in one RCT that measured QoL. This questionnaire was constructed by interviewing neuromuscular experts and MG patients through focus groups. The shorter MG-QoL-15 (15-question scale) used to measure in other studies reporting this outcome, was designed to capture the "role-physical" and "social functioning" subscale of the Short Form Health Survey (Burns et al. 2008).

The QMGS was the only linear scale for which a correlation to a categorical scale was reported. QMGS correlated strongly (r=0.54) with the MGFA (Alabdali et al. 2014), however no details of whether the comparison was using the MGFA scale as a categorical or linear variable was provided. (Burns, Conaway & Sanders 2010). Correlations between various linear scales for severity and QoL are given in Table 15.

(Suggested guidelines for interpreting the strength of the correlation using the Pearson's correlation coefficient are strong 0.5−1.0, moderate 0.3−0.5 and weak <0.3)

Table 13 The functional or clinical categorical scales used to assess patients in the included studies

Scale	Remission	Ocular disease	Mild disease	Moderate disease	Severe disease	Advanced disease
Historical Osserman clinical stage (Osserman & Genkins 1971)	No symptoms	Stage I: Ocular signs only	Stage IIA: Generalized mild muscle weakness	Stage IIB: Generalized moderate weakness and/or bulbar dysfunction	Stage III: Acute fulminating presentation and/or respiratory dysfunction	Stage IV: Late generalized weakness
Modified Osserman classification (Jensen & Bril 2008)	Class 0 No symptoms	Grade 1 Ocular signs and symptoms	Grade 2 Mild generalized symptoms	Grade 3 Moderate generalized symptoms, bulbar dysfunction, or both	Grade 4 Severe generalized weakness, respiratory dysfunction, or both	-
MGFA classification (Jaretzki et al. 2000)	No symptoms	Grade I: Any ocular muscle weakness	Grade II: Mild weakness affecting muscles with or without ocular muscle weakness	Grade III: Moderate weakness affecting muscles with or without ocular muscle weakness	Grade IV: Severe weakness affecting muscles with or without ocular muscle weakness	Grade V: Defined by intubation, with or without mechanical ventilation and/or a feeding tube
Oosterhuis grade Functional status (Rønager et al. 2001)	Grade 1 Asymptomatic	-	Grade 2 Minor symptoms with repetitive exercise	Grade 3 Mildly disabled (symptoms readily apparent, with restrictions of more demanding exercise)	Grade 4 Patients restricted in daily activities and symptomatic at rest	Grade 5 Completely dependent on skilled care for support

Table 14 The categorical scales used to evaluate treatment effectiveness

Scale	Remission	Improved	Unchanged	Worse	Exacerbated
MGFA-PIS	Complete Stable Remission: The patient has no symptoms and has received no therapy for MG for at least 1 year Pharmacologic Remission: The patient has no symptoms but continues to take some form of therapy for MG Minimal Manifestations:	Improved A substantial decrease in pre-treatment clinical manifestations or a sustained substantial reduction in MG medications	Unchanged No substantial change in pre-treatment clinical manifestations or reduction in MG medications	Worse: A substantial increase in pre-treatment clinical manifestations or a substantial increase in MG medication	Exacerbation: Patients who have subsequently developed clinical findings greater than permitted in the study research protocol Died of MG:

Scale	Remission	Improved	Unchanged	Worse	Exacerbated
	The patient has no symptoms of functional limitations but has some weakness on examination of some muscles.				Patients who died of MG, of complications of MG therapy, or within 30 days after thymectomy.
Relative MGAS	Score = 0.95: The patient has recovered	Score = 0.80− 0.95: The patients are basically cured Score = 0.50−0.79: There are evident effects Score = 0.25−0.49: The conditions of patients are improved	Score < 0.25: No treatment effect.	-	-

MGFA-PIS = Myasthenia Gravis Foundation of America post-intervention status (Jaretzki et al. 2000)
Relative MGAS = the relative score of the Myasthenia Gravis absolute score (MGAS; scored 0−60) is the per cent change in the before treatment and after treatment scores (Wang et al. 2016)

Table 15 The MG severity and/or QOL linear scales used to assess patients in the included studies

Scale	Number of questions	Scoring per question	Total score range	Normal	Most severe	Minimal clinically important difference	Correlation
MG severity							
QMGS	13	0−3	0−39	0	39	**By baseline score:** 0-16 MCID ≥2 points 17-39 MCID ≥3 points **Overall:** ≥3.5 points	MGFA: r=0.54 MG-QoL-15: r=−0.41, p=0.0007 MMT: r=0.73, p<0.0001
MGC	10	4 possible scores per Q: varies 0−9	0−50	0	50	≥3-points	MG-QoL-15: r=0.68 MG-ADL: r=0.80
MG-ADL	8	0−3	0−24	0	24	≥2 points	QMGS: r=0.583, p<0.001
MMS	9	7: 0, 5, or 10 2: 0−15	0−100	100	0	≥20-points	QMGS: r=0.869, p=0.0001
MMT	30	0−4	0−120	0	120	2≥ points	QMGS: r=0.69

Scale	Number of questions	Scoring per question	Total score range	Normal	Most severe	Minimal clinically important difference	Correlation
MSS	5	4: 0−3 1: 0−4	0−16	16	0	-	-
QoL							
MG-QoL-15	15	0−4	0−60	0	60	≥6 points	QMGS: r=0.55, p<0.001 MG-ADL: r=0.70, p<0.001 MMT: r=0.44, p<0.001
MG-QoL-60	60	0−4	0−240	0	240	>15 points	QMGS: r=0.53, p<0.001 MG-ADL: r=0.72, p<0.001 MMT: r=0.46, p<0.001

MCID = minimal clinically important difference;
MG-ADL = MG activities of daily living is a validated scale scored 0–3 for 8 specific symptoms characteristic of myasthenic weakness, namely: talking, chewing, swallowing, breathing, ability to brush teeth or comb hair, ability to arise from a chair, diplopia and ptosis (Wolfe et al. 1999);
MGC = MG composite, a (5 min) score using 10 items from QMGS, MG-ADL, or MMT (Burns, Conaway & Sanders 2010);
MG-QOL-15 = Myasthenia Gravis Quality-of-life (15 question) was designed to capture the "role-physical" and "social functioning" subscale of the Short Form Health Survey. Questions (scored 0-4) about frustration, trouble using eyes, trouble eating, limitations of social activities, enjoyment of hobbies and fun activities, meeting needs of family, planning around condition, effect on occupation, difficulty speaking, trouble driving, depression, trouble walking, trouble getting around in public, feeling overwhelmed, and personal grooming (Burns et al. 2008);
MG-QOL-60 = Myasthenia Gravis Quality-of-life (60 question) was derived from interviews with neuromuscular experts and MG patient focus groups and consisted of domains for Mobility, Symptoms, Emotional Well-Being, General Contentment, Thinking and Fatigue, Family/Social Well-Being and Additional Concerns (Barnett et al. 2013; Mullins et al. 2008);
MMS = Myasthenia muscle score is the sum of nine independent observations, four items assessing the muscular strength of the trunk and limbs and five items assessing the cranial muscles (Gajdos et al. 1993; Sharshar et al. 2000);
MMT = Manual muscle test is the sum of strength or function values assigned by the examining physician to 30 muscle groups usually affected by MG (Sanders, Tucker-Lipscomb & Massey 2003);
mRS = modified Rankin severity scale
MSS = Myasthenia severity scale; dyspnoea: 1 (intubated) to 4 (none), cough: 1 (intubated) to 3 (normal), Ocular: 1 (weakness at rest) to 3 (none), Bulbar 1 (weakness at rest) to 3 (none), Extremities: 1 = worst affected muscle 3/5 or less, 2 = worst affected muscle 4/5 motor strength or weakness on fatigue, 3 = no detectable weakness (Qureshi et al. 1999);
QMGS = Quantitative MG score includes 13 items about the onset time of diplopia, blepharoptosis, the strength to close the lips, swallow and vocalize, duration of the outstretched times of both arms and legs, vital capacity, grip of both hands, time to raise head in horizontal position. Each item was graded on a scale of 0 (normal), light (1), medium (2) and severe (3).(Jaretzki et al. 2000)

B.6. RESULTS OF THE SYSTEMATIC LITERATURE REVIEW

IS IT SAFE?

Summary – What is the safety of IVIg compared to PE for patients with MG?

Although there were many studies contributing to the evidence base for safety, most of the studies were quite small. This is especially true for the higher level studies (RCTs) which were almost certainly too small to identify rare AEs, or to compare groups on rates of AEs. The larger cohort studies were of more appropriate size to identify AEs, and were consistent with the RCTs in finding fewer AEs in the patients undergoing IVIg. However, as patients were not randomised in the observational studies, there is likely to be confounding due to clinical condition of the participants.

Indication 1: Patients in or at risk of myasthenic crisis

Overall, there were fewer adverse events for patients given IVIg compared to those given PE, but some events were more common to particular treatments. This result may by unreliable due to selection bias, as the literature indicates that PE is the favoured treatment for patients in crisis and in need of intubation, as it appears to achieve a quicker response than IVIg.

Indication 2: Patients with MG preparing for surgery

There was evidence indicating that more patients required intubation and experienced post-operative crisis on PE compared to IVIg, but the results may be confounded by the preference to use PE in myasthenic crisis.

Indication 3: Patients needing to change maintenance therapy for MG

There was insufficient evidence to make conclusions about the safety of IVIg compared to standard therapies other than PE.

In adults, there were significantly more headaches and vomiting in the IVIg maintenance patients, and more venous access problems (citrate reaction, restricted venous access so as to delay treatment and vasospasm) in the PE patients, but overall there were no differences between groups for minor AEs. There were too few serious AEs to conclude either treatment was safer than the other.

In children there were no significant differences in the rate of AEs between those receiving IVIg and PE, but this result may be unreliable due to the small study sizes.

A large proportion of patients receiving SCIg experienced headaches, injection site reaction and nausea, but there were few serious AEs.

A summary of the evidence included for safety of IVIg for *Criteria V3* Indications 1 and 2 and IVIg or SCIg for Indication 3 is provided in Table 11 (SRs) and Table 12 (primary studies). The full evidence profile table (with explanatory footnotes), incorporating all critical and important outcomes, can be found in Appendix C Studies included in the Systematic Review. A summary of the clinical benefits and harms of Ig for MG is provided in Table 48 to Table 51.

Three SRs compared AEs between patients receiving either IVIg or PE for the management of MG. Two of the SRs (Alabdali et al. 2014; Gajdos, Chevret & Toyka 2012) did not perform any meta-analysis due to the dissimilarity across studies, and therefore reported studies individually. Gajdos, Chevret and Toyka (2012) included only RCTs comparing IVIg with any other medical therapy (or placebo). The two more recent SRs (Alabdali et al. 2014; Ortiz-Salas et al. 2016) included Level II and Level III studies. Ortiz-Salas et al performed meta-analysis between similar outcomes and populations from the included RCTs. There were three RCTs common to the SRs all of which compared IVIg with PE (Barth et al. 2011; Gajdos et al. 1997; Rønager et al. 2001). Outcomes of the meta-analysis are presented first, followed by individual studies pearled from the SRs, and those identified in the literature search.

AE results from one recent RCT (NCT02473952) were identified on the clinicaltrial.gov website, and included in this assessment. This article did not strictly meet the PICO criteria as the comparator was placebo. It was included as these were the only results available which compared IVIg to placebo in a population on standard maintenance therapies listed as comparators for Indication 3 (for example IS, IM), therefore had the potential to show incremental benefit of IVIg over these therapies.

AEs due to administration of the treatment and side effects of the treatment itself were not often separated in the study data. They are discussed together in this report and given individual comment where appropriate.

INDICATIONS 1 AND 3: ADVERSE EVENTS META-ANALYSIS

The SR by Ortiz-Salas et al performed a meta-analysis on adverse event overall incident data from four individual clinical trials (Barth et al. 2011; Gajdos et al. 1997; Liu et al. 2010; Rønager et al. 2001) (Figure 5). According to the *Criteria V3* provided by the NBA, the population included by Gajdos et al, 1997 aligns with Indication 1 (crisis), whereas the other three study populations align more closely with Indication 3 (maintenance). As MG patients with Indication 1 and 3 are likely to experience different AEs, or similar AEs of different severity, a meta-analysis of these studies may not accurately reflect individual populations and therefore should be considered with caution. The authors reported that AE severity could not be established because it was not categorised in the study articles.

The meta-analysis found no statistically significant difference between IVIg and PE for the likelihood of adverse events (OR 0.65; 95% CI 0.16, 2.57).

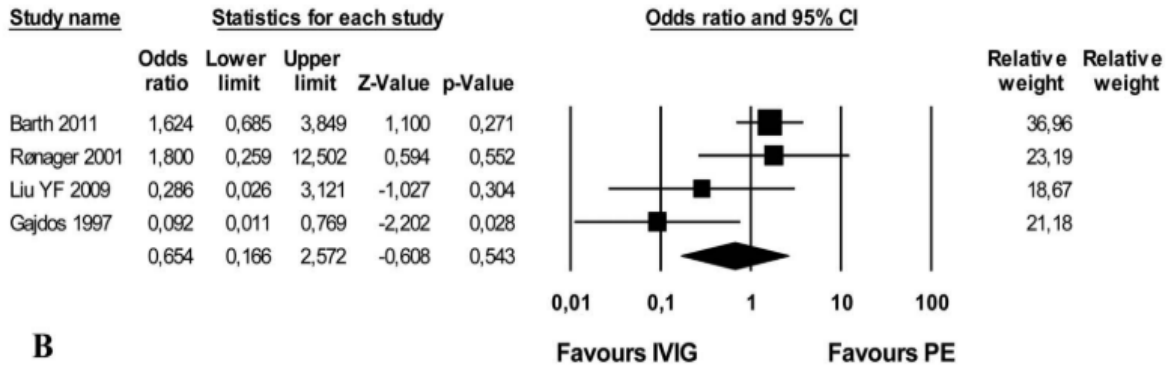

Figure 5 Comparison of adverse effects for IVIg versus PE in clinical trials (Ortiz-Salas et al. 2016)

INDICATION 1: PATIENTS IN OR AT RISK OF MYASTHENIC CRISIS

Adverse events for IVIg compared to PE

Adverse events were reported in one RCT (level II) (Gajdos et al. 1997) and five retrospective comparative cohort studies (level III-2) (Mandawat et al. 2010; Murthy et al. 2005; Panda et al. 2004; Pittayanon, Treeprasertsuk & Phanthumchinda 2009; Qureshi et al. 1999). The RCT (Gajdos et al. 1997) compared IVIg and PE in patients with MG exacerbation who largely met the *Criteria V3* for Indication 1. The inclusion criteria were: appearance within the previous month of at least one of difficulty swallowing, acute respiratory failure or major functional disability responsible for the discontinuation of physical activity. Prior to IVIg or PE treatment, the majority of patients were in disease stage 4 or 5 (61% in the PE group; 67% in the IVIg group). To fully describe the disease stage of all patients according to the study's functional scale, baseline data are given in Table 16. The data for patients at stages 1 and 2, and stages 4 and 5 were not separated. There were 87 patients in total included in the RCT, with 46 randomised to IVIg, these were further randomised to IVIg (0.4 g/kg) for either 3 or 5 consecutive days for a dosage comparison. Adverse events were not separated for IVIg dose. The RCT was assessed as moderate for risk of bias.

Table 16 Disease stage of patients prior to exacerbation, stratified by treatment (Gajdos et al. 1997)

Functional stage and description	Number of patients - IVIg	Number of patients - PE
1 - complete remission OR 2 - minor symptoms allowing normal non-exertional activity	5 (11%)	6 (15%)
3 – moderate symptoms allowing occupational or partial daily activity	10 (22%)	10 (24%)
4 – major disability requiring discontinuation of occupational activity OR 5 – major disability requiring continuous help by other or mechanical ventilation	31 (67%)	25 (61%)

IVIg = intravenous immunoglobulin therapy; PE = plasma exchange therapy

One of the cohort studies (Mandawat et al. 2010) was a large retrospective analysis of 1,606 patients performed with data from an administrative database. Hospitalised patients diagnosed with MG or in MG crisis and who underwent either IVIg or PE treatments were included and analysed separately. Patients identified as having MG crisis were considered to meet the *Criteria V3* for Indication 1[5].

The four other retrospective cohort studies that compared AE data between small patient groups were assessed between moderate and high for risk of bias (Murthy et al. 2005; Panda et al. 2004; Pittayanon, Treeprasertsuk & Phanthumchinda 2009; Qureshi et al. 1999). All but one of these (Qureshi et al. 1999) compared complications per crisis episode, as some patients experienced more than one crisis and hospital admission.

Selection bias could not be ruled out in the cohort studies. In particular, the large study by Mandawat et al reported baseline data that reflected a significantly higher number of patients who underwent PE experienced acute respiratory failure and were intubated compared to those given IVIg ($P < 0.0001$). Considering that other literature nominates PE is the faster acting treatment of the two (Barth et al. 2011; Qureshi et al. 1999), it is probable that patients in respiratory crisis were given PE in preference to IVIg. It is possible that this preference extends to the other cohort studies.

All studies reported more AEs or a greater proportion of patients experiencing AEs when given PE compared to IVIg. The difference between treatments did not always reach statistical significance, and some particular events were more common to PE or IVIg. Hypotension was a common AE in the PE group, but was relatively easily treated. Headaches and elevated blood urea were more common in those treated with IVIg, but once again these were considered minor symptoms.

In the RCT (Gajdos et al. 1997) there were more AEs observed in the patients who were randomised to PE treatment than in those who underwent IVIg (Table 17). The proportion of patients experiencing an AE was 19.5% (95% CI 7.4%, 31.6%) in the PE group compared to 2.2% (95% CI 0, 6.4%) in the IVIg group, the difference showing statistical significance ($p = 0.01$, Fisher's exact test). In the PE group, eight patients experienced events, with two serious enough to require discontinuation of treatment (one femoral thrombosis and one retroperitoneal haematoma). A further two patients did not complete PE treatment and were transferred to the IVIg group, due to difficulty obtaining vascular

[5] Patients were identified by the ICD-9-CD code 358.01 for acute MG crisis or of an MG patient had a secondary diagnosis of acute respiratory failure by coded518.81, and/or required mechanical ventilation during the same admission.

access in one patient and angina pectoris in the second. The transfer was made prior to the start of treatment.

Data on AEs from the large retrospective cohort by Mandawat et al (Mandawat et al. 2010) supported the RCT results. Mandawat et al found a significantly greater number of AEs in the PE group for complications overall, and for all other reported AEs, including cardiac complications (unadjusted complication rate 30.06% versus 14.79%; $p = 0.0001$) and systemic infections (unadjusted systemic infection rate 9.45% versus 1.18%; $p < 0.0001$). In their analyses of possible baseline covariates, the authors found that crisis patients receiving PE were more likely to have been discharged to a rehabilitation facility ($p < 0.001$) and less likely to have been treated at a rural hospital ($p < 0.01$) but hospital size, teaching status and hospital region were not different between groups.

Table 17 Number of adverse events in patients undergoing IVIg compared with PE

Study ID, Country Level of evidence Risk of bias	Event	IVIg n with event (%)	PE n with event (%)	Difference p-value (95% CI)
(Gajdos et al. 1997), France Level II Moderate	Patient number	46	41	-
	Haemolysis	0	1	
	Bleeding disorder	0	2	
	Catheter related venous thrombosis	0	1	
	Fever (≥38^{0}C)	0	2	
	Chills	0	2	
	Headaches	0	0	
	Nausea, vomiting	1	1	
	Systolic blood pressure <80 mm Hg	0	2	
	Tachycardia	0	1	
	Other	0	2	
	Total events	1 (2.2%)	14 (34%)	p = 0.0001 (16.2%, 47.2%)[a]
	Patients with ≥ 1 event	1 (2.2%)	8 (19.5%)	P = 0.01[b]
(Mandawat et al. 2010), USA Level III-2 Moderate	Patient number	169	529	-
	Any complication	25 (14.79%)	159 (30.06%)	P < 0.0001[b]
	Cardiac	20 (11.83%)	120 (22.68%)	P = 0.001
	Acute renal failure	2 (1.18%)	25 (4.73%)	P = 0.038
	Systemic infection	2 (1.18%)	50 (9.45%)	P < 0.0001
	Thrombotic complications	1 (0.59%)	18 (3.40%)	P = 0.05
(Murthy et al. 2005), India Level III-2 High	Crisis episodes[c] (there were 23 crises in 21 patients)	8	15	-
	Hypotension	0	2 (13.3%)	p = 0.29 (-20.5%, 37.8%)[a]
	Elevated blood urea and serum creatinine	1 (12.5%)	0	p = 0.70 (-19.4%, 33.8%)[a]
(Pittayanon, Treeprasertsuk & Phanthumchinda 2009), Thailand Level III-2 Moderate - high	Crisis episodes[c] (there were 33 episodes in 26 patients)	9	21	Overall difference between groups
	Ventilator or hospital acquired pneumonia	1 (11.1%)	4 (18.2%)	p = 0.073[b]
	Others[d]	1 (11.1%)	9 (40.9%)	
	None	7 (77.8%)	9 (40.9%)	
(Panda et al. 2004), India Level III-2 High	Crisis episodes[c] (there were 12 episodes in 11 patients)	4	8	NR
	Hypotension	0	1 (12.5%)	
(Qureshi et al. 1999), USA Level III-2 Moderate	Patient number	26	28	
	All complications	5 (19.2%)	13 (46.4%)	P = 0.07[e]
	Elevated blood-urea nitrogen	2 (7.7%)	0	-

IVIg = intravenous immunoglobulin therapy; NR = not reported; PE = plasma exchange therapy

[a] Chi squared test, MedCalc online calculator

[b] Fisher's exact test (Gajdos et al. 1997), (Mandawat et al. 2010)

[c] The article reported treatment type per crisis episode

[d] Other complications were aspiration pneumonia, catheter elated infection, urinary tract infection, haemothorax, pneumothorax, chylothorax, acute renal failure and sepsis. There was one incidence of sepsis amongst the IVIg treated episodes.

[e] EpiInfo 6.6 (Qureshi et al. 1999)

Adverse events for IVIg 1 g/kg compared to 2 g/kg (IVIg dose comparison)

One RCT compared two IVIg doses in patients with MG exacerbation and reported the AEs for each group (Gajdos et al. 2005). MG exacerbation was described in the same way as in the previous study assessed and therefore is closely aligned with *Criteria V3* Indication 1 (Gajdos et al. 1997). In the dose comparison RCT group one was given 1 g/kg IVIg on day 1 and placebo on day 2, whereas group two was given 1 g/kg IVIg on days 1 and 2 (1g/kg versus 2 g/kg IVIg). The double-blind study was assessed as low risk of bias and randomised 168 patients from multiple centres.

AEs were reported for the first 15 days after randomisation and treatment. There was no significant difference found for cumulative AE incidence between the two doses (mean ± SD - group 1: 40.48 ± 5.36; group 2: 46.59 ± 5.32; p = 0.39). AE frequencies for both groups are given in Table 18. For individual AEs, there was a similar incidence in both groups except for headaches, where a statistically higher frequency was seen in the lower dosed 1 g/kg total group (p = 0.05).

Table 18 Comparison of main adverse events between groups 1 and 2 within 15 days of randomisation (Gajdos et al. 2005)

Adverse event	Group 1 (n = 84) IVIg 1 g/kg total n (%) patients with ≥ 1 episode	Group 2 (n = 88) IVIg 2 g/kg total n (%) patients with ≥ 1 episode	Difference p-value [a]
Fever	10 (11.9%)	13 (14.8%)	0.66
Chills	3 (3.6%)	5 (5.7%)	0.72
Myalgia	1 (1.2%)	1 (1.1%)	>0.99
Headaches	11 (13.1%)	2 (22.7%)	0.05
Nausea or vomiting	5 (6.0%)	6 (6.8%)	>0.99
Skin reactions	1 (1.2%)	1 (1.1%)	>0.99
Other	16 (19%)	16 (18.2%)	0.69
Cumulative incidence	40.48 ± 5.36	46.59 ± 5.32	0.39

IVIg = intravenous immunoglobulin therapy

[a] Fishers exact test (Gajdos et al. 2005)

INDICATION 2: PATIENTS PREPARING FOR SURGERY

Adverse events (including myasthenic crisis) for IVIg compared with PE

One RCT (Alipour-Faz et al. 2017) and one retrospective matched cohort study (Jensen & Bril 2008) compared AEs between patients given IVIg or PE in preparation for thymectomy. The patient numbers were very small and the studies were not well powered to reach conclusions. The single centre RCT included 24 adult patients with generalised MG and thymoma and abnormal AChRAb levels. In the retrospective study, patients who were given IVIg prior to thymectomy were identified on database records. These patients were then matched with similar cases from a total cohort of 105 surgical patients who received PE prior to thymectomy. There were nine patients in each group.

The retrospective comparison reported data on treatment side effects for the IVIg group only, although the authors commented that in the PE group there was difficulty with line insertion, transient hypotension, and asymptomatic coagulation abnormalities. The RCT reported on the frequency of post-operative intubation and myasthenic crisis. Alipour-Faz et al found that intubation was required significantly more frequently in the PE group (2/12 versus 7/12; p = 0.01). Frequency of crisis also favoured the IVIg group, with the two patients who went into crisis receiving PE (Table 19).

Table 19 Frequency of adverse events in patients receiving IVIg compared to PE

Study ID, Country Level of evidence Quality	Event	IVIg n with event/N (%)	PE n with event/N (%)	Difference p-value and/or 95% CI
(Alipour-Faz et al. 2017), Canada Level II Moderate risk of bias	Post-operative intubation Myasthenic crisis	2/12 (16.7%) 0	7/12 (58.3%) 2 (16.7%)	P = 0.01[a] P = 0.63 (-22.3%, 27.2%)[b]
(Jensen & Bril 2008), Canada Level III-3 Low risk of bias	Headache Dizziness Nausea Hypotension Fever Diarrhoea Skin rash	2/9 (22%) 1/9 (11%) 2/9 (22%) 1/9 (11%) 1/9 (11%) 1/9 (11%) 1/9 (11%)	NR	-

IVIg = intravenous immunoglobulin therapy; NR = not reported; PE = plasma exchange therapy

[a] Chi squared test (Alipour-Faz et al. 2017)

[b] Chi squared test, MedCalc online calculator

Post-operative myasthenic crisis in patients given IVIg, PE or Immunosuppressive therapy

In one other retrospective analysis (Leuzzi et al. 2014), 177 MG patients who underwent thymectomy were assessed for predictive factors associated with post-operative myasthenic crisis (POMC). In this single centre study 44 (24.8%) patients underwent PE, and 34 (19.3%) underwent IVIg prior to surgery (Table 20). Of the whole group, 79.4% were on IS therapies (specific drugs not stated) for MG management at the time of surgery. The study reported that preoperative PE was independently associated with POMC by simple logistic regression (p = 0.021) but this was not confirmed by multivariate analysis (p = 0.066). IVIg and IS therapy were not associated with POMC either by simple regression or multivariate analysis. Multivariate analysis for predictive factors for any complication found that higher Osserman classification (stage III-IV or IIB), longer duration of MG (>2 years) and no immunosuppressive therapy were independent predictors of higher incidence of complications associated with thymectomy. As patients were not randomised to therapies and therapy groups were not compared, these results should be considered cautiously when trying to determine the safety of IVIg compared to other treatments. Other non-randomised evidence has shown that a preference for PE for patients in crisis cannot be ruled out (Mandawat et al. 2010).

Table 20 Likelihood of post-operative myasthenic crisis by therapy type (Leuzzi et al. 2014)

Event	IVIg n with event/N (%)	PE n with event/N (%)	IS n with event/N (%)
Proportion of surgery patients undergoing therapy	34/176 (19.3%)	44/177 (24.8%)	141/177 (79.7%)
Myasthenic crisis in those on therapy	5/34 (14.7%)	10/44 (22.7%)	18/141 (12.8%)
Myasthenic crisis in those not on therapy	17/142 (12.0%)	12/133 (9.0%)	4/36 (11.1%)
OR (unadjusted) (95% CI) p value	1.27 (0.43, 3.72) P = 0.666	2.97 (1.18, 7.45) P = 0.021	1.17 (0.34, 3.70) p = 0.788
OR (adjusted[a]) (95% CI) p value	1.05 (0.26, 4.19) P = 0.939	3.59 (0.92, 14.04) P = 0.066	0.63 (0.15, 2.64) p = 0.527

IS = immunosuppressive therapy; IVIg = intravenous immunoglobulin therapy; OR = odds ratio; PE = plasma exchange therapy

[a] Adjusting cofactors: Osserman stage, pulmonary resection, duration of MG, BMI. The specified model correctly classifies 88.55% of observations.

INDICATION 3: ADULTS UNDERGOING MAINTENANCE THERAPY

Adverse events in patients treated with IVIg compared with PE maintenance

Adverse events for IVIg and PE were compared in three RCTs (level II) (Barth et al. 2011; Liu et al. 2010; Rønager et al. 2001) and one comparative retrospective cohort study (level III-2)(Mandawat et al. 2010). Two of the RCT study populations included patients with moderate to severe disease. Barth et al (2011) included 84 adults aged 19 to 84 years with moderate to severe MG who required a change in therapy (meeting criteria for *Criteria V3* Indication 3). Rønager et al (2001) was a cross-over design that included 12 patients who received both IVIg and PE by the end of the trial. Patients with moderate to severe generalised MG meeting criteria of Osserman Class 3 to 5 and Oosterhuis functional status of 4 to 5 were included (see Table 13, *Section B.5* for description of functional scales). All of the patients in the cross-over study were on IS treatment. Liu et al (2010) included 40 patients with late onset MG - age of onset was 51.1 ± 2.1 Years for the PE group and 52.7 ± 2.3 years for the IVIg group). The late-onset patients were distributed fairly evenly between IVIg and PE treatments across clinical grades IIA, IIB and III or mild to moderate severity (Osserman classification, Table 13).

The cohort study (Mandawat et al. 2010) was a large retrospective analysis of 1,606 patients performed with data from an administrative database. Hospitalised patients diagnosed with MG (n = 908) or in MG crisis (n = 698) and who underwent either IVIg or PE treatments were included and analysed separately. It was not possible to tell if the patients identified as having been hospitalised with MG but not in crisis met the NBA *Criteria V3* for maintenance IVIg eligibility (MGC score ≥ 4), as MG severity scores were not reported.

IVIg doses were similar between the studies although the time over which the dose was given varied (details given in the study profiles table Apendix C). Mandawat et al did not report details about IVIg and PE doses.

Results for the three RCTs and one retrospective cohort study comparing AEs between groups receiving IVIg or PE therapy for maintenance of MG are displayed in Table 21. In adults with MG, including those with adult onset MG, there were more events of headache and nausea/vomiting in the IVIg group compared to the PE group. Reported AEs related to intravenous line access occurred only in the PE group. Barth et al also reported that one patient in the PE group had congestive heart failure but this was unlikely to be related to treatment, and one patient had a myocardial infarction that was considered related to treatment in the same group. The study did not report whether the difference between groups was significant. In an unadjusted analysis, Mandawat et al did not find any difference between treatment groups for AEs but the authors did not perform an adjusted analyses for separated maintenance and crisis populations.

Table 21 Adverse events for IVIg compared with PE for MG maintenance

Study ID, country Level of evidence Quality	Event	IVIg n with event/N (%)	PE n with event/N (%)	Difference p-value (95% CI)
(Barth et al. 2011), Canada Level II Low risk of bias	Allergic reaction	2/41 (4.9%)	0/43	P = 0.14 (-4.03%, 16.1%)[a]
	Nausea, vomiting	7/41 (17.0%)	0/43	P = **0.005** (5.17%, 31.2%)
	Headache	8/41 (19.5%)	0/43	P = **0.0025** (7.12%, 34.0%)
	Chills	2/41 (4.9%)	0/43	P = 0.14 (-4.03%, 16.1%)
	Fever	3/41 (7.3%)	0/43	P = 0.073 (-2.20%, 19.4%)
	Haemolytic anaemia	1/41 (2.45%)	0/43	P = 0.30 (-5.99%, 12.6%)
	Hypertension	1/41 (2.4%)	0/43	P = 0.30 (-5.99%, 12.6%)
	Citrate reaction	0/41	6/43 (14.0%)	P = **0.013** (2.67%, 27.3%)
	Poor venous access delaying treatment	0/41	4/43 (9.3%)	P = **0.047** (-.948%, 21.6%)
	Vasospasm	0/41	8/43 (18.6%)	P = **0.0039** (6.27%, 32.6%)
	Vasovagal reaction	0/41	2/43 (4.7%)	P = 0.16 (-4.51%, 15.5%)
	Myocardial infarction	0/41	1/43 (2.3%)	P = 0.30 (-5.99%, 12.6%)
(Liu et al. 2010), China Level II Moderate risk of bias	Hypotension	0/15	2/15 (13.3%)	P = 0.15 (-9.23%, 37.8%)[a]
	Haematoma	0/15	1/15 (6.7%)	P = 0.32 (-14.4%, 29.9%)
	Vomiting	1/15 (6.7%)	0/15	P = 0.32 (-14.4%, 29.9%)
	Anaphylaxis	0/15	0/15	-
(Mandawat et al. 2010), USA Level III-2 Moderate risk of bias	Patient number	171	737	-
	Mortality	(0.58%)	(0.41%)	P = 0.56[b]
	Any complication	(10.53%)	(11.40%)	P = 0.89
	Cardiac	(7.60%)	(9.50%)	P = 0.55
	Acute renal failure	(1.17%)	(0.27%)	P = 0.16
	Systemic infection	(1.7%)	(1.63%)	P = 1.00
	Thrombotic complications	(0.58%)	(0.27%)	P = 0.46
(Rønager et al. 2001), Denmark Level II High risk of bias	Number of AEs	14	7	
	Hypotension	0	4	
	Nausea, vomiting	3	1	
	Septicaemia	0	1	
	Deep vein thrombosis	0	1	
	High temperature	5	0	
	Headache	7	0	
	Patients with no AE	4/12 (33.3%)	8/12 (66.7%)	P = 0.11 (-5.64%, 61.0%)[a]

AE = adverse event; IVIg = intravenous immunoglobulin therapy; MG = myasthenia gravis; PE = plasma exchange therapy

[a] Chi-squared test, MedCalc online calculator

[b] Fisher's exact test (Mandawat et al. 2010)

Adverse events in patients treated with IVIg compared with placebo for maintenance

Standard therapies for MG such as IS, IM, prednisone (PN), methylprednisolone (MPN), pyridostigmine or azathioprine are comparators listed in the PICO for *Criteria V3* Indication 3. There were no studies comparing IVIg alone with any of these comparators. Patients on IVIg are often taking standard therapies as well as IVIg in trials. However, data on the incremental benefit of IVIg in addition to

standard therapies has the potential to inform the questions of this assessment, therefore articles that compared IVIg to placebo or no additional therapy in patients that were on standard therapies were included.

A RCT identified from a conference abstract had published online data for AEs (in the clinical trials database) (Griffin et al. 2017b). Although it is not technically 'published' data, the study has been included because it was the only evidence identified which assessed the incremental benefit of IVIg over standard treatment in a maintenance population. Patients were included if they had symptomatic generalised MG, and were randomised to either IVIg (human) 10% caprylate/chromatography purified (IVIg-C) or placebo delivered intravenously. Patients continued their standard therapies but these were not specified in the data available. Patients were followed for 24 weeks and data on AEs were reported on the clinicaltrials.gov website (NCT02473952).

The 62 participants were recruited from North America and Europe. The primary outcome of the trial was change in symptoms measured with the QMGS, however these results were not yet posted online or published. There were more patients that didn't complete the trial in the placebo group (n = 8) compared to the IVIg-C group (n = 2) (p = 0.052). Of those given placebo there were 6 withdrawals by participant (reason not given). There were two withdrawals in each arm due to AEs.

There were nine serious AEs in the IVIg-C arm, and five in the placebo arm of the trial. The number of patients impacted were similar between groups – 5 (16.67%) in the IVIg-C arm and 4 (12.5%) in the placebo group. Serious AEs are compared in

Table 22. For non-serious AEs, the frequency was higher but still similar between arms – 22 (73.33%) patients affected in the IVIg-C arm and 21 (65.63%) affected in the placebo arm. There were no statistically significant differences between treatment groups. There were no data for AEs associated with individual standard therapies.

Table 22 Serious adverse events for symptomatic MG patients randomised to IVIg-C or placebo (NCT02473952)

Event	IVIg-C Number of events (% of patients)	Placebo Number of events (% of patients)	Difference P value (95% CI)[a]
Total affected	5/30 (16.67%)	4/32 (12.50%)	P = 0.644 (-12.98%, 22.66%)
Cardiac disorders			
Atrial fibrillation	1/30 (3.33%)	0/32	P = 0.30 (-7.73%, 16.67%)
Cardiopulmonary failure	1/30 (3.33%)	0/32	P = 0.30 (-7.73%, 16.67%)
Gastrointestinal disorders			
Haemorrhoids thrombosed	1/30 (3.33%)	0/30	P = 0.30 (-7.73%, 16.67%)
Infections and infestations			
Pneumonia	1/30 (3.33%)	0/30	P = 0.30 (-7.73%, 16.67%)
Septic shock	1/30 (3.33%)	0/30	P = 0.30 (-7.73%, 16.67%)
Injury, poisoning, procedural complications			
Lower limb fracture	0/30	1/32 (3.13%)	p = 0.33 (-8.51%, 15.75%)
Wrist fracture	0/30	1/32 (3.13%)	p = 0.33 (-8.51%, 15.75%)
Nervous system disorders			
Myasthenia gravis	3/30 (10%)	1/32 (3.13%)	P = 0.28 (-7.35%, 22.7%)
Ischaemic stroke	0/30	1/32 (3.13%)	p = 0.33 (-8.51%, 15.75%)
Cerebral haemorrhage	0/30	1/32 (3.13%)	p = 0.33 (-8.51%, 15.75%)
Psychiatric disorders			
Panic attack	1/30 (3.33%)	0/32	P = 0.30 (-7.73%, 16.67%)

IVIg-C = IVIg (human) 10% caprylate/chromatography purified; MG = myasthenia gravis

[a] Chi-squared test, MedCalc online calculator

Adverse events in adults receiving IVIg maintenance

One study reported the number of AEs in a case series of patients receiving IVIg for maintenance therapy (Hellmann et al. 2014). Fifty-two adults of all MG classes were identified in a retrospective analysis. They had failed or were contraindicated to other therapies. The authors' opinion was that IVIg was associated with three major disadvantages: i) it is associated with AEs as serious as myocardial infarction and stroke; ii) it is expensive; iii) it is cumbersome, requiring hospitalisation or several hours at a day clinic. However, as there was no comparison with PE or other treatments, this is opinion rather than evidence, and benefits of IVIg may outweigh the risks when standard therapies are no longer suitable. By way of comparison, Barth et al (2011) had noted two myocardial events in the group randomised to PE, although one event was not thought to be related to treatment (Table 23).

Table 23 Adverse events in a case series receiving IVIg MG maintenance (Hellmann et al. 2014)

Country Level of evidence Risk of bias	Event	Frequency n with event (%)
Israel Level IV Low	Headache Mild anaphylactic reaction Myocardial infarction Minor stroke	8/52 (15.4%) 1/52 (1.96%) 1/52 (1.96%) 1/52 (1.96%)

IVIg = intravenous immunoglobulin therapy; MG = myasthenia gravis; PE = plasma exchange therapy

INDICATION 3: CHILDREN UNDERGOING IVIG MAINTENANCE THERAPY

Adverse events for children treated with IVIg or PE maintenance

One study compared IVIg and PE in children. Liew et al (Liew et al. 2014) included only patients with juvenile MG with mean age of onset of 8 years [Q1: 2, Q3: 13 years] (n = 33). Of the 33 patients, 10 received IVIg only and seven received PE only, allowing a comparison between the groups. Of those in the IVIg group, two experienced pyrexia and rigors (20%) severe enough to cease treatment, and one in the PE group developed central-line sepsis. The numbers were not statistically compared. Liew et al (2014) did not describe the MG class and treatment tolerance in the patient groups well, however the authors reported that both treatments were well tolerated (Table 24).

Table 24 Adverse events for IVIg compared with PE in children (Liew et al. 2014)

Country Level of evidence Quality	Event	IVIg n with event/N (%)	PE n with event/N (%)	Difference p-value (95% CI)[c]
USA Level III-2 Moderate risk of bias	Pyrexia & rigors[a] Central line sepsis[b]	2/10 (20%) 0/10	0/7 1/7 (14.2%)	P = 0.22 (-18.2%, 51.0%) P = 0.76 (-26.8%, 36.7%)

IVIg = intravenous immunoglobulin; PE = plasma exchange

[a] pyrexia and rigors led to discontinuation of IVIg treatment in two patients
[b] one patient on PE developed central-line sepsis requiring hospitalisation
[c] Chi-squared test, MedCalc online calculator

Adverse events for children treated with IVIg plus MPN or high dose IV MPN alone

A second study in children (Wang et al. 2016) compared those treated with IVIg plus MPN with an observation group who received high dose IV MPN alone (n = 70). This study can potentially inform the question of incremental benefit of IVIg over MPN alone in children. The disease class of the patients ranged from type I to type III, but the types were not defined. It is likely that the patients were of lower severity than those defined by the *Criteria V3* for Indication 3. The authors did not state separate AEs for treatment groups, but reported that there was no difference in AE incidence between

groups on analysis (p = 0.666). Across both groups two patients experienced numbness of respiratory muscle, seven developed more severe myasthenia, and three suffered respiratory paralysis.

INDICATION 3: PATIENTS UNDERGOING SCIG MAINTENANCE THERAPY

Adverse effects for patients receiving SCIg maintenance

Two case series, both from Canada, reported AEs occurring with SCIg maintenance treatment. The patients were of mild to moderate disease severity, (MGFA class II or III, see Table 13 for information on disease severity) so are not as serious as those that meet the *Criteria V3* for Indication 3 (moderate to severe MG). However, it is probable that sub-cutaneous delivery is more likely to be used in less severe cases where patients have not been hospitalised. The studies were the only relevant ones identified for SCIg so they have been included in this assessment.

One series was a prospective open label phase 3 trial that included 22 adult MG patients with mild to moderate worsening of myasthenic symptoms (defined as a change from MGFA class I to II/III or class II to III) (Beecher, Anderson & Siddiqi 2017). Patients received 2g/kg of Ig at weekly intervals over 4 weeks, in a dose escalating manner. The second was a retrospective case series of patients with MG treated with SCIg in a single institution (n = 9) (Bourque et al. 2016). The nine patients included were all of MGFA class II or II prior to SCIg, and six were already receiving IVIg maintenance and agreed to transfer to SCIg. Their initial target weekly dose was calculated at 120% of their IVIg dose. Three other patients were started on SCIg at 20g per week, with subsequent doses based on clinical response. The mean dose for all nine patients was 25.1 g weekly.

Across both studies AEs were, on the whole, minor (Table 25). In the study by Beecher, Anderson and Siddiqi headache was common to the majority of SCIg recipients (77.3%). The authors commented that SCIg was likely to have fewer serious AEs than IVIg, due to slower rate of infusion and lower peak IgG concentration following infusion. Bourque et al also noted no systemic symptoms that could be attributed to SCIg, although most patients experienced mild subcutaneous tenderness or pruritus on the day of infusion with 'frequent circumscribed bruising' (numbers not reported). One patient experienced more serious bruising and ecchymosis which was of concern. There were no emergency department attendances or ICU admissions among the nine patients.

Table 25 Adverse events for patients receiving SCIg maintenance therapy

Study ID, Country Level of evidence Quality	Event	Frequency n with event (%)
(Beecher, Anderson & Siddiqi 2017), Canada Level IV Low risk of bias	Headache Injection site reaction Nausea Joint pain Diarrhoea Emesis Abdominal pain Dry cough Parasthesias Tinnitus Fatigue	17/22 (77.3%) 14/22 (63.6%) 6/22 (27.3%) 4/22 (18.2%) 4/22 (18.2%) 3/22 (13.6%) 2/22 (9.1%) 1/22 (4.5%) 1/22 (4.5%) 1/22 (4.5%) 1/22 (4.5%)
(Bourque et al. 2016), Canada Level IV Low risk of bias	Prominent ecchymosis	1/9 (11.1%)

SCIg = subcutaneous immunoglobulin therapy

IS IT EFFECTIVE?

Summary – What is the effectiveness of IVIg compared to PE for patients with MG?

Indication 1: Patients in or at risk of myasthenic crisis

In one large retrospective cohort analysis, mortality was significantly more frequent in the patients receiving PE compared to those receiving IVIg (P = 0.002). The difference in mortality rates may not be as large as indicated by the data, given the baseline population characteristics indicate patients given PE are more likely to have systemic infection ($p < 0.0001$). Patients at a more critical stage, for example requiring intubation, may be more likely to be given PE as it is thought to act more quickly. Two smaller studies did not find any difference in mortality between the patients treated with IVIg or PE.

The MGC was not used in any studies to measure change in symptoms for the MG crisis population. For other symptom measures (MMS and MSS) there was a similar improvement from baseline at 15 days, with no conclusive differences between groups receiving IVIg and PE.

Indication 2: Patients with MG preparing for surgery

In patients who were preparing for surgery there was no difference in symptom change (change in Osserman grade) between IVIg and PE groups although symptoms improved in both groups following surgery. Patients had a shorter intubation period on average and fewer required intubation when randomised to IVIg compared to PE in one study. In contrast, benefit perceived by patients favoured PE over IVIg using a subjective tool in another study. Overall there was no strong evidence favouring IVIg or PE in patients preparing for surgery.

Indication 3: Patients needing to change maintenance therapy for MG

There were few conclusive differences between IVIg and other therapies for adults and children receiving maintenance therapy.

There was an incremental benefit in symptom improvement (QMGS) for adult patients given IVIg on top of standard maintenance therapies which peaked at 14 days. The benefit decreased with time after that.

There was no difference in the rate of infection between patients receiving IVIg or PE reported in the large retrospective cohort study (Mandawat et al. 2010). Although it was stated that the patients were not in crisis, it was difficult to tell if they met *Criteria V3* Indication 3.

There was a trend for greater improvement in patients given PE compared to IVIg in symptoms measured using the QMGS at 28 days and 16 weeks from start of treatment, with strongest improvement in symptoms seen in the first 2 weeks (results from three studies). Only a small degree of improvement appeared to be sustained for up to 16 weeks for either IVIg or PE. Longer term comparative studies may be more informative on the degree of

sustained symptom improvement, Accurate recording of baseline severity is needed as the degree of improvement may be influenced by the severity of symptoms at baseline.

For patients given SCIg, symptoms decreased for up to six weeks compared to baseline using the QMGS, MMT and MGC tools. QoL measured by MG-ADL, MG-QoL and a VAS scale also improved. There was no valid comparator in these studies so conclusions cannot be drawn from the data.

A summary of the evidence included for effectiveness of IVIg for *Criteria V3* Indications 1 and 2 and IVIg or SCIg for NBA Indication 3 is provided in Table 11 (SRs) and Table 12 (primary studies). The full evidence profile table (with explanatory footnotes), incorporating all critical and important outcomes, can be found in Appendix C Studies included in the Systematic Review. A summary of the clinical benefits and harms of Ig for MG is provided in Table 48 toTable 51.

Three SRs compared IVIg and PE for effectiveness in the management of MG. The SRs were pearled for relevant individual studies providing evidence of effectiveness. In all, evidence was provided by eight RCTs, eight comparative cohort studies and seven case series with before and after treatment data. One of the RCTs (NCT02473952) was identified through a meeting abstract (Griffin et al. 2017b) and mortality data on the clinicaltrial.gov website were included for effectiveness evidence. This trial and a second RCT that did not strictly meet the PICO criteria as the comparator was placebo, were included as they had the potential to show incremental benefit of IVIg over standard maintenance therapies listed as comparators for Indication 3 (IS, IM, PN) NCT02473952.

INDICATION 1: PATIENTS IN OR AT RISK OF MYASTHENIC CRISIS

Mortality for patients receiving IVIg or PE therapy

Three retrospective cohort studies (level III-2) compared the rate of mortality between patients treated with IVIg and PE (Mandawat et al. 2010; Murthy et al. 2005; Qureshi et al. 1999). Mandawat et al (2010), rated moderate for quality, performed a retrospective analysis of 1,606 hospitalised patients with MG with data from an administrative database. Patients included those undergoing maintenance therapy and in MG crisis; this latter group were considered to meet *Criteria V3* for Indication 1[6]. Patients who underwent either IVIg or PE treatments (n = 698), were included and analysed separately.

[6] Patients were identified by the ICD-9-CD code 358.01 for acute MG crisis or of an MG patient had a secondary diagnosis of acute respiratory failure by coded518.81, and/or required mechanical ventilation during the same admission.

In a bivariate analysis, unadjusted mortality rates were significantly higher in the PE group compared to the IVIg group (5.67% versus 0.59%; p = 0.002) amongst patients in crisis. An analysis of patient demographic and clinical differences between IVIg and PE groups in crisis patients was not able to determine any underlying differences related to the difference in mortality rates.

No multivariate analyses were conducted on the crisis patients alone, however a multivariate analysis of all crisis and maintenance patients in the cohort was undertaken and found no significant difference in mortality rates, when adjusted for significant co-variates (OR IVIg versus PE = 0.39; 95% CI 0.096, 1.72; p = 0.21). In a further analysis of the total patient population, PE, older age, more severe comorbidities, and hospital admission through the emergency department were variables associated with higher mortality (p < 0.05 for all variables) (Table 26). These data support the suggestion that PE is given in favour to IVIg for patients in serious crisis and requiring intubation (Qureshi et al. 1999; Sharma et al. 2013).

In two smaller retrospective cohorts the number of deaths were not statistically different between IVIg and PE treated groups (Murthy et al. 2005; Qureshi et al. 1999) (Table 26). Of the two deaths in the PE groups one was due to ventilator related infection and one due to cardiac arrest. In the IVIg groups one death was the result of sepsis, one due to withdrawal of care and one patient could not be stabilised or revived in crisis.

Table 26 Mortality in MG patients treated with IVIg compared to PE

Study ID, Country Level of evidence Quality	Population	IVIg n with event/N (%)	PE n with event/N (%)	Difference p-value (95% CI)
(Mandawat et al. 2010), USA Level III-2 Moderate risk of bias	MG patients in crisis identified through a multicentre database (bivariate analysis)	1/169 (0.59%)	30/529 (5.67%)	P = 0.002[a]
(Murthy et al. 2005), India Level III-2 High risk of bias	All patients with episodes of MG crisis identified from the MG case records of the senior author (there were 23 crises in 21 patients)	1/8 (12.5%)	1/15 (6.7%)	P = 0.65[b] (-15.5%, 40.8%)
(Qureshi et al. 1999), USA Level III-2 Moderate risk of bias	Patients identified retrospectively who had an episode of MG crisis and treated with either IVIg or PE	2/26 (7.7%)	1/28 (3.6%)	P = 0.51[b] (-11.11%, 20.81%)

IVIg = intravenous immunoglobulin; MG = myasthenia gravis; PE = plasma exchange

[a] Fisher's exact test (Mandawat et al. 2010)
[b] Chi-squared test, MedCalc online calculator

Rate of infection for patients receiving IVIg or PE therapy

Infections are a common risk in MG patients due to their immune insufficiency, but also in relation to vascular access for treatment and artificial ventilation. Three level III-2 studies compared the rate of infections between IVIg and PE groups in crisis patients (Mandawat et al. 2010; Pittayanon, Treeprasertsuk & Phanthumchinda 2009; Qureshi et al. 1999). Definitions of MG crisis were based on weakness of the respiratory muscles and/or the requirement for mechanical ventilation in all three studies. The types of infections reported were not exactly the same across studies: Mandawat et al reported systemic infections, Qureshi et al reported infections (not further described), and Pittayanon et al reported hospital acquired pneumonia (Table 27).

Infections of the types reported were all more frequent in the PE group compared to the IVIg group. Only the largest study found a significant difference between IVIg and PE for the rate of systemic infections (1.18% versus 9.45%; p < 0.0001). The authors also performed a multivariate logistic regression analysis, finding an odds ratio (OR) for acute respiratory failure of 4.89 (95% CI 3.51, 6.84; p < 0.0001) in favour of patients undergoing IVIg (Mandawat et al. 2010). This analysis, however, included both patients in the crisis and the non-crisis MG groups.

Table 27 Infection rates in patients given IVIg compared with PE

Study, Country Level of evidence Risk of bias	Population	Event	IVIg n with event/N (%)	PE n with event/N (%)	Difference p-value (95% CI)
(Mandawat et al. 2010), USA Level III-2 Moderate	MG patients in crisis identified through a multicentre database	Systemic infection	2/169 (1.18%)	50/529 (9.45%)	P < 0.0001[a]
(Pittayanon, Treeprasertsuk & Phanthumchinda 2009), Thailand Level III-2 Moderate - high	Episodes of MG crisis between 1 June 2001 and 30 June 2006 in the study hospital (there were 30 episodes treated in 26 patients)	Hospital acquired pneumonia (Infections per crisis episode)	1/9 (11.1%)	4/21 (18.2%)	Overall p = 0.073[b]
(Qureshi et al. 1999), USA Level III-2 Moderate	Patients with MG crisis who were treated with PE or IVIg in 4 university hospitals from Jan 1990 through Dec 1997	Infections	2/26 (7.7%)	6/28 (21.4%)	P = 16[c] (-6.21%, 32.6%)

IVIg = intravenous immunoglobulin therapy; MG = myasthenia gravis; PE = plasma exchange

[a] Fisher's exact test (Mandawat et al. 2010)

[b] There was no statistical difference found between groups. The overall p value was reported for all for all AEs (Pittayanon, Treeprasertsuk & Phanthumchinda 2009).

c Chi-squared test, MedCalc online calculator

Change in symptoms (myasthenic muscle score) following IVIg or PE

There were no studies identified that measured the improvement of symptoms using the MGC score for patients classified as Indication 1. One RCT used the myasthenia muscle score (MMS) to compare symptom improvement between patients given IVIg or PE (Gajdos et al. 1997; Gajdos et al. 2005). The MMS described by the authors is calculated from nine independent measurements of the trunk, limbs, neck and cranial muscles which are added to give a score of 0 (least strength), 5 or 10 (maximum strength). The MGC rates strength for a similar range of movements albeit with a different scoring system. Myasthenic strength scores are described and compared in *Section B.5*, Table 15.

The study (Gajdos et al. 1997) randomised 87 patients in MG crisis (criteria: the development in the last month of at least one of swallowing difficulty, acute respiratory failure, or major functional disability responsible for the discontinuation of physical activity) to either IVIg or PE. Prior to exacerbation the majority of patients in both treatment groups were rated for clinical status as level 4 (major disability requiring discontinuation of occupational activity) or 5 (major disability requiring continuous help or mechanical ventilation). The randomised groups were well balanced for baseline characteristics.

Patients receiving either IVIg or PE improved in MMS score ($p < 0.05$ after 2 days in both groups) but there was no significant difference between groups after 15 days (mean difference in MMS: -1.00, 95% CI -7.72, 5.72). This outcome was sourced from the SR by Gajdos, Chevret and Toyka, 2012 (Table 28).

Table 28 Change in MMS after 15 days for MG patients treated with IVIg compared to PE (Gajdos, Chevret & Toyka 2012)

Measure	IVIg N = 46 Mean (SD)	PE N = 41 Mean (SD)	Mean difference (95% CI)	Overall effect
Change in MMS	15.6 (15.96)	16.6 (16)	-1.00 (-7.72, 5.72)	P = 0.77[a]

IVIg = intravenous immunoglobulin therapy; MG = myasthenia gravis; MMS myasthenia muscle score; PE = plasma exchange therapy; SD = standard deviation;
[a] Analysis reported in Gajdos, Chevret and Toyka, 2012

Change in symptoms (myasthenic muscle score) following IVIg (1 g/kg) or IVIg (2 g/kg) (dose comparison)

One RCT (Gajdos et al. 2005) compared the change in MMS between patients randomised in an IVIg dose comparison. The comparison was made in a multicentre double-blind trial in which 168 patients received either 1 g/kg IVIg on day 1 and placebo on day 2, or 1 g/kg IVIg on day 1 and day 2. Patients met the same inclusion criteria as for those in the 1997 Gajdos et al study.

Mean improvement in MMS was higher in the group receiving the higher IVIg dose but the difference did not reach statistical significance. The author's conclusion was that a dose of 1 g/kg may be the best dose in clinical practice, as the higher dose showed no additional benefit and there may be cost benefits in using the smaller dose (Table 29). Results were sourced from the SR by Gajdos et al (Gajdos, Chevret & Toyka 2012).

Table 29 Change in MMS after 15 days for MG patients treated with IVIg (dose comparison) (Gajdos, Chevret & Toyka 2012)

Measure	IVIg (2 g/kg) N = 87 Mean (SD)	IVIg (1g/kg) N = 81 Mean (SD)	Mean difference (95% CI)	Overall effect
Change in MMS	19.33 (16.48)	15.49 (15.4)	3.84 (-0.98, 8.66)	P = 0.12[a]

IVIg = intravenous immunoglobulin therapy; MG = myasthenia gravis; MMS myasthenia muscle score; SD = standard deviation

[a] Result reported in Gajdos, Chevret and Toyka, 2012

Change in symptoms (myasthenia severity scale) following IVIg or PE

One retrospective cohort study (level III-2) used the myasthenia severity scale (MSS) to measure improvement in patients given either IVIg or PE (Qureshi et al. 1999). The MSS will give a score of 1 to 3 in three categories of patients function (cough, ocular and bulbar symptoms) and 1 to 4 for the category of dyspnoea. A score of 1 is given for the least strength and 3 or 4 for normal strength. The MGC rates strength for a broader range of functions than the MSS. Myasthenic symptoms scores are discussed further in *Section B.5*. In this study MG crisis was described as an acute episode of respiratory muscle weakness defined by forced vital capacity of ≤ 1.0 L, negative inspiratory force of ≤ 20 cm H_2O, or requirement of mechanical ventilation.

There was an improvement of MSS in both groups at two weeks post treatment, however the improvement was only statistically significant in the PE group (p = 0.009). Between IVIg and PE groups, there was better improvement in the PE group at two weeks following start of treatment but the significance of this result was not determined (Table 30). The study size and quality prevents a strong conclusion being made about clinical differences between groups.

Table 30 Change in MSS after 15 days for MG crisis patients treated with IVIg or PE (Qureshi et al. 1999)

Measure	IVIg N = 26; Mean (SD)	PE N = 28; Mean (SD)
Baseline MSS	7.5 (1.7)	6.9 (1.7)
MSS at 2 weeks	10.3 (3.2)	11.1 (2.5)
Change in MSS	2.8 (0.711) P = 0.054[a]	4.2 (0.571) P = 0.009[a]

IVIg = intravenous immunoglobulin therapy; MG = myasthenia gravis; MSS myasthenia severity score; PE = plasma exchange therapy; SD = standard deviation

[a] Univariate analyses were performed using EpiInfo 6.6

Change in Quality of Life

Quality of life was not reported in any of the studies assessing IVIg and PE for MG patients in or at risk of crisis.

Rate of remission

None of the studies comparing IVIg and PE in patients in or at risk of MG crisis reported on the rate of remission.

Disease stability for patients receiving IVIg or PE therapy

One retrospective cohort study (level III-2) reported on the time taken for the disease to stabilise, which was described as the median number of days for extubation (Murthy et al. 2005). The population was made up of patients of the primary author of the study who had been treated in MG crisis either with IVIg or PE. A second retrospective cohort study (level III-2) also reported on the duration of intubation (Pittayanon, Treeprasertsuk & Phanthumchinda 2009), with data collected from a hospital's records over 5 years. In both studies about twice as many patients were given PE as were given IVIg. The reason for this was not stated, but was possibly because PE is cheaper than IVIg to supply, or because IVIg was established as a therapy for MG later than PE. Another possibility is that clinicians feel that PE is faster acting in critical intubated patients than IVIg (Barth et al. 2011; Qureshi et al. 1999). The studies were set in India and Thailand, and participant numbers were low (n = 21 and 33). Results were found to be similar between treatment groups (Table 31).

Table 31 Disease stability for MG crisis patients treated with IVIg or PE

Study ID, Country Level of evidence Quality	Measure N	IVIg	PE	Mean difference Days ± SD (95% CI), p
(Murthy et al. 2005), India Level III-2 High risk of bias	Median days for extubation (range) N = 21	10 (7-39)	8 (7-12)	NA
(Pittayanon, Treeprasertsuk & Phanthumchinda 2009), Thailand Level III-2 Moderate to high risk of bias	Mean duration of intubation (days ± SD) N = 33	10.3 ± 4.6	12 ± 11.1	1.7 ± 3.86 (-6.21, 9.61) P = 0.66[a]

IVIg = intravenous immunoglobulin therapy; MG = myasthenia gravis; MSS myasthenia severity score; NA = not applicable; PE = plasma exchange therapy; SD = standard deviation

[a] Comparison of means test, MedCalc online calculator

Time to treatment response for patients receiving IVIg or PE therapy

Gajdos et al (Gajdos et al. 1997) reported the estimated time to treatment response in their RCT, where treatment response was defined as a 20 point gain in MMS. In the study, treatment response was recorded for the first 15 days following treatment for randomised IVIg and PE groups. Of the 87 patients randomised, treatment response was observed in 48 (55%) at the 15 day follow-up. Responders and median response times per treatment group are shown in Table 32. Although both outcomes favoured PE, there was no statistically significant difference between patients treated with IVIg and PE.

In a dose comparison assessment Gajdos et al (Gajdos et al. 2005) also reported treatment response, defined as in Gajdos et al (1997). Individual group data were not stated, but the authors found that there was no evidence of a time x treatment interaction for treatment response rates (p = 0.36).

Table 32 Treatment response for MG crisis patients treated with IVIg or PE (Gajdos et al. 1997)

Measure	IVIg	PE	Overall effect P value (95% CI)
Proportion (%) with a treatment response (20-point gain in MMS over 15 days)	22/46 (47.8%)	26/41 (63.4%)	P = 0.15 (-5.16%, 34.5%)[a]
Median treatment response time (days)	15	9	RR of response = 0.67 (95% CI 0.38, 1.18) P = 0.14[b]

IVIg = intravenous immunoglobulin therapy; MG = myasthenia gravis; MMS myasthenia muscle score; PE = plasma exchange therapy; RR = relative risk; SD = standard deviation

[a] Chi-squared test, MedCalc online calculator
[b] Log-rank test (Gajdos et al. 1997)

Time to relapse

None of the studies comparing IVIg and PE in patients in or at risk of MG crisis reported on the time to relapse.

Need for ventilation or other life support systems for patients receiving IVIg or PE therapy

There were no studies meeting the inclusion criteria that reported the change in need for ventilation in crisis patients.

INDICATION 2: PATIENTS PREPARING FOR SURGERY

One RCT (level II) and one retrospective matched cohort study (level III-2) were identified that assessed the effectiveness of IVIg and PE in MG patients preparing for thymectomy surgery. The RCT (Alipour-Faz et al. 2017) randomised 24 patients who were listed for thymectomy, 12 receiving IVIg and 12 receiving PE as preoperative preparation. Patients were excluded if they had exacerbation of

MG secondary to medication irregularity or change in dosage or infection. In the retrospective study (Jensen & Bril 2008), 43 patients were identified that had required immunomodulation prior to thymectomy. Of these, nine patients received IVIg alone, and were matched for comparison purposes on Osserman grade, gender and age to nine patients who received PE alone. No patients with preoperative Osserman grade 4 disease received IVIg, so grade 4 patients were excluded from the study.

Mortality

Neither of the studies which assessed pre-surgical MG patients reported on mortality rates.

Rate of infection for patients receiving IVIg or PE therapy

The retrospective matched cohort study reported that there was no sepsis observed in the study population (Jensen & Bril 2008). The RCT stated that two cases of myasthenic crisis in the group receiving PE were related to pneumonia infections. There were no cases of pneumonia or crisis in the IVIg group (Alipour-Faz et al. 2017).

Change in symptoms (Osserman grade) for patients receiving IVIg or PE therapy

One study (level III-2) compared the response to immunomodulation between treatment groups (Jensen & Bril 2008). A modified Osserman classification index was used to assess MG status using the following score guide: 0 = asymptomatic; 1 = ocular signs and symptoms; 2 = mild generalised symptoms; 3 = moderate generalised symptoms, bulbar dysfunction, or both; and 4 = severe generalised weakness, respiratory dysfunction, or both. All patients were either grade 2 or 3 at the pre-treatment assessment and no patients were treated with immunosuppression prior to surgery. Postoperative Osserman grading was performed at the first postoperative neuromuscular clinic visit.

In the analysis Osserman grade was assessed as a continuous variable. Symptoms improved following surgery and treatment in both groups, but there was no statistical difference in the degree of improvement between patients treated with IVIg and PE ($p = 0.55$). In both groups, two out of nine patients improved by two Osserman grades, however it is likely that the thymectomy contributed to improved status (Table 33).

Table 33 Change in symptoms (Osserman grade) in thymectomy patients given IVIg or PE (Jensen & Bril 2008)

Measure	IVIg	PE	Overall effect[b]
Pre-operative Osserman grade[a]	2.44 ± 0.53	2.44 ± 0.53	P = 1.00
Post-operative Osserman grade[a]	1.67 ± 0.87	1.44 ± 0.88	P = 0.60
Change in Osserman grade[a]	0.78 ± 0.83	1.00 ± 0.71	P = 0.55

IVIg = intravenous immunoglobulin therapy; PE = plasma exchange therapy

[a] Osserman grade considered as a continuous variable

[b] Comparisons were made using contingency table analyses

Change in Quality of Life for patients receiving IVIg or PE therapy

The study by Jensen et al reported on the patients' perceived benefit from the treatment they received (Jensen & Bril 2008). Because this was a subjective patient benefit, it was included as a quality of life outcome. Four out of nine patients in the IVIg treatment group reported no benefit, whereas all nine patients in the PE group reported some benefit. There was a statistically significant difference between groups favouring PE (Table 34). The perceived benefit of IVIg or PE was likely to have been impacted by the surgery but this was not discussed by the authors.

Table 34 Thymectomy patients' perceived benefit when treated with IVIg or PE (Jensen & Bril 2008)

Measure	IVIg	PE	Overall effect P value (95% CI)[a]
Some improvement	5/9 (56%)	9/9 (100%)	P = 0.029 (4.75%, 73.0%)
No benefit	4/9 (44%)	0/9	P = 0.029 (4.75%, 73.0%)

IVIg = intravenous immunoglobulin therapy; PE = plasma exchange therapy

[a] Chi-squared test, MedCalc online calculator

Rate of remission

There were no studies reported on remission rate in patients with MG undergoing surgery.

Disease stability and need for ventilation post-surgery for patients receiving IVIg or PE therapy

The RCT by Alipour-Faz et al (Alipour-Faz et al. 2017) compared the number of patients intubated post-operatively and the median intubation period following surgery between IVIg and PE patients. Another related outcome reported in this study was the number of post-operative myasthenic crises. These outcomes are reported in Table 35. There was a significant difference favouring IVIg for the number of patients intubated and the median intubation period postoperatively. The cases of crises were related to the occurrence of pneumonia after surgery. However, the number of patients in this study are too small to make strong conclusions about IVIg compared to PE.

Table 35 Intubation period and number of myasthenic crises in thymectomy patients treated with IVIg or PE (Alipour-Faz et al. 2017)

Measure	IVIg N = 12	PE N = 12	Overall effect P value (95% CI)
Median intubation period (hours, range)	0 (2-22)	13 (2-216)	P = 0.01[a]
Number of patients intubated postoperatively	2 (16.7%)	7 (58.3%)	p = 0.039 (3.03%, 667.0%)[b]
Number of patients with myasthenic crisis	0	2	NR

IVIg = intravenous immunoglobulin therapy; NR = not reported; PE = plasma exchange therapy

[a] Mann-Whitney *U* test for continuous variables (Alipour-Faz et al. 2017)

[b] Chi-squared test, MedCalc online calculator

Time to relapse

No studies meeting the inclusion criteria reported on this outcome.

INDICATION 3: ADULTS UNDERGOING IVIG MAINTENANCE THERAPY

All-cause mortality in patients receiving maintenance IVIg or placebo

Results from a RCT not yet published in the peer reviewed literature were identified through a meeting abstract (Griffin et al. 2017b). Symptomatic patients on standard of care treatment and with a QMGS > 10 points at screening were randomised to receive either IVIg-C or placebo delivered intravenously. Patients were followed for 24 weeks and data on mortality and AEs were reported on the clinicaltrials.gov website (NCT02473952). Primary data on change in symptoms (QMGS) were not yet available. Standard of care treatments were not described in the available data online or in the meeting abstract. Thirty patients were randomised to IVIg-C and 32 to placebo.

There was one patient death in the trial, which occurred in the patient group receiving IVIg-C (1/30, 3.33%). There was no statistically significant difference between the IVIg-C and placebo groups for this outcome.

Rate of infection in patients receiving maintenance IVIg or PE

Two studies compared the number of infections between maintenance patients receiving IVIg or PE. The RCT by Rønager et al (Rønager et al. 2001) used a crossover design in which all 12 patients received both IVIg and PE separated by a 16 week observation period. One case of septicaemia was reported, which occurred in a patient who had a severe reaction while undergoing PE. In the retrospective cohort study by Mandawat et al (Mandawat et al. 2010), cases of systemic infection were found to occur in similar proportions in both the IVIg and PE groups (Table 36).

Table 36 Rates of infection for IVIg compared with PE for MG maintenance patients

Study ID Country	Level of evidence Quality	Event	IVIg n with event/N (%)	PE n with event/N (%)	Difference p-value (95% CI)
(Mandawat et al. 2010) USA	Level III-2 Moderate risk of bias	Systemic infection	3/171 (1.7%)	12/737 (1.63%)	P = 1.00 (-1.57%, 3.39%)[a]
(Rønager et al. 2001) Denmark	Level II High risk of bias	Septicaemia	0/12 (0%)	1/12 (8.3%)	P = 0.0001 (33.8%, 61.8%)[b]

IVIg = intravenous immunoglobulin therapy; MG = myasthenia gravis; PE plasma exchange therapy

[a] Fisher's exact test (Mandawat et al. 2010)
[b] Chi-squared test, MedCalc online calculator

Change in symptoms (QMGS) in adults receiving maintenance IVIg or PE

None of the studies assessing symptom improvement for patients receiving IVIg for maintenance therapy used the MGC tool, so studies were included if they used other standardised tools (see *Section B.5 Outcome measures and Analysis* for a comparison of tools). QMGS is a MG specific tool and was the most commonly used measure of symptoms across the studies included. A decrease in QMGS indicates a decrease in the severity of symptoms. The MGC is a modified version of the QMGS, taking less time to perform with patients. Three RCTs (Barth et al. 2011; Liu et al. 2010; Rønager et al. 2001) and one case series with pre and post-treatment outcomes (Eienbröker et al. 2014) assessed symptom improvement using the QMGS. Despite using the same tool, the three studies used different scales for reporting changes. Outcomes are reported in Table 37.

Barth et al randomised 84 patients to either IVIg or PE, and scored the QMGS at baseline, and 14, 21 and 28 day follow-ups using the standard scoring method (see *Section B.5* for a description of scales). In the cross-over trial by Rønager et al QMGS measures were extended to 16 week clinic follow-ups. Rønager et al reported a modified scoring system for the QMGS, using a final score between 0 and 3, the results of individual subtests being divided by the total number of tests performed. This scoring system provides smaller changes from baseline in comparison to those reported by Barth et al. In the small RCT by Liu et al, a late-onset population was assessed for symptoms at one follow-up time point, 14 days after treatment. Change from baseline was reported as per cent improvement in the QMGS. The case series with pre and post treatment results observed patients over a 24 month period and recorded the QMGS at that time and prior to treatment. The differences in methods and outcome measures in these studies precluded meta-analysis of the results.

Barth et al and Rønager et al found similar results for improvement in the first four weeks. According to the QMGS, symptom improvement was greater in the PE group, but did not reach statistical significance. The change could be considered clinically significant in both treatment groups according to the MCID (change from baseline ≥ 3; see Table 15) at 14 and 21 days, and also at day 28 for PE. After four weeks Rønager et al found that the treatment effect wore off in both treatment groups as there was no significant change from baseline in QMGS at 8 and 16 weeks. The change in score from baseline in Rønager et al's study is illustrated in Figure 6. The same trend could be seen occurring earlier in the Barth et al RCT, as difference from baseline decreased between 21 and 28 days after treatment.

Supporting the early benefits of treatment recorded by Barth et al and Rønager et al, Liu et al found a significantly greater improvement in the PE compared to the IVIg group at 2 weeks (per cent change in QMGS: $p < 0.01$). Baseline QMGS was higher in the Liu et al RCT population of late onset MG patients, than in Barth et al (mean QMGS ± SD: IVIg 16.5 ± 1.1 and PE 19.4 ± 2.2 versus IVIg 14.26 ±

4.0 and PE 14.44 ± 3.8). The higher severity of symptom level at baseline may have been a contributing factor in greater improvement overall in Liu et al's study. However there were no data collected beyond two weeks by Liu et al to determine whether the results were sustained. In analysis of baseline covariates, Barth et al determined that patients with more severe disease (higher QMGS), and the presence of AChRAb antibodies had a better response to treatment ($p = 0.0005$ and $p < 0.0001$ respectively).

In contrast, Eienbröker et al (baseline mean QMGS ± SD: 20.6 ± 5.9) observed that there had been a sustained improvement in symptoms from baseline at the longer time point of 24 months for patients receiving IVIg. However, without a comparator in this study, the results on change in QMGS cannot confirm a difference in effect between IVIg and PE. Comparative studies with long term outcomes in maintenance populations may contribute more information to the current picture.

In a further analysis, Barth et al compared the proportion of responders between IVIg and PE groups. Barth et al defined responders as those who experienced at least a 3.5 point improvement in their QMGS, and at day 14, this outcome was 51% in the IVIg group and 57% in the PE group, with no statistically significant difference between them ($p = 0.5$, χ^2 test).

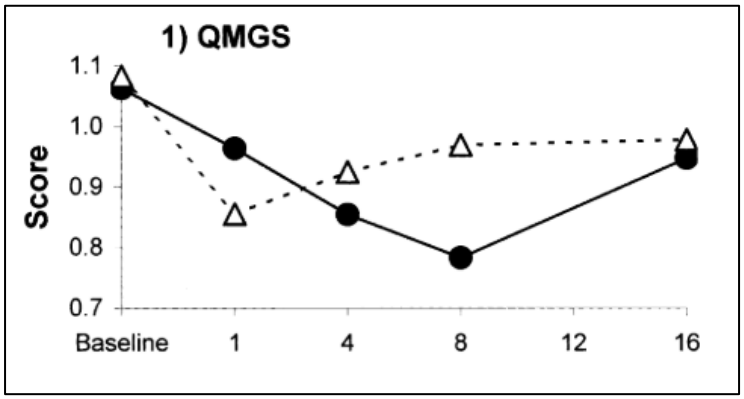

Figure 6 Change in QMGS from baseline to 16 weeks (Rønager et al. 2001)

Table 37 Change in QMGS for patients on IVIg or PE maintenance therapy

Study ID, Country Level of evidence Quality	Measure	IVIg	PE	Difference p-value
(Barth et al. 2011), Canada Level II Low risk of bias	Change in QMGS (mean ± SD)[a] Day 0-14 Day 0-21 Day0-28	 3.2 ± 4.1 3.3 ± 3.6 2.6 ± 4.0	 4.7 ± 4.9 5.3 ± 5.5 4.7 ± 5.7	 p = 0.13 p = 0.07 p = 0.08[a]
(Rønager et al. 2001), Denmark Level II High risk of bias	Change in QMGS (mean)[b] Base line to week 1 Base line to week 4 Base line to week 8 Base line to week 16	 0.10 (p > 0.05) 0.23 (p < 0.05) P > 0.05 p > 0.05	 0.23 (p < 0.05) P < 0.05 P > 0.05 P > 0.05	 No difference No difference NR NR
(Liu et al. 2010), China Level II Moderate risk of bias	QMGS (% ± SD improvement) Baseline to 14 days	 23.8 ± 3.7%	 60.8 ± 3.5%	 P < 0.01[c]

IVIg = intravenous immunoglobulin therapy; NR = not reported; PE plasma exchange therapy; QMGS = quantitative myasthenia gravis score; SD = standard deviation

[a] ANOVA was used to determine change in QMGS from baseline. A repeated measures analysis at day 28 showed no difference between treatments from baseline throughout the study (p = 0.26) (Barth et al. 2011)
[b] Wilcoxon's sign test (Rønager et al. 2001)
[c] Paired *t*-test (Liu et al. 2010)

Change in symptoms (MGFA class) in adults receiving maintenance IVIg

One case series (Hellmann et al. 2014), used the MGFA class to assess symptoms before and after patients received maintenance IVIg. Patients had been classified as MGFA class 3, 4 or 5 at the start of IVIg (moderate to severe disease status). Hellmann et al reported that out of 52 patients receiving IVIg, 37 (71%) had at least a mild improvement (reduced by one MGFA class) and 38% experienced moderate improvement (reduced by two MGFA classes) (Table 38). The 37 responders had been on IVIg maintenance therapy for at least one year and an average of 5.9 years (range 1-17). Patients who did not respond after a loading and two follow-up doses were discontinued from treatment. In factor analysis between responders and non-responders, seronegativity, ocular disease and non-bulbar symptoms at onset were found to be associated with no response. Generalised MG symptoms, age at disease onset and duration of disease were not different between responders and non-responders.

Table 38 Change in MGFA class in patients receiving maintenance IVIg (Hellmann et al. 2014)

Change in MGFA class	n patients with event/N (%)
No change	15/52 (28%)
Improvement by 1 class	23/52 (45%)
Improvement by 2 classes	14/52 (27%)

IVIg = intravenous immunoglobulin therapy; MGFA = Myasthenia Gravis Foundation of America

Change in symptoms (QMGS) for patients receiving maintenance IVIg or placebo

Standard therapies for MG such as PN, MPN, or azathioprine are comparators listed in the PICO for *Criteria V3* Indication 3. There were no studies comparing IVIg alone with these comparators, and patients on IVIg are often taking standard therapies as well as IVIg in trials. However, data on the incremental benefit of IVIg in addition to that of standard therapies are likely to be able to inform the questions of this assessment, therefore studies that compared IVIg to placebo or no additional therapy in patients that were on standard therapies were included.

Zinman, Ng and Bril (Zinman, Ng & Bril 2007) performed a double blind RCT in 51 patients who were randomised to either IVIg or placebo delivered intravenously. The majority of patients were taking one or more standard MG therapies at baseline including anticholinesterases, corticosteroids, azathioprine and cyclophosphamide, but there were no differences in medications between arms on analysis. At baseline 55% of participants were rated > 10.5 by the QMGS, or moderate to high severity.

QMGS was the primary measure of symptom improvement at 14 and 28 days from start of treatment. There were decreases in symptoms at both follow-ups in both treatment groups, but the degree of improvement decreased over time. The authors reported that no patients in the IVIg group declined in health status, but six in the placebo groups did decline. There was a significantly greater improvement for the IVIg group compared to placebo at day 14 ($p = 0.047$), but at day 28, the difference was not statistically significant ($p = 0.055$). In the IVIg group, there was a MCID (change in QMGS from baseline ≥ 2; see Table 15) at day 14 and 28, but the authors commented on the dubious clinical significance of such a small change from baseline. In the placebo group, improvement was not clinically significant at 14 or 28 days. Results are shown in Table 39.

In a separate analysis of those with a severity rating of QMGS > 10.5, improvement at day 14 was three times more likely in the IVIg group compared with placebo (23% versus 8% improved) and this result was statistically significant ($p < 0.015$, χ^2 analysis) (Figure 7). In covariance analysis, the change in QMGS from baseline to day 28 and from day 14 to day 28 showed sustained improved disease status but no further improvement in the IVIg group. When the lower severity group (QMGS < 10.5 at baseline) were analysed separately patients showed no response to IVIg ($p = 0.914$). Findings indicate an incremental benefit for patients on IVIg if they are moderate to severe in disease status, at least in the first few weeks of treatment. However, there were only 28 patients in this sub-group analysis, and it is not possible to tell what impact the other standard MG therapies had on improvement.

Table 39 Change in symptoms (QMGS score) for IVIg compared to placebo (Zinman, Ng & Bril 2007)

Measure	IVIg (n = 24)	Placebo (n = 27)	Difference p-value[a]
Baseline QMGS (mean ± SD)	12.3 ± 4.9	12.5 ± 5.5	p = 0.897
Change in QMGS			
Day 0-14	-2.54	-0.89	p = 0.047[a]
Day 0-28	-3.00	-1.19	p = 0.055
Day 14-28	-0.46	-0.30	p = 0.823

IVIg = intravenous immunoglobulin therapy; QMGS = quantitative myasthenia gravis score; SD = standard deviation

[a] Significant by analysis of covariance

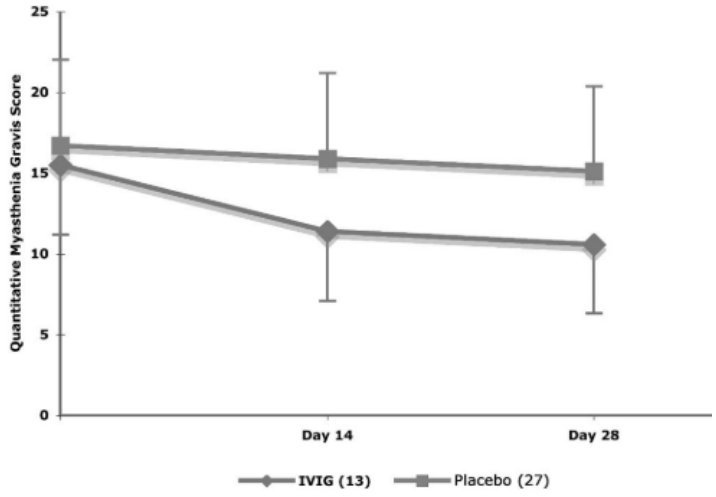

Figure 7 Mean change in QMGS score in patients with moderate to severe disease (QMGS > 10.5 at baseline) (Zinman, Ng & Bril 2007)

IVIg = intravenous immunoglobulin therapy; QMGS = quantitative myasthenia gravis score

Change in Quality of Life (MG-QoL-60 and MG QoL-15) in adults receiving IVIg or PE

Quality of life (QoL) was measured in the RCT by Barth et al (MG-QoL-60), and reported in Barnett et al 2013 (Barnett et al. 2013). Both the MG-QoL-60 and MG-QoL-15 tools were reported from 62 patients included in the analysis, although the MG-QoL-15 data were extracted from the MG-QoL-60 questionnaire. Not all patients in the original RCT completed the MG-QoL because it was not made available at the start of the trial, however the baseline demographic data of those who completed the tool did not differ from the original population. The MG-QoL score was compared between IVIg and PE treated groups, which had similar baseline QoL.

There was no statistically significant difference found in change in QoL between IVIg and PE treatment groups for either the MG-QoL-60 or 15 item questionnaires, 14, 21 or 28 days from start of treatment. QoL increased compared to baseline at all time points, but it appeared to plateau in the PE group,

while continuing to increase over 28 days in the IVIg group (Table 40). Whilst the clinical significance of the improvement in QoL was not discussed in the study, the improvement did correspond with clinical improvement (as measured by the QMGS).

Table 40 Change in QoL in patients either IVIg or PE maintenance therapy (Barnett et al. 2013)

QoL measure	IVIg mean ± SD	PE mean ± SD	Difference p-value[a]
Change in MG-QoL-60			
Day 1-14	-13 ± 17	-19 ± 22	0.41
Day 1-21	-11 ± 29	-18 ± 27	0.3
Day 1-28	-23 ± 32	-17 ± 23	0.4
Change in MG-QoL-15			
Day 1-14	-6 ± 9	-7 ± 8	0.52
Day 1-21	-7 ± 10	-8 ± 9	0.8
Day 1-28	-9 ± 11	-5 ± 5	0.2

IVIg = intravenous immunoglobulin therapy; MG-QoL = myasthenia gravis quality of life questionnaire (15 or 60 item version); PE plasma exchange therapy; QoL = quality of life; SD = standard deviation

[a] Student *t*-test (Barnett et al. 2013)

Rate of remission in adults receiving maintenance IVIg or PE

One RCT (n = 30) reported on the time to remission and compared the outcome between late-onset patients treated with IVIg and PE maintenance therapy (Liu et al. 2010). A classification of remission was based on relative score for therapeutic efficacy. The relative score was calculated as (pre-QMGS – post-QMGS)/pre-QMGS. A score of ≥ 95% was classed as a recovery, 80-95% as partial recovery, 50-80% as notably effective, 25-50% as improvement and ≤ 25% as ineffective. A score above 25% was classed as clinical remission, and above 50% as clinically effective. Fourteen days after the beginning of treatment, 80% of patients receiving PE had a relative score indicating treatment was clinically effective, compared to 40% of the patients receiving IVIg. The proportion of patients achieving remission was not reported. The relationship of remission time to relative scores was not defined in the article, however, the time to remission for the PE group was significantly lower than the IVIg group (Table 41).

Table 41 Remission time for patients receiving either IVIg or PE maintenance therapy (Liu et al. 2010)

Measure	IVIg mean ± SD	PE mean ± SD	Difference p-value[b]
Remission time (days)[a]	8.4 ± 1.54	6.7 ± 0.34	P < 0.01

IVIg = intravenous immunoglobulin therapy; PE plasma exchange therapy; SD = standard deviation

[a] Clinical remission was defined as a relative score > 25%

[b] Paired *t*-test (Liu et al. 2010)

Disease stability

No studies meeting the inclusion criteria reported on this outcome in maintenance populations.

Time to relapse

No studies meeting the inclusion criteria reported on this outcome in maintenance populations.

Need for ventilation or other life support systems in adults receiving maintenance IVIg or PE

The RCT by Liu et al (Liu et al. 2010) reported the number of patients requiring mechanical ventilation during the study period, after 14 days from start of treatment. The number needing support decreased in the group who received PE, and the outcome favoured PE over IVIg ($p < 0.05$). It was not stated how many patients were on ventilators at the start of the trial in either group.

Table 42 Ventilation needs for patients receiving either IVIg or PE maintenance therapy (Liu et al. 2010)

Measure	IVIg n with event/N (%)	PE n with event/N (%)	Difference p-value
Number using respiratory support after 14 days	6/15 (40%)	2/15 (13%)	P < 0.05[a]

IVIg = intravenous immunoglobulin therapy; PE plasma exchange therapy;

[a] Paired *t*-test (Liu et al. 2010)

INDICATION 3: CHILDREN UNDERGOING IVIG MAINTENANCE THERAPY

Two retrospective comparative studies (level III-2) specifically assessed IVIg therapy for maintenance in children (Liew et al. 2014; Wang et al. 2016). The studies did not use standardised tools to measure symptom improvement but instead described their own methodology. Liew et al (2014) compared IVIg with PE therapy in 33 juveniles with ocular and generalised MG, and analysed the groups separately. Wang et al (2016) performed a retrospective case-control study comparing 35 children who had received IVIg and methylprednisolone (MPN) with 35 children who had received a high dose of IV MPN (15-20 mg/kg/day) alone. This latter study was included as it has the potential to show incremental benefit of IVIg therapy over standard maintenance therapy (MPN).

Three non-comparative studies were also included. The first, a case series with before and after treatment data, was included as it reported on the use of IVIg for MG in Australian children (Nosadini et al. 2016). The data came from a large retrospective analysis of young patients treated at the Westmead Children's Hospital NSW, with central or peripheral neurology diseases who had been treated with IVIg. Two additional case series also provided before and after data following IVIg treatment in children (Selcen et al. 2000; VanderPluym et al. 2013).

Change in symptoms (response to treatment) in children receiving maintenance IVIg or PE

In the study by Liew et al (Liew et al. 2014), seven patients who received PE alone, and 10 who received IVIg alone, were compared separately from those who received both IVIg and PE over the course of maintenance treatment. All 17 children had generalised MG, but their age was not specified. The overall study population included 70% with pre-pubertal onset of disease (< 13 years) and 30% had post-pubertal onset (13-18 years). The study reported the proportion of patients who responded to treatment. Response was evaluated by an objective physical examination (including fatigability and MMT) and patient reported improvement in functional abilities. The PE group responded better than the IVIg treatment group (patients improved IVIg 50% versus PE 100%; p = 0.04) (Table 43).

Although the difference was statistically significant, the small patient numbers and the non-standardised tools used for measuring effectiveness in the study by Liew et al preclude any conclusions from being made about the effectiveness of IVIg or PE.

Table 43 Response to treatment in children given either IVIg or PE as maintenance therapy (Liew et al. 2014)

Measure	IVIg n with event/N (%)	PE n with event/N (%)	Difference p-value
Response to treatment[a]	5/10 (50%)	7/7 (100%)	P = 0.04[b]

IVIg = intravenous immunoglobulin therapy; MMT = manual muscle test; PE = plasma exchange therapy

[a] Combined assessment of clinical physical examination (including MMT and fatigability) and patient reported improvement
[b] Fisher's exact test (Liew et al. 2014)

Change in symptoms (absolute score and total effective rate) in children receiving IVIg plus IV MPN or IV MPN alone

The retrospective case control study by Wang et al (Wang et al. 2016) compared the response to treatment between observation and control groups. Data were collected from a hospital neurology department on patients attending over a 5 year period during which they received standard treatments such as PN and pyridostigmine. Patients in the observation group received a 5 day course of IVIg (0.4g/kg/day) and a high dose of MPN (15-20 mg/kg/day) administered intravenously over 3 to 5 days, and the control group received the MPN only. There were 35 children in each group.

Wang et al reported response to treatment (per cent) based on a composite 'absolute score' (MGAS) described by the authors. The absolute score assessed muscle strength of upper eyelid, fatigue test of upper eyelid, horizontal eye movement, facial muscle strength, fatigue test of upper limbs, fatigue test of lower limbs, swallowing and respiration function. A maximum score of 60 points was possible. Patients given IVIg and MPN were more responsive than those given IV MPN alone using this measure (p < 0.05). Wang et al also compared the number who were cured fully or cured to some degree and found that there were more who showed at least some improvement in the IVIg plus IV MPN group than the MPN alone group (p = 0.022). Results are summarised in Table 44. Again, although a

statistically significant difference was found, an incremental benefit of IVIg over MPN was not unexpected. The non-standardised tool means the results should be interpreted with caution.

Table 44 Change from baseline in absolute score and the proportion cured in patients treated with IVIg plus IV MPN or high dose IV MPN alone for MG maintenance (Wang et al. 2016)

Measure	IVIg + IV MPN	High dose IV MPN alone	Difference p-value
Absolute score (mean ± SD)[a]			
Change from baseline	12.98 ± 7.33	8.84 ± 7.27	P < 0.05 (paired *t*-test)
Cured (n with event/N; %)[b]			
Recovered	9/35 (25.7%)	5/35 (14.3%)	
Basically cured	11/35 (31.4%)	8/35 (22.9%)	
Evidence effects	6 (17.1%)	7/35 (20%)	
Improved	7/35 (20%)	6/35 (17.1%)	
No effects	2 (5.7%)	9/35 (25.7%)	
Total effective rate[c]	94.29%	74.29%	P = 0.022 (χ^2 test; χ^2 = 5.285)

IV = intravenous; IVIg = intravenous immunoglobulin; MG = myasthenia gravis; MPN = methylprednisolone therapy; SD = standard deviation

[a] Items included in the absolute score were muscle strength of upper eyelid, fatigue test of upper eyelid, horizontal eye movement, facial muscle strength, fatigue test of upper limbs, fatigue test of lower limbs, swallowing and respiration function. Maximum score = 60.
[b] Based on the relative score = (before treatment absolute score – after treatment absolute score)/ before treatment absolute score*100%. A score of 0.95 = recovered; 0.80 to 0.95 = basically cured; 0.50 to 0.79 = evident effects; 0.25 to 0.49 = improved condition; < 0.25 = no effect
[c] The total effective rate = recovery + basically cured + evident effects + improved

Change in symptoms (modified Rankin Scale, modified Osserman classification, clinical data) for children receiving IVIg

Three case series in paediatric populations reported before and after treatment data on symptom improvement (Nosadini et al. 2016; Selcen et al. 2000; VanderPluym et al. 2013). From the baseline data it is likely that cases in each series represented a mixture of the three NBA *Criteria V3* indications. They have been included for Indication 3 as this is the most likely indication for the majority of patients. The case numbers ranged from nine to 34.

Twelve children with MG received IVIg treatment at the Westmead Children's Hospital over the period from January 2000 to June 2014 (Nosadini et al. 2016). In all, 196 children who received IVIg for various indications were assessed. Disease severity was measured retrospectively from baseline and last follow-up clinical data using the modified Rankin Scale (mRS), which is used for assessing neurological disability, but is not specific to MG. Scores were given for the type of ongoing impairment such as cognitive/learning, behavioural, motor, visual and epilepsy. A score of 0-2 was rated as a good outcome, with 0 = no symptoms, 1 = no significant disability despite symptoms, 2 = slight disability, 3 = moderate disability, 4 = moderately severe and 5 = severe disability.

Children with MG were among those who experienced the best response to IVIg. Results were reported graphically for the per cent mRS improvement and shown here in Figure 8. Among the 12

patients, the proportion with a 'good' outcome (mRS 0-2) increased from 16.7% to 91.6% following IVIg treatment. This results was statistically significant using the chi-squared test (MedCalc online calculator: 95% CI 35.9%, 88.7%; p = 0.0003).

Two other case series reported improvement in symptoms following IVIg therapy. Selcen et al found that eight out of nine juvenile patients (89%) who were given IVIg had an improved functional status after infusion. Functional status was measured with the modified Osserman classification, and the median duration of improvement was 25 days. A tenth patient developed severe hypotension and did not complete the infusion (Selcen et al. 2000). In the case series by VanderPluym et al, 21 of 34 juveniles (62%) with generalised myasthenia improved after short term IVIg in a 2 year surveillance program. Method of symptom assessment was not reported, but was likely to be based on clinical data (VanderPluym et al. 2013).

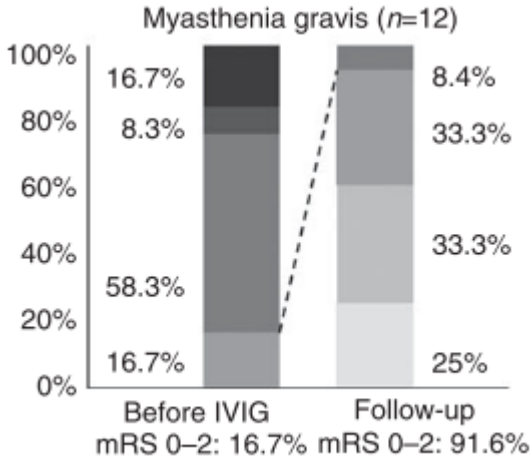

Figure 8 Change in modified Rankin Scale in children from the acute phase of disease (before IVIg administration) to last follow-up (Nosadini et al. 2016)

IVIg = intravenous immunoglobulin therapy; mRS = modified Rankin Scale

Need for ventilation or other life support systems in children receiving maintenance IVIg plus IV MPN or IV MPN alone

The retrospective case control study by Wang et al (Wang et al. 2016) compared the number of children requiring mechanical ventilation between observation and control groups from data collected from a hospital neurology department over a 5 year period.

There were similar results in both groups, with two patients in the IVIg plus high dose IV MPN group (observation group) and 3 in the high dose IV MPN alone group (control group) that required mechanical ventilation during their treatment period (Table 45).

Table 45 Number of patients needing breathing machines on either IVIg or PE maintenance (Wang et al. 2016)

Measure	IVIg + IV MPN n with event/N (%)	IV MPN n with event/N (%)	Difference p-value (95% CI)
Number using breathing machine	2/35 (5.71%)	3/35 (8.57%)	P = 0.666 (χ^2 test; χ^2 = 0.186)

IVIg = intravenous immunoglobulin therapy; IV MPN = intravenous methylprednisolone therapy; PE plasma exchange therapy;

INDICATION 3: PATIENTS UNDERGOING SCIG MAINTENANCE THERAPY

Change in symptoms (QMGS, MGC, MGFA, MMT) in patients receiving maintenance SCIg

Two recent Canadian case series with pre and post-treatment data (level IV) assessed the change in symptoms for patients receiving SCIg (Beecher, Anderson & Siddiqi 2017; Bourque et al. 2016). For objective measures, Beecher, Anderson and Siddiqi assessed symptoms using the QMGS, MMT and MGC tools, and Bourque et al used change in MGFA class. Beecher, Anderson and Siddiqi (2017) was the only study identified that used the MGC tool, and the data collected provides a comparison between the MGC, QMGS and MMT. The population was 22 participants who were enrolled prospectively, and followed for 6 weeks with SCIg (2g/kg) infused at weekly intervals over 4 weeks. Bourque et al (2016) was a retrospective study that identified patients on a hospital database who had received SCIg at 20g/100ml infusions. Patients were encouraged to change over from maintenance IVIg or to start Ig for the first time by subcutaneous infusion. Only nine patients in all had agreed to receive SCIg and were included in the analysis. Individual patient data were reported.

According to Beecher, Anderson and Siddiqi, patients showed a continuous improvement over 6 weeks on SCIg and when compared to baseline, QMGS, MGC and MMT scores showed significant difference at all follow-up time points (Table 46).

MGFA class improved in four out of nine patients in the population identified by Bourque et al after 4 weeks on SCIg. One each of three patients at MGFA class III at baseline improved to class I, II and IIb, and one MGFA class II at baseline improved to class I (Bourque et al. 2016).

Due to the lack of a suitable comparator in these studies, it is not possible to make any conclusions from the data.

Table 46 Change in symptoms in patients given either SCIg as maintenance (Beecher, Anderson & Siddiqi 2017)

Measure	Baseline mean ± SD	Week 2 mean ± SD (p)[a]	Week 4 mean ± SD (p)[a]	Week 6 mean ± SD (p)[a]
QMGS	14.9 ± 4.1	12.2 ± 4.6 (p = 0.001)	11.3 ± 4.9 (p < 0.0001)	9.8 ± 5.6 (p < 0.0001)
MMT	16.8 ± 9.5	10.8 ± 7.2 (p = 0.002)	6.4 ± 5.8 (p < 0.0001)	5.2 ± 4.5 (p < 0.0001)
MGC	17.4 ± 5.2	11.0 ± 3.9 (p < 0.0001)	7.1 ± 4.4 (p < 0.0001)	5.6 ± 4.5 (p < 0.0001)

MGC = myasthenia gravis composite score; MMT = manual muscle test; QMGS = quantitative myasthenia gravis score; SCIg = subcutaneous immunoglobulin therapy; SD = standard deviation

[a] All comparisons are with baseline. One-way repeated-measures analysis of variance with post hoc Tukey honesty significant difference was used. (Beecher, Anderson & Siddiqi 2017)

Change in Quality of Life (MG-ADL, MG QoL, TSQM, VAS) in patients receiving SCIg

Beecher, Anderson and Siddiqi (Beecher, Anderson & Siddiqi 2017) and Bourque et al (Bourque et al. 2016) provided data on QoL using a number of subjective tools. Beecher, Anderson and Siddiqi reported data on 22 patients using the MG-ADL at baseline, and 2, 4 and 6 weeks after start of treatment. The smaller Bourque case series (n = 9) reported data on the MG-QoL, MG-ADL and the visual analogue scale (VAS) tools at baseline and at 4 weeks. Bourque et al used the MG-QoL-15 questionnaire. The VAS is a subjective patient score on response to therapy, giving a score of 0 to the worst possible control of MG up to 10 for best possible control. The MG-ADL is a validated scale of 0-3 for eight specific MG characteristics related to daily life. See *Section B.5* for further descriptions of outcome measures for MG. Results from the studies are provided in Table 47.

The MG-ADL was significantly decreased from baseline at final follow-ups, indicating an improvement in the ability to perform daily activities after start of treatment in both studies. Similarly, the MG-QoL-15 and VAS indicated improvement in patient quality of life over the same 4 week treatment period in the study by Bourque et al. The small number of patients and lack of comparator in these studies prevent clear conclusions from the results, however they are consistent with an improvement in QoL in conjunction with SCIg therapy.

Table 47 Change in QoL scales in patients given either SCIg as maintenance therapy

Study ID, country Level of evidence Quality	Measure	Baseline mean ± SD	Week 2 mean ± SD (p)	Week 4 mean ± SD (p)	Week 6 mean ± SD (p)
(Beecher, Anderson & Siddiqi 2017), Canada Level IV Low risk of bias	MG-ADL	9.5 ± 3.0	7.4 ± 2.4 (p=0.0009)[a]	5.9 ± 3.3 (p<0.0001)[a]	4.6 ± 3.0 (p<0.0001)[a]
(Bourque et al. 2016), Canada Level IV Low risk of bias	MG-ADL	7.7	-	5.6 (p=0.005)[b]	-
	MG-QoL-15	20.4	-	13.7 (p=0.003)[b]	-
	VAS	5.8		8.2 (p=0.005)[b]	-

MG-ADL = myasthenia gravis activities of daily living scale; MG-QoL-15 = myasthenia gravis quality of life questionnaire (15 question version); SCIg = subcutaneous immunoglobulin therapy; SD = standard deviation; VAS = visual analogue scale

[a] All comparisons are with baseline; one-way repeated-measures analysis of variance with post hoc Tukey honesty significant difference was used. (Beecher, Anderson & Siddiqi 2017)

[b] All comparisons are with baseline; paired two-tailed *t*-test (Bourque et al. 2016)

B.7. INTERPRETATION OF THE CLINICAL EVIDENCE

It is important to classify the therapeutic profile of the proposed therapeutic medical service (IVIg therapy) in relation to its comparators (i.e. whether it is therapeutically superior, inferior or equivalent to the comparator). See Appendix D for detailed evidence profile tables.

INDICATION 1

On the basis of the evidence profile (summarised in Table 48), **it is suggested that, relative to PE, IVIg has superior safety (GRADE ⊕⊕⊕⊖) and non-inferior effectiveness (GRADE ⊕⊕⊖⊖) for MG patients in or at risk of crisis (*Criteria V3* Indication 1).**

One RCT and several cohort studies were consistent in their findings that IVIg was safer than PE for MG patients in crisis. The difference reached statistical significance in the RCT and a large cohort study. However, selection bias was suspected in the cohort studies, as PE is a favoured treatment for myasthenic crisis due to its suspected faster action. The evidence was less consistent for effectiveness, but overall it supported a conclusion of non-inferiority of IVIg compared to PE.

INDICATION 2

On the basis of the low quality evidence profile (summarised in Table 49), **it is suggested that, relative to PE, IVIg has uncertain safety (GRADE ⊕⊕⊖⊖) and uncertain effectiveness (insufficient evidence for GRADE) for MG patients preparing for surgery (*Criteria V3* Indication 2).**

Evidence from one small RCT found no significant difference in the frequency of AEs between IVIg and PE treatments for patients undergoing thymectomy, but the body of evidence was considered too small to make a confident conclusion about the safety of IVIg compared to PE. The quality of evidence on effectiveness was considered too low to make any conclusions about IVIg compared to PE.

INDICATION 3

On the basis of the evidence profile (summarised in Table 50 and Table 51), **it is suggested that, relative to standard therapies (with the exception of PE) no conclusions can be made regarding the safety (GRADE ⊕⊕⊖⊖) and effectiveness (GRADE ⊕⊕⊖⊖) of IVIg. In the comparison with PE, IVIg has non-inferior safety (GRADE ⊕⊕⊕⊖) and non-inferior effectiveness (GRADE ⊕⊕⊕⊖) for MG patients needing a change of maintenance therapy (*Criteria V3* Indication 3).**

The evidence comparing IVIg with other maintenance therapies (excluding PE) was not sufficient to make any conclusions on the questions of safety and effectiveness.

Compared to PE, IVIg was found to have non-inferior safety and non-inferior effectiveness for MG patients given these maintenance therapies. This conclusion was largely based on symptom improvement measured by the QMGS that favoured PE, but was found to be not statistically different between IVIg and PE. The evidence came from one RCT of low risk of bias and several lower level studies. Overall the evidence was of moderate GRADE quality.

The evidence on IVIg in the juvenile MG population and for SCIg in MG was insufficient to make any conclusions.

Table 48 Balance of clinical benefits and harms of IVIg relative to PE in MG patients in or at risk of MG crisis (*Criteria V3* Indication 1), as measured by the critical patient relevant outcomes in the key studies

Outcome	Participants Studies	Effect	GRADE	Comments
Safety				
Adverse events (% patients with an event)	n=897 k=1 RCT, 5 Ret CoH	There were fewer adverse events associated with IVIg compared to PE	⊕⊕⊕⊖ Moderate quality	There were fewer AEs overall occurring in patients who received IVIg compared to PE. This result was consistent across studies. Selection bias could not be ruled out in the cohort studies, and this may reduce the effect, but benefit is still likely.
Effectiveness				
Mortality (% patients)	n=773 k=3 Ret CoH	There was no difference between IVIg and PE	⊕⊕⊖⊖ Low quality	There were fewer deaths occurring in patients who received IVIg compared to PE, but suspicion of selection bias in one large cohort study prevents this result from being reliable.
Infection rate (% patients with an event)	n=778 k=3 Ret CoH	There was no difference between IVIg and PE	⊕⊕⊖⊖ Low quality	There were fewer infections overall occurring in patients who received IVIg compared to PE. Suspicion of selection bias in one large cohort study, and inconsistent reporting of infections prevents this result from being reliable.
Change in MMS (change in score at 15 days from baseline)	n=87 k=1 RCT	There was no difference between IVIg and PE	⊕⊕⊕⊖ Moderate quality	There was no benefit for patients receiving IVIg over those who received PE found by change in MMS at 15 days.

GRADE Working Group grades of evidence
⊕⊕⊕⊕ **High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
⊕⊕⊕⊖ **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
⊕⊕⊖⊖ **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
⊕⊖⊖⊖ **Very low quality:** We are very uncertain about the estimate.

AE = adverse event; IVIg = intravenous immunoglobulin therapy; MG = myasthenia gravis; MMS = myasthenia muscle score; NA = not applicable; PE = plasma exchange therapy; Ret CoH = retrospective cohort study; RCT = randomised controlled trial;

Table 49 Balance of clinical benefits and harms of IVIg relative to PE in MG patients preparing for surgery (*Criteria V3* Indication 2) as measured by the critical patient relevant outcomes in the key studies

Outcome	Participants Studies	Effect	GRADE	Comments
Safety				

Outcome	Participants Studies	Effect	GRADE	Comments
Adverse events (% patients intubated)	n=24 k=1 RCT	No conclusion could be made	⊕⊕⊖⊖ Low quality	Overall there were fewer AEs occurring in patients who received IVIg compared to PE, however the participant numbers in the RCT were so small that the study did not have power to make a strong conclusion.
Effectiveness				
Effectiveness	-	No conclusion could be made	-	The evidence for effectiveness was of too poor quality to make any conclusions about the effectiveness of IVIg compared to PE

GRADE Working Group grades of evidence
⊕⊕⊕⊕ **High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
⊕⊕⊕⊖ **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
⊕⊕⊖⊖ **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
⊕⊖⊖⊖ **Very low quality:** We are very uncertain about the estimate.

AE = adverse event; IVIg = intravenous immunoglobulin therapy; MG = myasthenia gravis; PE = plasma exchange therapy; RCT = randomised controlled trial;

Table 50 Balance of clinical benefits and harms of IVIg relative to comparators (therapeutics other than PE) in MG patients changing maintenance therapy (*Criteria V3* Indication 3) as measured by the critical patient relevant outcomes in the key studies

Outcome	Participants Studies	Effect	GRADE	Comments
Safety				
Adverse events (% patients with any event) IVIg v placebo	n=62 k=1 RCT	No conclusions could be made	⊕⊕⊖⊖ Low quality	There was no difference in frequency of AEs detected between groups. Patients in both arms were on other maintenance therapies, the impact of which was not determined.
Effectiveness				
Mortality (% patients with event) IVIg v placebo	n=62 k=1 RCT	No conclusions could be made	⊕⊕⊖⊖ Low quality	There was no difference in frequency between groups. . Patients in both arms were on other maintenance therapies, the impact of which was not determined.
Change in QMGS (change in score from baseline to day 28) IVIg v placebo	n=51 k=1 RCT	No conclusions could be made	⊕⊕⊖⊖ Low quality	The symptom improvement in the IVIg group at 28 days was not statistically significant. At 14 days the difference was stronger (p = 0.03). Some patients in both arms were taking one or more standard therapies. This outcome may show an incremental benefit of IVIg over standard therapies

Outcome	Participants Studies	Effect	GRADE	Comments
Change in absolute score in children (mean change from baseline) IVIg + MPN v MPN alone	n=70 k=1 Ret CoH	No conclusions could be made	⊕⊕⊖⊖ Low quality	Symptom improvement favoured IVIg but may be unreliable due to poor study quality. Patients were also given other standard therapies over the course of the study. This outcome may show incremental benefit of IVIg over high dose IV MPN.

GRADE Working Group grades of evidence
⊕⊕⊕⊕ **High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
⊕⊕⊕⊖ **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
⊕⊕⊖⊖ **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
⊕⊖⊖⊖ **Very low quality:** We are very uncertain about the estimate.

AE = adverse events; IVIg = intravenous immunoglobulin therapy; MG = myasthenia gravis; MPN = methylprednisolone therapy; PE = plasma exchange therapy; QMGS = quantitative myasthenia gravis score; Ret CoH = retrospective cohort study; RCT = randomised controlled trial;

Table 51 Balance of clinical benefits and harms of IVIg relative to PE in MG patients changing maintenance therapy (*Criteria V3* Indication 3) as measured by the critical patient relevant outcomes in the key studies

Outcome	Participants Studies	Effect	GRADE	Comments
Safety				
Adverse events (% patients with any event)	n=1,034 k=3 RCTs, 1 Ret CoH	There was no difference between IVIg and PE	⊕⊕⊕⊖ Moderate quality	There was no difference in frequency of AEs detected between groups. This outcome may be impacted by selection bias in the cohort studies, however the results are consistent across all studies.
Adverse events (% children with pyrexia and rigors or central line sepsis)	n=17 k=1 Ret CoH	No conclusions could be made	⊕⊖⊖⊖ Very low quality	The frequency of AEs was lower in children given PE but the difference was not statistically significant. This result may be unreliable due to small participant numbers.
Effectiveness				
Infection rate (% patients with event)	n=920 k=1 RCT, 1 Ret CoH	There was no difference between IVIg and PE	⊕⊕⊖⊖ Low quality	There was no difference in frequency of infections between groups. This outcome may be impacted by selection bias in the cohort study, and the RCT was underpowered for a strong conclusion.
Change in QMGS (mean change in score from baseline to 14 days or % change from baseline)	n=124 k=2 RCTs	There was no difference between IVIg and PE	⊕⊕⊖⊖ Low quality	The RCTs both favoured PE with one trial finding clinically important improvements in both IVIg and PE groups without a statistically significant difference between groups, and the other finding a statistically significantly greater improvement in the PE group compared to the IVIg group, but it is

Outcome	Participants Studies	Effect	GRADE	Comments
				not possible to tell if this is clinically significant. These results are based on small participant numbers.
Change in QMGS (mean change in score from baseline to 21 days)	n=84 k=1 RCT	There was no difference between IVIg and PE	⊕⊕⊕⊖ Moderate quality	Symptom improvement favoured PE at 21 days but was not statistically significant. Results were from a single small RCT with low risk of bias.
Change in QMGS (mean change in score from baseline to 28 days)	n=84 k=1 RCT	There was no difference between IVIg and PE	⊕⊕⊕⊖ Moderate quality	Symptom improvement favoured PE at 28 days but was not statistically significant. Results were from a single small RCT with low risk of bias.
Change in QoL (change in MG-QoL-60 from baseline to day 28)	n=62 k=1 RCT	There was no difference between IVIg and PE	⊕⊕⊕⊖ Moderate quality	Improvement in QoL favoured IVIg but there was no statistical difference between groups. Results were from a single RCT with low risk of bias.
Response to treatment in children (% children who responded measured with non-standardised tools)	n=17 k=1 Ret CoH	No conclusions could be made	⊕⊖⊖⊖ Very low quality	Response in children was better for those given PE. This result may be unreliable due to non-standardised tools and small participant numbers.

GRADE Working Group grades of evidence
⊕⊕⊕⊕ **High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
⊕⊕⊕⊖ **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
⊕⊕⊖⊖ **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
⊕⊖⊖⊖ **Very low quality:** We are very uncertain about the estimate.

AE = adverse events; IVIg = intravenous immunoglobulin therapy; MG = myasthenia gravis; MG-QoL-60 = myasthenia gravis quality of life 60 questions; PE = plasma exchange therapy; QMGS = quantitative myasthenia gravis score; QoL = quality of life; Ret CoH = retrospective cohort study; RCT = randomised controlled trial

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SECTION C TRANSLATION ISSUES

For Indication 1, the clinical assessment identified clinical effectiveness non-inferiority for IVIg versus PE, with superior safety outcomes. Therefore a full economic evaluation is relevant, and translation of study data for the economic evaluation will be necessary.

For Indication 2, analysis of the clinical effectiveness and safety data showed available data was insufficient to identify any conclusive differences between IVIg and PE, in either of these outcomes. Therefore only a partial economic analysis, comparing costs can be presented, some translation is still relevant for this analysis.

Section B found little evidence describing the patterns of use of the various comparators relevant to *Criteria V3* Indication 3, therefore literature was searched for additional sources to inform estimates of resource use for the economic analysis. The identified circumstances of use are summarised in C.3 without further translation and the application of Australian costing is detailed in Section D. As Indication 3 involves ongoing treatment, time horizon and extrapolation issues are relevant.

Where possible, economic analyses will be conducted to include trial-based costing together with a stepped analysis to derive base case cost-analyses for the Australian setting.

C.1. OVERVIEW

The economic analyses for *Criteria V3* Indications 1 and 2 are derived from trial-based cost analyses of IVIg vs PE, in MG crisis (Gajdos et al. 1997) and pre-operatively (Alipour-Faz et al. 2017), respectively. Potential applicability issues associated with trial-based economic analyses are;

- Are the treatment patterns associated with both IVIg and PE in the RCT by Gajdos 1997 applicable to Australian practice and usage data for Indication 1?
- Are the pre-surgical treatment patterns and surgical outcome data associated with IVIg and PE in the RCT by Alipour-Faz, 2017 applicable to Australian practice and usage data for Indication 2?

These are small short-term studies with apparently complete data on their reported outcomes. However for Indication 1, the study adverse events are clinically serious and are associated with potential mortality and morbidity. Therefore exploratory modelling includes extrapolation of long-term QALY consequences with respect to estimated morbidity and mortality rates that would be present in a whole population setting.

The economic analysis for *Criteria V3* Indication 3 involves ongoing maintenance treatments potentially over a patient's lifetime. Potential extrapolation issue are;

- What is the appropriate time horizon for economic analysis for Indication 3?
- Which resource costs are recurring (and which are not) when administering the various long-term maintenance therapies?

No comparable quality of life data or direct utility estimates were available in the clinical trials, therefore additional translation studies were required to estimate the QALY decrements associated with adverse events.

C.2. APPLICABILITY TRANSLATION ISSUES

INDICATION 1

Are the Australian circumstances of use of IVIg and PE for myasthenic crisis consistent with the clinical study evidence?

Detail regarding the delivery of treatment for *Criteria V3* Indication 1 is summarised in Table 52 below, with descriptions of the Gajdos et al 1997 study interventions and circumstances by which they were delivered, compared with available Australian data and information on Australian practice.

Table 52 Applicability issues comparing the RCT (Gajdos et al. 1997) to Australian practice for Indication 1

	Evidence Base: (Gajdos et al. 1997)	Australian data and reported practice
IVIg dose(s), administration frequency and duration	Patients in the IVIg group received daily 0.4-gm/kg doses of IgG for 3 or 5 consecutive days. *i.e. a total of either 1.2g/kg or 2.0g/kg IVIg was given*.	NBA data[a] suggests an average usage of 230g per patient, and an average weight of 81kg (see Section D.4). Therefore the total dose given in Australia may be higher, around 2.8g/kg.
PE dose (plasma volume), frequency and duration	PEs of 1.5 volumes each were consecutively performed on days 1, 3, and 5. One plasma volume (PV) was calculated according to the following formula: PV = (1 - hematocrit) X 70 X body weight (kg). *Assuming normal haematocrit and 81kg bodyweight this equates to a 4.5L exchange (see Section D.4).*	(Paton & Baldwin 2014) describe PE given for MG crisis in an Australian ICU; as 3 L or 5 L exchanges given daily to ICU patients. Average length of stay in ICU for PE patients was 4 days.
PE fluid replacement composition	Replacement fluid was composed of equal parts of 4% diluted albumin and artificial gelatin solution	(Paton & Baldwin 2014) describe PE given for MG crisis in an Australian ICU; as a mixture of FFP and human albumin 4% or human albumin 4% alone over a 6–14 h period. PE was administered daily with FFP frequently used as a portion of the replacement fluid.
Management of adverse events and 2nd line treatment	Gajdos reports a 4.4% discontinuation rate (due to serious adverse events) in the PE arm (no discontinuations in the IVIg arm), however the publication does not identify how the MG crisis is subsequently management.	Given the gravity of MG crisis, the need to treat and the availability of IVIg in the Australian setting, it is assumed that any patient who discontinues PE mid-treatment due to adverse events would be commenced on IVIg.

IVIg = intravenous immunoglobulin; NBA = National Blood Authority; PE = plasma exchange; PV = plasma volume; MG = myasthenia gravis; ICU = intensive care unit; FFP = fresh frozen plasma

[a] Source: 'HTA Data April2019.xlsx' workbook provided by the NBA.

The plan for the economic analysis is to present costing results based on the clinical trial with a stepped evaluation adjusting the relevant inputs to those based on Australian data and publications, and will

incorporate the assumption that a full dose of IVIg would be provided following where PE treatment is unable to be completed due to an adverse event.

INDICATION 2

Are the Australian circumstances of use of IVIg and PE in at-risk MG patients prior to surgery, consistent with the clinical study evidence?

A summary of the relevant applicability issues regarding delivery of *Criteria V3* Indication 2 treatments are summarised in Table 53, with descriptions of the Alipour-Faz 2017 Study clinical interventions, and the circumstances by which they were delivered, along with a comparison to available Australian data and information on Australian practice.

Table 53 Applicability issues comparing (Alipour-Faz et al. 2017) to Australian practice for Indication 2

	Evidence Base: (Alipour-Faz et al. 2017)	Australian data and reported practice
IVIg dose(s), administration frequency and duration	Patients in the IVIg group received 1g/kg doses of IgG for 2 consecutive days approximately 10-30 days prior to scheduled surgery.	NBA data[a] and estimates are that usage of IVIg supplied under Indication 2 is approximately 156g per patient (see Section D.4). If the average weight of patients is 81kg, this equates to approximately 1.93g/kg per patient, or; 0.96g/kg per day for 2 days.
PE dose (plasma volume), frequency and duration	PE of 1L volumes each were performed five times, on alternate days 10-30 days before procedure.	No information was identified that described pre-operative PE treatment in MG patients specifically in the Australian setting.
PE fluid replacement composition	The plasma replacement fluid was Albumin 5%.	No information was identified that described pre-operative PE treatment in MG patients specifically in the Australian setting.
Surgery resource use	Alipour-Faz describe that 7/12 PE group patients were postoperatively intubated (for median time 13h), but in the IVIg group only 2/12 patients were intubated (p value = 0.01) for 2 and 22 hours). A slight difference in the average surgery duration (PE 0.71 hours more than IVIg) was shown between groups (p value = 0.05). The duration of hospitalization, ICU length of stay and dose of corticosteroid were measured without significant difference between groups.	No data on resource use differences was identified specific to the Australian setting.

IVIg = intravenous immunoglobulin; NBA = National Blood Authority; PE = plasma exchange; MG = myasthenia gravis; ICU = intensive care unit.

[a] Source: 'HTA Data April2019.xlsx' workbook provided by the NBA.

The NBA data on the number of patients receiving IVIg for this Indication, combined with the estimated volume of use for Indication 2 (see *Section D.4*) estimate an average IVIg dose that is reasonably consistent with the clinical trial, particularly if some patients do not complete the second day of IVIg therapy due to adverse events. No information was identified that described Australian clinical practice for administering PE specifically in this clinical context, therefore the applicability of the trial is difficult to assess in this regard.

Consideration was given to whether the differences in intubation and surgery times identified in the study are likely to reflect true clinical experience and, if so, whether there are resource cost implications.

The loss of clotting factors following repeated albumin based PE is noted to predispose patients to bleeding ((Shunkwiler et al. 2018); this is consistent with the trend to increased intra-operative blood loss in thymectomy post PE (shown vs no PE) reported in (Reis, Cataneo & Cataneo 2019; Saeteng et al. 2013); even small increases in bleeding may explain an increased surgery time in patients pre-treated for surgery with PE.

The difference in surgery duration (surgery after IVIg averaged 3.46 hours, being 0.71 hours less than surgery after PE which lasted on average 4.17 hours) represents a 17% reduction in theatre time. To account for this, the direct operating theatre costs (primarily wages) in the IVIg group will be adjusted accordingly in *Section D.4*. Sensitivity analysis will also be presented for the alternative assumption that the study operating time difference would not be effected by choice of pre-treatment.

Although intubation times were also significantly different, this is not identified to alter hospital resource consumption unless it is associated with an increased ICU time, but this was not demonstrated with significance in the study; therefore no resources are assumed to be directly impacted by the intubation period finding.

The plan for the economic analysis is to present costing results based on the clinical trial with a stepped evaluation adjusting IVIg dosing inputs to those based on Australian data.

C.3. EXTRAPOLATION TRANSLATION ISSUES

INDICATION 1

Are there potential long-term effects from the safety differences identified in the trial which are not captured in the clinical trial outcomes?

The clinically relevant adverse events which were identified in the Gajdos trial, and only associated with PE, were single incidents of retroperitoneal haematoma (RH) and femoral thrombosis (FT); in each case it is reported that PE treatment was stopped, but no longterm sequelae were reported. However, the literature and clinical advice provided from the Ig Review Reference Group identified that such events are associated with morbidity and mortality, particularly RH, such that if these were to occur over a larger population some loss of life or ongoing quality of life may occur (Daliakopoulos, Stavros I. et al. 2008; Daliakopoulos, S. I. et al. 2010).

In addition, although not recorded in this study, exploratory analysis also considered infection and sepsis a potential adverse event associated more frequently with PE, based on the clinical advice and

broader literature (described further in *C.4.1. Which safety (adverse effect) differences identified in the clinical analysis should be incorporated into the economic evaluation?*). Additionally hospital acquired sepsis is associated with mortality and longterm morbidity ((Kaukonen et al. 2014; Westphal et al. 2019)) .

The potential for mortality and ongoing morbidity associated with these serious adverse events requires an extended time horizon in the exploratory modelled analysis. The mean age of MG patients in the model is assumed to be approximately 66 years (based on NBA data). Given life expectancy in MG patients is similar to the general population (Section A.4) and at 66 year of age, normal life expectancy in Australia is 18.9 years for men and 21.5 years for women[7], a modelled time horizon of 15 years is determined to be a reasonable, albeit conservative, time horizon over which to estimate the ongoing consequences of adverse events.

INDICATION 3

What is the appropriate time horizon for the economic analysis of maintenance IVIg?

The economic analysis for *Criteria V3* Indication 3 involves maintenance treatments for refractory MG, 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 MG under Indication 3 were not available, however average durations of IVIg used for ongoing maintenance therapy that were found in published literature are presented in Table 54.

[7] from ABS Life Tables 2015-2017: available at https://www.abs.gov.au/ausstats/abs@.nsf/mf/3302.0.55.001

Table 54 Duration of IVIg used as maintenance therapy in MG

Reported Duration of IVIg Maintenance Therapy	Description of Population	Source
IVIg maintenance treatment was successfully discontinued following completion of the study in 70% patients within 1.5 to 3 years.	10 consecutive patients (7 women) with an acute exacerbation of MG. Age 25–70 years with disease duration 2-8 years. (Israel)	(Achiron et al. 2000)
The mean duration of IVIg therapy was 7.5 years (range 1- 13 years). (The mean IVIg administration frequency was 2.8 months).	13 patients (10 female, mean age 62 years) on regular IVIg therapy for at least 1 year. Patients had severe attacks (moderate-severe functional loss) without adequate response to standard therapies, who could not receive/refused corticosteroid or immunosuppressive treatments due to their side effects. (Turkey)	(Sorgun et al. 2014)
15/52 (29%) of patients did not improve after the initial treatment year and were not given ongoing treatment. 37/52 (71%) were responders at 1 year and received ongoing maintenance IVIg for an average of 5.9 years (range 1 to 17).	52 patients considered for chronic IVIg therapy (48 had failed to respond adequately to prednisone, azathioprine or a combination, in 9 patients steroids were not administered due to a relative contraindication or to avoid exacerbation of significant other illness such as osteoporosis or diabetes). Responders were; 59% female, had disease onset at average age 45.9 years (range 10–81) and had average disease duration of 8.4 years (range 2 to 38). (Israel)	(Hellmann et al. 2014)
Not reported. Ongoing use at the end of study is described is described as occurring in some patients (mean follow-up 3.2 years).	54 children with juvenile MG. (United States)	(Liew et al. 2014)
All patients received immunoglobulin over a period of 24 months. None of the patients prematurely discontinued.	Sixteen patients (6 men, 10 women) with a mean age of 59 years, who had generalized anti-acetylcholine receptor–positive MG with insufficient response to standard long-term, high-dose immunosuppressants. The treatment intervals were either held constant or were increased because of clinical stabilization in every patient. (Germany)	(Eienbröker et al. 2014)

IVIg = intravenous immunoglobulin; MG = myasthenia gravis

The Ig Review Reference Group identified that maintenance Ig provided for an extended duration, such as 10 years, was rare in practice, and this would be an appropriate maximum treatment duration to cost. This is consistent with the literature, which reported average durations of 5.9 years and 7.5 years in the two sources reporting treatment duration with long-term follow-up.

Clinical advice received during the Assessment[8] identified that the use of IVIg under this Criteria was not always intended to be ongoing but IVIg would sometimes be to provide benefit whilst waiting for newly prescribed comparator immunosuppression regimens to become effective; which in some cases could take a long time (e.g. it may take up to 18 months in MG patients).

To enable comparison over various timeframes the cost analysis presents cost estimates of maintenance IVIg use over time horizons of 1, 2, 5 and 10, years.

[8] Immunoglobulin Review Reference Group

What are the recurring cost patterns associated with long-term maintenance therapies?

The pattern of resource use over the long-term was investigated and is described for each of the therapies costed under Indication 3. A summary of the costing patterns and any relevant costing issues is presented in Table 55.

Table 55: Treatment circumstances of use relevant to resource use and cost estimates

Treatment strategy	Description of practice issues relevant to cost analysis
IVIg	Maintenance IVIg treatment is described under Indication 3 with an induction phase (higher intensity dosing) followed by routine maintenance cycles. Therefore, costs in year 1 will be higher than subsequent years. The NBA *Criteria V3* state that neurologist reviews are required within 4 months of initiation and annually, however this is assumed to likely occur for any new MG treatment, therefore this is not added to the cost analysis.
PE	Repeated maintenance PE therapy requires suitable long-term vascular access, for example; implantable vascular access devices (IVADs), including tunnelled central venous catheters (TCVCs), or, less commonly, AV fistulae.(Ipe & Marques 2018) In Australia it is estimates most patients have infuser ports, and only 5% have IV fistulae.[a] All venous access methods are associated with an incidence of infection which requires management and costing. TCVCs are relatively straightforward to insert requiring approximately an hour of theatre time (commonly under medium-conscious sedation) and an x-ray to confirm correct placement. (Clark et al. 2016) It is assumed that a tCVC will typically require replacement every 3.5 years (based on a study in hemodialysis patients (Shi et al. 2017)). Creation of an AV fistula is a significant vascular surgery requiring pre-operative ultrasound planning, anaesthesia and overnight hospital admission (Sunshine Coast Hospital and Health Service 2015). The 'expected duration' a fistula lasts before requiring removal or revision has a wide reported range of 4-30 years. In this analysis it is assumed to be a one-off cost.
Surgery	Thymectomy is a one-off surgical procedure. All costs are presented in Year 1.
Pharmaceuticals	
Pyridostigmine	Pyridostigmine is generally first-line MG management and it is assumed that all patients attempting to manage severe mg with pharmaceuticals will be on pyridostigmine to the maximally tolerated dose. This cost is expected to be similar each year.
Prednisolone	Corticosteriods are routine second-line MG management, however it is estimated approximately 33% of Indication 3 patients will be intolerant to ongoing steroid use.[a] The remaining patients are assumed to be on reasonably high doses and while there may be some titration of dose either up or down depending on effectiveness, the overall cost is assumed to be similar each year.
Mycophenolate mofetil	Immunosuppression with mycophenolate mofetil is considered likely to be the most common third-line agent used in Australia.[a] Blood counts should be monitored 4 weekly which needs to be included in the cost analysis. (PI) While there may be some titration of dose either up or down depending on effectiveness, the overall cost is assumed to be consistent each year.
Azathioprine	Azathioprine is a potential third-line agent for ongoing management. Liver enzymes and blood counts are required regularly and will need to be included in the cost analysis. While there may be some titration of dose either up or down depending on effectiveness, the overall cost is assumed to be similar each year (Drugs & Therapy Perspectives 2001).
Methotrexate	Immunosuppression with methotrexate is another potential third-line agent for ongoing management. It is administered weekly and co-prescribed with folic acid (generally dosed 5 days a week, also on an ongoing basis). Liver enzymes and blood counts are required regularly and will also need to be included in the cost analysis. While there may be some titration of dose either up or down depending on effectiveness, the overall cost is assumed to be similar each year.
Cyclophosphamide	Cyclophophamide is typically reserved for severe refractory cases, however that is consistent with the patient population of interest. An Australian article describes remission-induction pulsed IV cyclophosphamide every 4 weeks for 6 months, followed by ongoing maintenance with oral dosing (Buzzard et al. 2015). All patients receiving cyclophosphamide require blood and liver monitoring and IV therapy requires hospital supervised administrations, therefore these costs need to be

Treatment strategy	Description of practice issues relevant to cost analysis
	included. Due to the IV induction, cyclophosphamide costs will be highest in year 1, then remain constant for year 2 and beyond, where oral treatment is maintained.
Ciclosporin	Immunosuppression with ciclosporin is another potential third-line agent. Renal function should be monitored 4 weekly (PI) and liver enzymes and blood counts may also be monitored, which need to be included in the cost analysis. While there may be some titration of dose either up or down depending on effectiveness, the overall cost is assumed to be similar each year.
Rituximab	Although not registered or PBS reimbursed for use in MG, rituximab is provided in some public hospitals for refractory patients. Administration schedules vary, however a fixed dose (1g x 2 doses, 14 days apart) schedule appears common in Australia (Chan et al. 2018). Maintenance dosing is harder to characterise and appears to be provided on an as required basis, rather than scheduled. Data from Chan et al identifying can be used to estimate an average of an additional 1g was provided to patients every 2 years. This pattern of dosing with relevant administration costs will be applied to the cost analysis.

AV= arterio-venous; IVIg = intravenous immunoglobulin; MG = myasthenia gravis; IV = intravenous; IVAD = implantable vascular access device; PBS = Pharmaceutical Benefits Scheme; PE = plasma exchange; PI = Patient Information; TCVC = tunnelled central venous catheter
[a] clinical advice provided by the Immunoglobulin Review Working Group

Detail on the prices of the resources used in each of the potential Indication 3 therapies is provided in Section D.4.

C.4. TRANSFORMATION ISSUES

The Ig Review Reference Group requested that the difference in safety outcomes observed in the evidence for Indication 1 and reviewed Section B, be translated into quality adjusted life years. The relevant translation issues are presented below.

For Indication 2, there was insufficient evidence to determine any difference in clinical or safety outcomes. The difference in surgical time identified in the clinical assessment of Indication 2 was not associated with a patient-relevant health outcome and therefore, although impacting resource use, it is not associated with a QALY difference.

With respect to Indication 3, no differences were observed in clinical or safety outcomes when comparing IVIg to PE, and there was inadequate evidence to quantify differences in effectiveness or safety that may exist between IVIg and the other potential comparators. However, evidence in broader populations receiving PE indicate a safety concern with respect to IV access-related infection and an exploratory cost-utility analysis was undertaken at the request of the Ig Review Reference Group.

INDICATION 1

C.4.1. Which safety (adverse effect) differences identified in the clinical analysis should be incorporated into the economic evaluation?

Although the clinical assessment did not identify a difference in effectiveness outcomes, a difference in safety outcomes was identified, such that a cost comparison or cost-minimisation analysis alone

does not provide adequate information to compare the value of Ig vs PE in Indication 1. A detailed summary of the adverse events associated with IVIg and PE in Indication 1 patients with statistical analysis was presented in Section B.6, Table 17.

There were only small patient numbers in the RCT and likely bias in the non-randomised studies, therefore an estimate of economic impacts (e.g. quality of life and resource use differences) based on this data are highly uncertain. It unlikely that the adverse event profile captured in the clinical trial with 41-46 patients per arm would represent the range of adverse types and rates that would occur when providing either therapy over the relevant Australian population; however the differential in adverse events between arms is broadly consistent with the observational study data (shown in Table 17, Section B.6) which is reassuring.

Generally the adverse events in Gajdos are not described in detail; it appears that many are transient and of little clinical or economic significance given the context that the patient has MG crisis and is in an ICU hospital setting. For example; e.g. headache, hypotension, tachycardia and nausea/vomiting are assumed to have no incremental impact on quality of life or resource use in this context. Therefore, no adverse events associated with IVIg are relevant to the economic evaluation, and only the serious adverse effects associated with PE need incorporation.

Two PE-associated adverse events are described as highly clinically significant by Gajdos; a retroperitoneal haematoma and a femoral thrombosis. Retroperitoneal haematoma is a rare but very serious, potentially life-threatening adverse event associated with anticoagulation and apheresis; typically requiring intensive care for a week; this would have quality of life and resource use implications. Likewise, femoral thrombosis is a serious adverse event requiring medical management and monitoring over many weeks and will also have quality of life and resource use implications. These events are therefore included in the economic analysis, each in 2.44% (i.e. 1/41) of patients.

Although Gajdos did not identify infection as a clinically relevant adverse event; this is a recognised adverse event associated with PE (Vucic & Davies 1998), and was reported as a relevant safety outcome, in the non-randomised studies of PE used for MG crisis. Statistically significant differences in the rates of infection in these studies are reported in Table 27; Mandawat identified an 8.23% excess in the rate of systemic infection associated with PE, and Pittayanon et al 2009 identified a 7.1% excess in ventilator or hospital-acquired pneumonia. The Ig Review Reference Group advised that PE-associated systemic infection, e.g. septicaemia, of clinical and economic significance (e.g. resulting in extended ICU stay); may be expected occasionally, and suggested that a scenario analysis explore this. For this analysis two different rates of infection are tested;

- A rate of 7.67%, based on the average observed infection rates in Mandawat and Pittaynon.
- A rate of 4.88%; assuming that the two PE patients in Gajdos reporting ‘fever’ represent economically relevant infection. This is lower than the infection rates in the observational

studies but may be reasonable given not all identified infections would necessarily have serious consequences.

Although none of the studies report mortality as being directly associated with PE, (Mandawat et al. 2010) mortality rates trended to favour IVIg, and the bleeding and thrombotic risks reported are recognised to be serious and potentially life-threatening.

Clinical advice provided during the assessment suggested that mortality secondary to sepsis would likely be the largest contributing factor to overall mortality associated with PE. Australian data identified that the mortality rate for severe sepsis in ICU patients in 2012 was 18.4% (Kaukonen et al. 2014). However, this data was not specifically restricted to hospital-acquired sepsis, and mortality in hospital-acquired sepsis appears to be greater (Westphal et al. 2019). The exploratory long-term model will apply a mortality rate of 18.4% to sepsis-affected patients. Although not strictly structured as such, it is assumed that for modelling purposes, this mortality rate would be sufficient to capture all PE-associated mortality (as additional mortality due to other serious adverse events is relatively small).

The sensitivity analyses will test an alternative method of estimating PE-associated mortality, based on a broad study of all plasma exchange use over 3.5 years at the University of Connecticut combined with literature reports available at that time (for numerous conditions). This analysis identified 8 deaths to be directly associated with 15,658 procedures, or a mortality rate of 0.05% (Mokrzycki & Kaplan 1994). The applicability of this data is uncertain given the age of the evidence, and the setting and patients are different: this would likely be less than the mortality in Indication 1 as this population includes lower risk patients, not in MG crisis or receiving emergency treatment.

A summary of the economically relevant adverse events to be incorporated in Section D is presented in Table 56 below.

Table 56 Safety outcomes associated with PE to be considered in the economic analysis

Adverse event	Rate	Source	Inclusion in Analysis
Retroperitoneal haematoma	2.44%	Gajdos	Costs and QALYs in trial-based analysis
Femoral thrombosis	2.44%	Gajdos	Costs and QALYs in trial-based analysis
Systemic Infection	7.67% - 4.88%	Upper rate from Mandawat and Pittayanon, lower rate based on 'Fever' in Gajdos.	Costs and QALYs in exploratory model
Death following sepsis	18.4%	Kaukonen 2014 (Australian ICU sepsis data)	QALY loss in exploratory model
Alternative overall Mortality	0.05%	Not reported as a direct PE-related event in the setting of MG, but has been reported in broader PE literature (Mokrzycki & Kaplan 1994)	QALY loss in exploratory SA

MG = myasthenia gravis; PE = plasma exchange; Ig = immunoglobulin; QALYs = quality adjusted life years; SA = scenario analyses.

Transformation of the relevant safety outcomes into QALYs is detailed in C.4.2 to enable incorporation into the cost-utility analysis presented in Section D. Identification of the resource use and costs associated with the safety outcomes has been described as a modelling issue in Section D.4.

C.4.2 What are the quality of life effects associated with differences in safety outcomes between IVIg and PE used in myasthenic crisis?

The acute adverse events of retroperitoneal haematoma, femoral thrombosis and systemic infection all represent serious conditions associated with significant loss in quality of life until resolution. In the case of thrombosis, ongoing anti-thrombotic therapy is recommended for 3 months, and some discomfort and disutilty is expected over this time.

No quality of life data relevant to the adverse safety profile of PE was presented in the clinical studies, therefore the a search of Tufts CEA Registry of Utility values and the literature was performed to inform the translation of the relevant adverse events into utility values and estimate quality of life decrements. A lack of good quality estimates for the disutility associated with the adverse events relevant to this analysis presents a serious limitation; the use of the identified utilities is highly uncertain and the QALY increment should not be interpreted as precise but, at best, broadly indicative.

What are the utility estimates associated with relevant adverse effects?

The utility estimates which are incorporated in the model are presented in Table 57. The key concerns with these values are:

(i) The various utility values are taken from various research which has used different methodologies (eg EQ-5D, time-trade-off and standard gamble) and therefore may be inconsistent; the Assessment model has used consistent sources where possible and there are no obvious face-validity concerns.

(ii) Utility values for some adverse events were not found, therefore the assigned utilities are based on 'similar' clinical conditions (e.g. utility for femoral thrombosis is based on broad 'DVT'; and retroperitoneal haemorrhage is based on gastrointestinal haemorrhage), therefore these may be inaccurate.

(iii) Utility decrements are not derived in the context of an MG patient, therefore the applicability is uncertain.

Table 57 Utility values associated with MG and adverse events of PE therapy, as reported in the literature

Health State or Event	Utility value	Source	Comment
MG crisis	0.20	(Barnett, Bril & Bayoumi 2019)	EQ-5D derived estimate of utility for MG class IVA (no class V/Crisis score available). This is considered baseline utility in crisis for the initial 6 days, to identify if AE results in further decrement.

Health State or Event	Utility value	Source	Comment
MG crisis – partially resolved	0.5 – 0.7	Assumed	Stepped utility between MG crisis which should be improving by day 7, with resolution at day 13.
MG crisis resolved (remission)	0.94	(Barnett, Bril & Bayoumi 2019)	EQ-5D derived estimate. Applied from Day 13 after crisis; baseline utility from which to calculate any AE-related decrement.
MG average utility	0.84	(Barnett, Bril & Bayoumi 2019)	Average of EQ-5D derived estimates across mixed study group. Assumed to apply to long-term survival loss estimated in exploratory analysis.
Retroperitoneal haematoma (in hospital)	0.45	(Guest, Watson & Limaye 2010)	Assumed to be the same as GI haemorrhage (reported as EQ-5D values in (Sandercock et al. 2002); however these values were not identified in the publication).
Femoral thrombosis	0.81	(Hogg et al. 2013)	DVT utility estimate based on standard gamble questions.
Anticoagulation therapy	0.948*	(Heisen et al. 2017)	Multiplier for while on anticoagulation treatment.
Serious infection, e.g. pneumonia, septicaemia	0.035	(Galante et al. 2011)	Mean EQ-5D derived estimate for hospitalised pneumonia in a UK population. Used in sensitivity analysis only.
Post-sepsis survival	0.8	(Fowler et al. 2003)	Tufts CEA quality score 6/7 Alternative values: survivors of sepsis 0.60 ((Green et al. 2006): Tufts score 4.5/7) 0.69 ((Ridley 2006): Tufts score 3.5/7) 0.77 ((Kip et al. 2018): sepsis 12 months after discharge: Tufts score 6/7)
Death	0	Assumed	Used in exploratory analysis.

MG = myasthenia gravis; PE = plasma exchange; AE = adverse event; GI = gastrointestinal; DVT = deep vein thrombosis; CEA = Cost-effectiveness Analysis; UK = United Kingdom.

A comprehensive utility study in MG patients, (Barnett, Bril & Bayoumi 2019) identified estimates for different grades of disease and using different measurement tools, however did not include crisis (Grade V). The lowest estimate of utility in Grade IV was 0.2; this is a likely overestimate of the utility in crisis given that (Landfeldt et al. 2017) estimates the utility in a 'Duchenne Muscular Dystrophy patient with intubation (day and night)' as 0.051.

Similarly, there is uncertainty around the utilities associated with adverse events. Retroperitoneal hematoma can be a life-threatening event and is likely to take many weeks to resolve [(Daliakopoulos, S. I. et al. 2010)] however only one estimate of utility explicitly associated with this event was identified, which was subsequently identified to be based on an estimate of utility associated with gastrointestinal haemorrhage (and reasonably consistent with alternative estimates for GI bleed). No utility values for the relatively more serious femoral thrombosis were identified, rather utilities were only estimated for generalised deep vein thrombosis (DVT - generally lower leg) and therefore these may result in an underestimate of the QALY decrement. A range of utilities associated with pneumonia were identified; however the severity or hospitalisation status rarely well described. The selected value of 0.035 represents the mean estimate of hospitalised pneumonia using an EQ-5D assessment in a United Kingdom population (Galante et al. 2011) (see Supplement).

How should the utility values be applied to estimate QALY decrements for adverse events?

It is assumed that the adverse safety events are transient, and the literature describes the adverse event utilities as applying for periods of a week to a month. In this analysis the QALY decrement needs to be calculated, initially at least, in the context of baseline utility for an MG crisis patient, while suffering crisis, and then for the time after which the crisis has resolved, but the adverse event is still present.

The median time to treatment response in Gajdos is reported in Section B.6, Table 32. A statistically significant difference across treatment arms was not identified, therefore an overall average estimate of 12 days is assumed to apply with either IVIg or PE treatment.

Utility decrements are calculated by taking the difference in utility associated with the adverse event away from the baseline. However, while patients are in crisis, their baseline utility is worse than the adverse event utility and it is irrational to assume a 'negative decrement' (i.e. that the adverse event improves utility) therefore no decrement is applied for adverse events while the patient has not yet recovered from the crisis. There is no means available to combine the ordinal preference data used to inform utilities of 'MG crisis' and the nominated 'adverse event health state' to enable estimation of an 'MG crisis plus adverse event' health state. The retroperitoneal haematoma and femoral thrombosis disutilities are assumed to last the entire 30 day period. When infection is included this is assumed to apply for 10 days beyond the recovery time for MG (based on (Halton et al. 2009) where central line-acquired infection is associated with an additional 10 days of hospital stay (2.5 in ICU and 7.5 in a normal ward).

A summary of the calculated utility decrements and associated QALY losses for the adverse events is presented in Table 58.

The estimation of QALY losses due to mortality is calculated as follows: The assumed background utility rate for chronic MG patients living MG patients is 0.84, based on the median overall EQ-5D derived utility in (Barnett, Bril & Bayoumi 2019), and a life expectancy of 15 years is expected (see Section C.3.1). Therefore, each fatality would result in a loss of of 9.017 QALYs (15 years at 0.84 utility, discounted at 5% pa). This is applied to the percentage of patients who experience sepsis-related mortality. Alternative estimates for mortality loss and life expectancy are tested in Sensitivity Analyses (including a flat 0.05% fatality rate across all PE patients based on (Mokrzycki & Kaplan 1994).

In addition, clinical advice received during the assessment indicated that some patients who experience a severe life-threatening adverse event have some irreversible organ damage and their quality of life remains impaired. This advice is consistent with the literature about ICU and sepsis discharge patients generally, and other economic models incorporating a post-sepsis health state (Fowler et al. 2003; Gerth et al. 2019; Green et al. 2006; Kip et al. 2018; Ridley 2006). Incidence data and utility values in the context of MG patients were not available, and the quantitiative applicability of the sources of possible utility estimates is highly uncertain, therefore the most conservative

estimate of QALY loss due to ongoing morbidity after sepsis has been applied. Assuming that sepsis survivors have an annual QALY decrement of 0.04 (*0.84 (average from Barnett) less 0.80 (from Fowler)*) applied over 15 years (with discounting).

Table 58 Calculated total QALY decrement per event due to adverse events of PE therapy

Days	1-3	4-6	7-9	10-12	13-15	16-18	19-21	22-24	25-27	28-30	Total decrement
Baseline Utility (No adverse events)											
MG crisis; then remission	0.2	0.2	0.5	0.7	0.94	0.94	0.94	0.94	0.94	0.94	
Utility with Adverse Events (whichever utility is lowest; baseline or AE associated utility)											
Retro-peritoneal Haematoma	0.2	0.4	0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.45	18 days @ 0.49 + 3 days @ 0.25 + 3 days @0.05 =
Decrement	**0**	**0**	**-0.05**	**-0.25**	**-0.49**	**-0.49**	**-0.49**	**-0.49**	**-0.49**	**-0.49**	
QALY decrement per event											0.02663 QALYs
Femoral Thrombosis	0.2	0.2	0.2	0.2	0.81	0.81	0.81	0.81	0.81	0.81	18 days @ 0.13 =
Decrement	**0**	**0**	**0**	**0**	**-0.13**	**-0.13**	**-0.13**	**-0.13**	**-0.13**	**-0.13**	
QALY decrement per event											0.00641 QALYs
3 months anticoagulant therapy											
Utility multiplier of 0.948	Baseline utility (0.94) x 0.948 = 0.8911. Daily decrement = 0.94 – 0.8911 = 0.04889										90 days @ 0.049 = 0.01205 QALYs
QALY decrement per event											0.01205 QALYs
Serious infection											
Infection Utility	0.2	0.2	0.5	0.035	0.035	0.035	0.035	0.89	0.89	0.89	9 days @ 0.905+ 3 days @ 0.665 =
Decrement	0	0	0	-0.665	-0.905	-0.905	-0.905	0	0	0	
QALY decrement per event											0.01305 QALYs
Exploratory modelled mortality and morbidity in sepsis											
Utility decrement per sepsis death (15 years, discounted):											9.01671 QALYs
Utility decrement per sepsis survivor (15 years, discounted):											1.50278 QALYs

AE = adverse events; MG = myasthenia gravis; PE = plasma exchange; QALY = quality-adjusted life years
Source: See Table 57 for published sources of health state utility values.

INDICATION 3

C.4.3. Should safety profile (adverse effect) differences be incorporated into the economic evaluation?

The clinical assessment did not identify differences in safety outcomes between IVIg and PE in Indication 3, however clinical advice received during the assessment suggested that this may be due to inadequate statistical power. Literature regarding long-term PE therapy more generally (i.e. not necessarily in MG patients) suggests that PE is associated with increased risk of infection, including

septicaemia, associated with the IV access requirements (Vucic & Davies 1998). Therefore over the long-term, the safety profile of IVIg has been speculated to be superior. Given there is no comparative information to support this assumption, the base case economic analysis does not account for inferior safety or an increased infection rate in the comparison of IVIg and PE for indication 3. However given plausibility of the claim and the lack of long-term evidence to the contrary, an exploratory analysis identifying the potential economic impact of an increased infection rate is presented for consideration.

The severe complication rate in PE procedures (observed over a 4.5 year period) in (Vucic & Davies 1998) was 0.7%; with infection at the venous access site occurring in 0.5% of procedures and sepsis accompanying this in 0.2% of procedures. It is assumed patients with sepsis are admitted to hospital.

For the exploratory analysis purposes, the utility decrement associated with serious infection is estimated to be 0.905 (based on the difference in utility between MG in remission; 0.94 and utility with serious infection a 0.035, as identified in Section C.4.2). The septicaemia hospital admission codes (6A-C) have a weighted average length of stay of 6.87 days. If the disutility is applied to hospitalisation time this represents a QALY decrement of 0.01704 per infection episode.

SECTION D ECONOMIC EVALUATION

D.1. OVERVIEW

The interpretation of the clinical evaluation in B.7 is that, relative to the relevant comparator (PE for Indications 1, and 2, various therapies for Indication 3), IV Immunoglobulin has:

- For Indication 1 patients: (myasthenic crisis): superior safety and non-inferior effectiveness
- For Indication 2 patients: (prior to surgery and/or thymectomy): uncertain safety and uncertain effectiveness
- For Indication 3 patients: (moderate to severe MG, failed 2 other therapies): non-inferior safety and non-inferior effectiveness vs PE, but uncertain safety and uncertain effectiveness vs surgical or pharmaceutical comparators.

Table 59 sets out the framework that was used to classify the clinical evidence in Section B so that a decision could be made about the type of economic analysis to undertake in this Section.

Table 59 Decision algorithm for undertaking an economic evaluation in the setting of the Ig Review.

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

x = health forgone (at cost). An economic evaluation is not warranted and continued use of Ig should not occur in this circumstance unless there are other supportive factors.

F = undertake a full economic evaluation. These may take the form of cost-utility analyses (preferred if adequate data are available) or cost effectiveness analyses in terms of clinically relevant outcome(s).

? = high levels of uncertainty will occur in an economic evaluation (if it is feasible to construct one). A cost analysis (partial economic evaluation) could be performed.

$ = cost minimisation analysis (partial economic evaluation that explicitly assumes no significant differences in health outcomes, associated with either effectiveness or safety, and analyses cost-differences only).

a where the conclusions with respect to effectiveness and safety are not congruent, then analyses identifying all relevant health consequences (i.e. effectiveness and safety outcomes in opposing directions of benefit) need to be presented. If a CUA is presented, this should capture effectiveness and safety collectively. If a CUA is not possible, then a single CEA may not capture all health consequences adequately and so a CCA is likely to be required. Where possible, the CCA should be quantitative, but in the absence of adequate data, a minimum qualitative identification of consequences should be presented.

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

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

Source: Schubert, C and Merlin T, Adelaide Health Technology Assessment, 2018

Indication 1 conclusion shaded blue, Indication 2 conclusion shaded orange, Indication 3 conclusion vs PE shaded green; vs surgery/pharmaceuticals shaded orange.

Based on the decision algorithm, full cost-utility analysis would occur for Indication 1. This has been undertaken however it should be noted that data on safety differences is based on limited patient numbers with little clinical information and no long-term follow-up or quality of life information. The cost utility analysis required extrapolation and transformations to estimate utilities (and therefore QALY differences) and these were not considered particularly accurate.

For Indication 2, based on the decision algorithm, a cost analysis is appropriate.

For Indication 3, based on the decision algorithm, a cost-minimisation analysis is appropriate for the comparison with PE, but only a non-comparative cost-analysis (noting that the results cannot inform cost-effectiveness) can be provided for all other comparators, noting there was insufficient evidence to assume equivalence between treatments. At the request of the Ig Reference Group and their advice that PE is less safe than Ig (due to septicaemia associated with central line access), a supplementary, exploratory cost-utility analysis wasundertaken. However, caution should be made in interpreting the results of this exploratory analysis, as it is based on inadequate evidence and should not be relied upon as a base case in decision-making.

D.2. POPULATIONS AND SETTINGS

The populations in the economic analysis are intended to represent the Australian population with MG who meet the BloodSTAR *Criteria V3* and are currently eligible for Ig. Demographic data on the patients currently accessing IVIg for MG in Australia has been provided by the NBA and Department of Health and indicates that patient ages currently range between 5 and 97 years, with an average patient age of 62 years. The average patient weight is 81kg (data sourced from the 'HTA Data April2019.xlsx' workbook provided by the NBA).

The estimations of average Immunoglobulin use (i.e. per dose and total use) for the MG population is directly sourced from the BloodSTAR database and therefore is directly applicable in terms of population and setting, however these data have not been divided into the three indications being considered, therefore assumptions have been made on the distribution of usage. All Australian patients receiving Ig for MG receive it intravenously, therefore a medically supervised setting (inpatient or day stay) is assumed.

The estimations of comparator use however are modelled based on data sourced from clinical trials with various populations and settings, therefore the applicability of these data is less certain. A summary of the populations in other data sources is described below with an assessment of applicability. For Indication 1, the severity of acute crisis necessitates hospitalisation and an ICU setting is assumed. For Indication 2, the context is preceding surgery, therefore an in-patient setting is assumed for both the intervention and the comparator. For Indication 3, ongoing maintenance treatment is assumed to be undertaken on an outpatient basis.

D.3. STRUCTURE AND RATIONALE OF THE ECONOMIC EVALUATION

A summary of the key characteristics of the economic evaluations is given in Table 60.

Table 60 Summary of the economic evaluations

	Indication 1 MG crisis	**Indication 2** MG patients pre-surgery	**Indication 3** Maintenance in refractory MG disease
Perspective	Healthcare system	Healthcare system	Healthcare system
Comparator	PE	PE	Various pharmacological treatments (anticholinesterases, immunomodulation), surgery or PE
Type of economic evaluation	Cost-utility analysis Cost-consequences analysis	Cost-analysis	Individual non-comparative cost-analyses. Exploratory cost-utility analysis of IVIg vs PE.
Sources of evidence	Gajdos 1997 is the basis of the clinical outcomes (single RCT detailed in *Section B*). Multiple additional references for utility values and to inform resource requirements (see C.4, D.4)	Alipour-Faz et al. 2017 is the basis of the clinical outcomes (single RCT identified in Systematic Review in *Section B*).	Various sources (no RCTs for most comparators in Systematic Review, *Section B*). Sources detailed in D.4
Time horizon	Base case: 3 months (Exploratory analysis including QALY loss due to fatal AE: 10 years)	4 weeks	1 year to 10 years
Outcomes	$ per QALY $ per adverse event avoided	Cost difference	Costs (including discounted costs)
Methods used to generate results	Trial-based analysis, with stepped analysis incorporating NBA IVIg usage data: cohort expected value analysis.	Trial-based analysis, with stepped analysis incorporating NBA IVIg usage data	Expected value analysis
Discount rate	NA	NA	5% pa
Software packages used	Excel	Excel	Excel

IVIg = intravenous immunoglobulin; MG = myasthenia gravis; NA = not applicable; NBA = National Blood Authority; PE = plasma exchange; QALY = quality adjusted life year; RCT = randomised controlled trial

See Table D.3.1 in the MSAC Therapeutic Guidelines.

The following published economic or costing studies of IV Immunoglobulin use in myasthenia gravis were identified when searching the literature, however none of these are 'cost-effectiveness analyses' *per se*.

For patients meeting Indication 1 (Myasthenic crisis – requiring airways support), a summary of economic findings is presented in Table 61:

Table 61 Published economic evaluations of IVIg use in patients with myasthenic crisis (Indication 1)

Publication	Description of analysis	Evaluation findings
Furlan JC, Barth D, et al. *Cost-minimization analysis comparing intravenous immunoglobulin with plasma exchange in the management of patients with myasthenia gravis.* Muscle Nerve. 2016 Jun;53(6):872-6. Canada	A cost-minimisation analysis comparing IVIg with PE for treatment of patients with MG exacerbation, using Ontario-based health cost data with clinical data from (Barth et al. 2011). Analyses were undertaken from the perspectives of a public healthcare insurer and a tertiary university hospital payer.	PE can be considered a short-term cost-minimising therapy (i.e. cost-saving) when compared with IVIg for treatment of MG exacerbation among patients with BMI >15.7 kg/m2, from the perspective of a public healthcare insurer. However it was more costly than IVIg from the perspective of the hospital payer when the costs of blood products were excluded.
Heatwole C, Johnson N, et al. *Plasma exchange versus intravenous immunoglobulin for myasthenia gravis crisis: an acute hospital cost comparison study.* J Clin Neuromuscul Dis. 2011 Dec; 13(2):85-94. United States	Cost-minimisation analysis of IVIg vs PE, based on two observational studies. Included costs: professional fees, hospital and ICU rates, medicines, IVIg, albumin, laboratory studies, implementing PE, catheter + placement/removal costs, and adverse event costs.	The average total difference in cost favoured the IVIg arm with an estimated savings of $22,326 per patient (US dollars). (Total average short term cost for utilizing plasma exchange was $101,140 per patient vs $78,814 for IVIg).
Mandawat A, Kaminski HJ, et al. *Comparative analysis of therapeutic options used for myasthenia gravis.* Ann Neurol. 2010 Dec;68(6):797-805. United States	A cohort of MG patients identified from a nation-wide (US) inpatient sample database (2000-2005), identified as receiving Ig or PE. Multivariate regression analysis was undertaken on disease predictors, complications, length of stay and inpatient costs. The MG crisis population was identified from within the broader population of MG patients and analysed individually.	In MG crisis patients, length of stay was significantly longer for patients receiving PE. (10 vs 5 days, $p < 0.001$) and inpatient costs were higher ($53,801 vs $33,924, $p < 0.001$) Overall, IVIg appears to have similar clinical outcomes (mortality and complications) and perhaps superior economic outcomes compared to PE.

BMI = body mass index; ICU = intensive care unit; IVIg = intravenous immunoglobulin; MG = myasthenia gravis; PE = plasma exchange; RCT = randomised controlled trial; US = United States

It is noted that both Furlan (Furlan et al. 2016b) and Heatwole (Heatwole et al. 2011) describe their analyses as cost-minimisation: implicitly stating that equivalent effectiveness is established, however on consideration of the Systematic Review findings described in *Section B*, this review did not consider the evidence available sufficient to form this conclusion with an acceptable degree of certainty.

The cost-minimisation by Furlan et al is a trial-based economic analysis of the Barth et al RCT (Barth et al. 2011), interpreting the RCT as identifying Immunoglobulin and plasma exchange as having similar effectiveness. In this analysis 'real-world' hospital cost data was obtained for 70 of the 84 patients enrolled in Barth; 74% (32/43) of PE patients and 93% (38/41) of IVIg patients. Additional costs were calculated using a schedule of physician fees and an estimate of blood product costs provided by the Canadian Blood Services and assuming a mean body weight of 70kg. Sensitivity analysis indicated that the cost differential between treatments is sensitive to body mass index, with PE becoming increasingly cost-saving as BMI increased. Although Canadian resource prices, and therefore the numerical results, are not directly applicable to the Australian setting, the perspective and context is

similar, and comparable results might be expected in the current analysis. A summary of the costs associated with identified treatment components and overall results is presented below (in 2014 Canadian dollars):

Table 62 Results of cost-minimisation analysis IVIg vs PE for MG exacerbation, from public healthcare insurer perspective (in 2014 Canadian dollars) (Furlan et al. 2016a)

Cost type	IVIg	PE	p-value
Hospital costs	$1,453.80 ± $77.48	$4,628.21 ± $120.58	<0.001
Blood Products	$6,823.60 ± 0	$1,455.83 ± $33.11	<0.001
Physician fees	$32.14 ± $61.16	$187.15 ± $1.53	<0.001
Total	**$8,309.72 ± $77.87**	**$6,271.19 ± $139.12**	**<0.001**

IVIg = intravenous immunoglobulin; PE = plasma exchange; MG = myasthenia gravis

Source: (Furlan et al. 2016a))

Both Heatwole (Heatwole et al. 2011) and Mandawat (Mandawat et al. 2010) were based on observational-data sources where the most significant contribution to the overall cost difference between treatments was due to differences in the duration of hospitalisation/ICU stay, and in each, PE was associated with longer admissions. Indirect resource use associated with treatment (e.g. management of adverse events) are included – either modelled directly (Heatwole et al. 2011) or implicitly captured in the hospital cost data (Mandawat et al. 2010). Therapy acquisition and administration costs are estimated in Heatwole et al (with IVIg having greater direct costa than plasma exchange with albumin), but are not disaggregated in Mandawat et al.

In both evaluations the inputs were based on data where selection bias had been identified as likely; sicker patients in greater respiratory distress are more likely to receive PE (due to it being commonly accepted that it has a quicker onset of action). Therefore, if identical cohorts were to receive each treatment, the cost difference may be less than as projected in the published analyses, or not occur. Furthermore, neither of the analyses are current with respect to costs (and possibly some aspects of care have also changed), and both relate to the US healthcare setting; therefore the actual and relative costs may be quite different to the current Australian setting (for hospitalisation, IVIg and PE).

There were no published economic evaluations identified analysing IVIg use in patients prior to surgery (Indication 2).

A summary of the published economic analyses in the MG maintenance setting potentially relevant to Indication 3, is shown below in Table 63.

Table 63 Published economic evaluations in patients with moderate-severe refractory MG (Indication 3)

Publication	Description of analysis	Evaluation findings
Chicaiza-Becerra LA, Garcia-Molina M, et al. *The cost-effectiveness of open or thoracoscopic thymectomy compared to medical treatment in managing myasthenia gravis without thymomas.* Rev Salud Publica (Bogota). 2012 Mar-Apr;14(2):260-70. **** Did not include immunoglobulin*** Colombia	A cost-effectiveness assessment of thoracoscopic thymectomy compared to i) open thymectomy and ii) medical therapy, for managing MG not associated with thymoma. The specific medical treatment modelled was: prednisolone 10mg days (57 to 74% of patients), pyridostimgine 223 mg day 2 to 3 mg/kg azathioprine or cyclosporine 4 to 5 mg/kg day (10% to 14% of patients).	A Markov model identified that thoracoscopic thymectomy was the most effective and least costly (it dominated the two alternatives). The cost per life year gained was, in CP 2008; 1,129,531 undiscounted and CP 805,179 with discount. Sensitivity analysis showed that the main variables affecting the results were; discount rate, the cost of a myasthenic crisis and the probability of complete remission.
Mandawat A, Kaminski HJ, et al. *Comparative analysis of therapeutic options used for myasthenia gravis.* Ann Neurol. 2010 Dec;68(6):797-805. United States	A cohort of MG patients identified from a nation-wide (US) inpatient sample database (2000-2005), identified as receiving IVIg or PE. Multivariate regression analysis was undertaken on disease predictors, complications, length of stay and inpatient costs. MG crisis patients were excluded from the separate analysis specific to a non-crisis population.	Adjusted mortality and complication rates were not significantly different between treatment groups. Length of stay was significantly longer (6 vs 4 days), and inpatient costs were higher ($26,662 vs $21,124) for MG patients receiving PE. Interpretation: Compared to PE, IVIg appears of similar clinically, and perhaps superior economically (length of stay, total inpatient charges) in the treatment of MG. Elderly and those with complex comorbid diseases including acute respiratory failure may be better treated with IVIg.
Wali A, Park C, et al. *Cost comparison between rituximab, plasmapheresis and intravenous immunoglobulin for refractory MuSK antibody positive myasthenia gravis.* American Association of Neuromuscular & Electrodiagnostic Medicine Annual Meeting Abstracts (Muscle & Nerve, Sept 2017) Abstract only United States	Treatments were assumed as near equivalent efficacy for the purposes of this analysis. A Markov model estimated discounted lifetime costs associated with Rituximab, PE, and IVIg for a 25-year old female with refractory MuSK positive MG (US, 2017 costs). Dose assumptions were: IVIg 70gm every 3 weeks; PE every 10 days; Rituximab 375mg/m2 x 4, twice yearly for life. TreeAge Pro was used for all cost-analyses and discounting was 3% per year.	Rituximab, PE, and IVIg were associated with lifetime costs of US $655,800, $1,323,300, and $2,210,380 respectively. Conclusion: Lifelong Rituximab costs approximately half that of PE and one-third that of IVIg (with stated assumptions). This supports insurance authorizations for Rituximab use in refractory MG.

CP = Columbian pesos; IVIg = intravenous immunoglobulin; MG = myasthenia gravis; PE = plasma exchange; US = United States

The cost-effectiveness analysis by Chicaiza-Becerra et al (Chicaiza-Becerra et al. 2012) is not informative to the current review. It does not include immunoglobulin in the medical management strategy for MG and neither the clinical nor the resource use modelling inputs are likely to be applicable to the current Australian health care setting (clinical inputs are drawn from a non-published systematic review of publications between 1989 and 2007, resource inputs relate to the Columbian healthcare system with prices based on official Columbian tariff rates of 2008).

The analysis by Mandawat et al, based on US hospital administrative claims data, identified that non-crisis MG hospital in-patients who had received immunoglobulin had reduced hospital stays and

overall lower hospital episode costs than non-crisis MG patients admitted for plasma exchange. However, this data is also observational with significant potential for selection bias and confounding, and it does not capture relative costs of management with Ig or PE in an outpatient settings which is particularly relevant for maintenance treatment of non-crisis MG.

A cost comparison including rituximab was published in abstract form only (Wali A 2017). This estimated costs for a single refractory patient in the US and assumed similar effectiveness across all treatments being compared. The evidence base for the assumptions in the analysis were not provided, therefore the reliability and applicability of the results are unknown.

Other published economic analyses of immunoglobulin use in MG which do not differentiate by the clinical criteria specified for access in Australia are summarised in Table 64.

Table 64 Other published economic evaluations of Ig use in MG (not matched to BloodSTAR *Criteria V3*)

Publication	Description of analysis	Evaluation findings
Guptill JT, Sharma BK, Marano A, Soucy A, Krueger A, Sanders DB. *Estimated cost of treating myasthenia gravis in an insured U.S. population.* Muscle Nerve. 2012 Mar;45(3):363-6. United States	In this study we estimated the costs paid by US health plans for treating MG in 2009 and determined the major cost drivers. 113 MG patients were matched by propensity scores with 339 non-MG patients from a comprehensive health-care insurance database. The mean annual costs paid by the health plan for treating MG, costs by place of service, and costs for IVIg and PE were determined.	Estimates a price of US$5,430 per session of IVIg and a price of US$1,306 per session of PE.(Furlan et al. 2016a; Guptill et al. 2012) Mean annual costs paid by the health plan per MG patient were $20,190 and costs attributable to treating MG were $15,675. Home health services accounted for 23% of MG patient costs and represented almost exclusively IVIg infusion costs. 6 MG patients had a total of 136 outpatient IVIg infusions at an average annual cost of $109,463 +/- $57,303.

MG = myasthenia gravis; IVIg = intravenous immunoglobulin; PE = plasma exchange; US = United States

None of the existing economic analyses are sufficiently applicable or generalizable to the Australian context to inform the MSAC of the costs or cost-effectiveness of IVIg, therefore new analyses are presented in this report.

STRUCTURE OF THE ECONOMIC EVALUATION

The results of the economic evaluations were calculated using Excel software.

The nature of the comparison and the structures of the analyses, particularly with respect to time horizon, varies across the different MG indications for Ig supply. A description of the context of each comparison is provided as follows.

Indication 1

For the comparison of an acute supply of Ig versus PE for a single MG crisis episode, the clinical evaluation did not identify differences in clinical effectiveness outcomes associated with the treatments. However a difference in safety was identified in the single RCT (Gajdos et al. 1997)with

patient adverse event rates of 19.5% (95% CI 7.4%, 31.6%) in the PE group compared to 2.2% (95% CI 0, 6.4%) in the IVIg group, p = 0.01. In the Ig group, the only adverse event reported was headache and it is assumed that this had no significant economic consequence. In the PE group, while most adverse effects were short-term and apparently administration-related, there were two serious adverse events which occurred in the RCT (retroperitoneal haematoma and femoral thrombosis), and a risk of sepsis identified separate to the clinical trial (see Section C.4.1). These serious adverse events potentially have mortality and long-term morbidity consequences, such that an extended modelled analysis is necessary to estimate cost-utility.

The serious adverse events required discontinuation of PE and medical management. Given the nature of the underlying indication however, it is assumed that it would then be necessary to also continue treatment of the MG crisis and switch these patients to IVIg.

Therefore, a short-term trial-based comparison of the acute treatments allowing for a single follow-up treatment over two weeks (i.e. a single crisis and short-term follow-up episode) is costed initally. The evidence on 'Time to response' from Gajdos 1997 identifies PE as acting in a shorter duration of time, which is at odds with the observational data from Heatwole et al (2011) and Mandawat et al (2010) reporting shorter hospital stays with IVIg. The observational data is highly likely to be confounded with selection bias and possibly other confounders. Given the lack of reliable unbiased data on hospitalisation duration, it is assumed adverse event free patients have no difference in hospital time, but serious adverse events do add to hospital days.

The structure of the extended model is slightly unconventional; rather than estimating total QALY outcomes associated with each arm of treatment and then determining the incremental difference, the approach used is to directly estimate the incremental QALY loss associated with adverse events from PE. The logic of this approach is consistent with the clinical assessment finding that health outcomes gained from treatment with IVIg versus PE were non-inferior, but the safety of PE was inferior. The QALY decrements were modelled over 15 years (as detailed in Section C.3.1), however there was no basis on which to estimate ongoing costs associated with PE adverse event-associated morbidity, and therefore the cost-effectiveness of IVIg is likely underestimated.

Indication 2

The relevant comparison in this context is the acute supply of Ig versus PE, preceding a specific episode surgery and/or thymectomy. The clinical evaluation did not identify evidence sufficient to conclude a difference or equivalence in health outcomes, regarding either effectiveness or safety, associated with the comparator treatments. Therefore, no assumption of equal effectiveness should be made and a simple short-term comparison of the costs of the acute management strategies is presented with Australian based resource usage estimates and costs.

Indication 3

The systematic review did not identify sufficient evidence to identify whether IVIg had superior or inferior effectiveness or safety to any of the comparators of surgery, prednisolone, pyridostigmine, azathioprine, methotrexate, cyclophosphamide, ciclosporin, mycophenolate mofetil and rituximab. In the comparison vs PE, it concluded IVIg had non-inferior effectiveness and safety. Therefore while the cost comparison is undertaken for all comparators, an assumption of equivalent health outcomes is only appropriate for PE and IVIg. The circumstances of ongoing use of these treatments, as predicted to occur in Australian practice are described in *Section C.3*.

As therapy may be ongoing, potentially long-term, time horizons of 1, 2, 5, and 10 years are costed. The analysis considers the total resource use and expenditure patterns associated specifically with each treatment on an annual basis, and compares cumulative costs over the stated time horizon, in undiscounted and discounted analyses.

Assumptions incorporated into the analyses

All analyses assume IVIg use only in the context of the specified indication, estimating cost-effectiveness for the single decision to treat with IVIg at that time. There is no single model that captures cost-effectivenss of IVIg access for all MG patients across any criteria, or for patients who may seek access to IVIg at multiple times over their life under different indication criteria.

Indication 1

- For the trial-base analysis, there are no differences in long-term health outcomes, whereas in the long-term exploratory model, serious adverse events are also associated with mortality and longterm morbidity.

- Where treatment is given without adverse event, there is no difference in duration of hospitalisation (time to response data from Gajdos 1997 favours PE, observational data on hospitalisation time from Mandawat favours IVIg), and minor adverse events have minimal clinical or economic consequences and have no estimable health utility difference or measurable resource use difference.

- Major thrombotic/bleeding events necessitate PE discontinuation (as per the RCT) and therefore initiation of IVIg, and a PE-related sepsis rate is expected. Additionally these events have an immediate impact on healthcare resource use (extended hospital stay) and patient utility.

Indication 2

- The base case assumes the significant difference in average operation time identified in the RCT is associated with a downstream effect (e.g. bleeding propensity) associated with the pre-surgery prophylactic treatment choice. This is tested in a sensitivity analysis.

- Operating time is directly associated with operating theatre resource use and therefore the time difference would have direct cost implications.

- The difference in operation time would have no effect on patient health or utility.

- Although duration on intubation varied this did not result in a significant difference in the duration of ICU stay, therefore this would not result in additional resource use.

Indication 3

- Patients who receive long-term PE require IV access; it is assumed 95% have a catheter (assumed to last on average three years, therefore modelled with a 33% replacement every year) and 5% receive an AV fistula which is assumed to last 10 years.

- Alternative pharmacological treatments are costed at maximum, or near maximum dose, given the population is defined as having severe and refractory MG.

- Monitoring for liver function, renal function and blood disorders is variable depending on treatments and included in the cost analysis.

- All patients receive regular medical/neurological consults and monitoring of disease related markers independently of the treatment choice therefore these costs are not included.

D.4. INPUTS TO THE ECONOMIC EVALUATION

The inputs used to inform costing are categorised and described throughout this section.

PATIENT DEMOGRAPHIC INPUTS

Inputs (including assumptions) regarding the patient population are show in Table 65.

Table 65 Patient population inputs

Description	Input value	Source	Analysis
Average Patient weight (base case)	81 kg	Bloodstar/STARS data 2017-18, 2018-19	**1, 2, 3**
Average patient BSA	1.9 m^2	Approximation based on patient weight data and estimated average height.	**3**
Hematocrit (normal range): men women average for PE costing:	45% to 52% 37% to 48% 47%	https://www.medicinenet.com/hematocrit/article.htm - estimated	**1**

BSA = Body Surface Area; PE = plasma exchange

CLINICAL MANAGEMENT INPUTS

Inputs (including assumptions) relating to the clinical management of MG, including the doses and administration patterns of therapies used in each of the indications are shown below.

For each of the indications the stepped analysis adjusts the dosage of Ig used from the trial-based (or Guideline based) dose, to an estimate of that used currently in the Australian setting. The estimates of Australian usage are based on information provided by NBA, where 514,257 g of Ig was provided to 1,174 MG patients, with the spread across the Indications 1, 2 and 3 being 201, 33 and 940 patients (17.1%:28%:80.1%), respectively. However usage in terms of grams was estimated to be distributed across Indications 1:2:3 in the proportions of 9%:1%:90%, respectively, as recommended by the NBA[9].

Based on the above data and estimates, the current annual indication-specific dosages per patient are estimated to be 230 g, 156 g and 492 g across Indications 1, 2 and 3, as shown in Table 66.

Table 66 Estimated usage (dose) of Ig used for each indication based on Australian usage data and estimates

	Total		Indication 1	Indication 2	Indication 3
Ig Usage (grams)	514 257g	Estimated distribution	9%	1%	90%
		Estimated grams use	46,283g	5,143g	462,831g
Number of Patients	1,174	Distribution	201	33	940
Average usage (dose)	**438g/patient**		**230g /patient**	**156g /patient**	**492g /patient**

Source: NBA spreadsheets with total usage and patient numbers by indication, NBA estimates of usage volumes across Indications.

[9] email 12/04/19 to AHTA from PBS Post Market Review Section, Office of Health Technology Assessment Policy Branch, Technology Assessment and Access Division, Department of Health.

Indication 1 therapy inputs are shown in Table 67. The dosing of IVIg in the trial; 0.4 g/kg for 3-5 days (totalling 1.2-2 g/kg), which is consistent with the 1566 Ig MSAC Referral Form dosing recommendation of 1-2 g/kg in 2-5 divided doses, but the current criteria also allow for an additional dose, if required, after two weeks. The Australian data and usage estimates suggest patients receive on average, a total of 2.8 g/kg, which is slightly higher than the clinical trial dose, but consistent with the NBA recommended dose, assuming the follow-up dose at two weeks is commonly given.

Table 67 Therapy dose, duration and use-related inputs for Indication 1 management of MG crisis

Input	Step	Value	Source
Dose & duration of IVIg	RCT	0.4 g/kg for 3 or 5 days (total: 1.2 g or 2 g per kg)	(Gajdos et al. 1997)
	Australian data	230 g/patient (= 2.8 g per kg)	'HTA Data April2019.xlsx' workbook provided by the NBA
Dose and duration of PE	RCT	Exchange volume: 1.5 PV, where; PV = (1 - hematocrit) X 70 X weight (kg) = 1.5 ([1-47%]*70*81) = 4.5 L Number of Exchanges: 3	(Gajdos et al. 1997). *Actual patient weights and haematocrit not published.* Fluid used: 50% Albumin 4% and 50% artificial gelatin
	Australian data	Exchange volume: estimated average, 4L Number of exchanges: 4 (estimated average)	(Paton & Baldwin 2014)(report use of 3-5L of 50% Albumin 4% and 50% FFP per exchange, given daily for a median duration 4 days.
	Sensitivity Analyses	Exchange volumes: range 3 - 5 L Number of exchanges: range 3-8 Plausible resource use extremes: 9L fluid over 3 exchanges 40L fluid over 8 exchanges	(Heatwole et al. 2011) Recommended fluid: Albumin 4%

PV = plasma volume; IVIg = Immunoglobulin; MG = myasthenia gravis; NBA = National Blood Authority; PE = plasma exchange; FFP = fresh frozen plasma

The Indication 2 clinical management inputs used in the cost analysis are shown in Table 68. The IVIg dosing in the trial (1 g/kg/day x 2 days) is consistent with the dose described in the 1566 Ig MSAC Referral Form (1-2 g/kg in 2-5 divided doses), and reasonably consistent with the estimated average Australian usage per patient, which is just slightly lower. The reduced use in Australian data may possibly be explained by a small number of patients discontinuing treatment after day one. For both IVIg and PE it is assumed that treatments occur 10−30 days before surgery (Alipour-Faz 2017), therefore administrations of each incur outpatient or day stay therapy costs for each day of pre-surgery treatment administration.

Table 68 Therapy dose, duration and use-related inputs for Indication 2, management of MG prior to surgery

Description		Input value	Source
Dose & duration of IVIg	RCT	1 g/kg/day x 2 days (=total of 162 g/patient)	(Alipour-Faz et al. 2017)
	Australian data	156 g/patient (equivalent to 0.96 g/kg x 2 days)	'HTA Data April2019.xlsx' workbook provided by the NBA
Dose and duration of PE	RCT	Exchange Volume: 1 L Number of exchanges: 5, on alternate days	(Alipour-Faz et al. 2017)
	Australian data	Assumed to be equivalent to RCT	No Australian data sources identified
	Sensitivity analysis	Exchange Volume: 1 L Number of exchanges: 2	(Yeh et al. 2005)

PV = plasma volume; IVIg = Immunoglobulin; MG = myasthenia gravis; NBA = National Blood Authority; PE = plasma exchange

The clinical inputs specifically related to the analyses for Indication 3 are shown in Table 69.

Table 69: Therapy dose, duration and use-related inputs for Indication 3, ongoing management of refractory MG

Description	Input value	Source
Induction dose of IVIg for MG Indication 3, trial based	1 g/kg for 2 days	(Barth et al. 2011) and consistent with 1566 Ig MSAC Referral Form
Maintenance dose range of IVIg for MG Indication 3, per protocol	0.4-1 g/kg (= 32g-81g)	1566 Ig MSAC Referral Form recommended
Maintenance IVIg dosing interval (administrations per year) per protocol	4-6 weekly (9-13 admin. p.a.)	1566 Ig MSAC Referral Form recommended
Dose of IVIg for MG Indication 3 (Usage derived estimate)	492g annually (=6.07 g/kg annually)	'HTA Data April2019.xlsx' workbook provided by the NBA
Initial/induction PE for refractory Indication 3 MG	5 exchanges over 2 weeks	(Barth et al. 2011)
PE (Albumin 4%) volume per exchange	3 L	https://www.mydr.com.au/seniors-health/myasthenia-gravis
Maintenance PE exchange frequency: high intensity regimen low intensity regimen	 1 exchange weekly 1 exchange 4 weekly	Clinical advice[1], consistent with range reported across multiple literature sources (Wali A 2017; Yamada et al. 2015)
Pyridostigmine oral	360 mg daily	Mestinon® Product Information
Prednisolone oral	50 mg daily	(Drugs & Therapy Perspectives 2001)
Azathioprine oral	3 mg/kg/day	(Drugs & Therapy Perspectives 2001)
Methotrexate (+folate)	17.5 mg weekly (+ 5 mg 5/7 days)	(Heckmann et al. 2011)
Cyclophosphamide – IV induction	1000 mg/m^2, 6 weekly	(Buzzard et al. 2015)
Ciclosporin oral	5 mg/kg/day	(TINDALL et al. 1993) and (Drugs & Therapy Perspectives 2001)
Mycophenolate mofetil oral	2.5 g daily	(Hehir et al. 2010)
Rituximab injection	2 g, 6 monthly	(Chan et al. 2018)
Thymectomy (surgery)	Once per lifetime	Assumed

IVIg = Immunoglobulin; MG = myasthenia gravis; NBA = National Blood Authority; PE = plasma exchange
1 Clinical advice from IVIg Review Working Group, received during assessment.

ADVERSE EVENT AND CLINICAL OUTCOME INPUTS

For Indication 1, differences in safety consequences associated with IVIg and PE were identified and are reported in Table 17, Section B.6.

The small patient numbers and lack of detail in the RCT evidence, along with potential bias in the non-randomised studies is such that the incorporation of adverse event data into the economic analysis should be interpreted with caution.

Nevertheless, in an attempt to quantify the implications of the difference between the adverse event profiles, QALY decrements due to adverse events associated with PE are calculated in Section C.4.2.

The estimated effect of adverse events on resource use is also estimated. The adverse events described in Gajdos include; haemolysis, bleeding disorder, thrombosis, fever, chills, headache, nausea and vomiting, increased blood pressure and tachycardia. Gajdos reports that only two events had clinical relevance in that they required discontinuation of PE therapy. As MG crisis is life-threatening it is assumed that these patients would require alternative treatment for their crisis episode, which would then be expected to be second-line IVIg in any Australian setting using PE first-line. In addition, the serious adverse events – e.g. major bleeds, thrombosis or infection complicate and extend medical requirements and would be expected to extend hospital stay. A summary of the clinical management requirements and resource implications associated with major adverse events is provided in Table 70. Although some longterm morbidity is anticipated following serious adverse events, the nature of this is not well described and therefore it has not been costed. This introduces likely bias in favour of PE in the CUA results.

With respect to the remainder of minor adverse events seen in Indication 1, given that patients are already hospitalised, likely in ICU, neither the quality of life effects, nor cost implications with respect to additional medical and nursing management are expected to be significant.

For Indication 2, Section B.6 reported a significant difference in post-operative intubation duration in Alipour-Faz 2017 (Alipour-Faz et al. 2017). This is discussed in Section C.2, and it was concluded that intubation duration would not materially affect resource use as patients were already in an ICU setting. However, Alipour-Faz also identifies a significant difference in surgery duration: in Section C.2 a translation to adjust the hospital resource costs to account for increased theatre time is planned.

Table 70: Clinical differences identified in the RCTs or additional literature with resource use implications

Input Description	IVIg	PE	Implications	Sources
Indication 1				
Retroperitoneal haemorrhage (RH)	0%	2.44%	Abdominal US, CT scan (included in hospital costs). The literature reports a wide range in complexity and management associated with RH. One study assumes 10% of patients would be admitted to a HDU for 5-7 days and all patients would be admitted to a general medical ward for ~10 days. Other case reports describe large bleeds with ICU stays 47-89 days. Additional resources assumed for base case: *Patients with a confirmed RH receive 6 units of RBC. *Hospital stay extended by 10 days in ICU and 5 days on ward.	Event Rate: Gajdos Clinical implications described in: (Guest, Watson & Limaye 2010), (Daliakopoulos, Stavros I. et al. 2008), (Daliakopoulos, S. I. et al. 2010)
Femoral thrombosis	0%	2.44%	Extent of active management (from monitoring through to pharmaceutical or mechanical thrombectomy) will vary substantially depending on patient risk characteristics and available expertise, noting that patient is in MG crisis and may already be intubated in ICU. Anticoagulation may be safely stopped after 3 months in most patients with a first-episode of DVT related to a major reversible risk factor (ie, recent surgery or trauma) Additional resources use to be costed: *Additional 1 day of ICU hospitalisation. *90 days anticoagulant therapy (e.g. rivaroxaban; 3 weeks 15mg twice daily, then 20mg daily)	Gajdos (event rate) Clinical implications described in: (Jaff et al. 2011), (Heisen et al. 2017) Rivaroxiban PI
Discontinuation of initial therapy and switch to alternative	0%	4.88%	PE patients unable to tolerate PE will require IVIg	(Gajdos et al. 1997)
Systemic Infection following MG crisis treatment	0%	4.88%	Patients with central line infections had on average an additional 2.41 days in ICU and 7.54 days on the ward. Additional resources use to be costed: Additional 10 days in hospital (2.41 in ICU, 7.54 on ward).	(Halton et al. 2009)
Indication 2: Hospital resource use				
Mean duration of surgery (hours)	3.46	4.17	Reduction in surgery hours (resource use) of 17%	(Alipour-Faz et al. 2017)
Indication 3: Exploratory analysis including PE-associated infection				
Septicaemia	0%	0.2%	Admission for sepsis.	(Vucic & Davies 1998)

RCT = randomised clinical trial; IVIg = intravenous immunoglobulin; PE = plasma exchange

RESOURCE COSTS

Inputs for all resource costs, in 2019 Australian prices, used in the various analyses are presented in the tables below.

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 Report on the Issues and Use of Ig in 2017/18 (NBA 2019b) (see also Table 109, Appendix G Economic analysis appendices). Analyses will be presented assuming:

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

These costs were also provided by the Applicant and were derived from the 2017/18 National Report on the issue and use of Ig in Australia (NBA 2019b). 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 $58.23[10]), as all costs (including that for 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. Table 71 summarises these alternative costs of immunoglobulin. 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.

Table 71: IVIg prices

Resource	Costs	Source
IVIg base case price	**$60.41 per g**	NBA nominated, see Table 109, Appendix G Economic analysis appendices
Highest IVIg price (for sensitivity analysis)	$140.18 per g	NBA nominated, see Table 109, Appendix G Economic analysis appendices
Alternative IVIg price (for sensitivity analysis)	$44.94 per g	NBA nominated, see Table 109, Appendix G Economic analysis appendices
Alternative price (weighted)	$94.51 per g	NBA nominated, see Table 109, Appendix G Economic analysis appendices
Alternative price (current published price)	$58.23 per g	NBA product list (https://www.blood.gov.au/national-product-list)

IVIg = intravenous immunoglobulin; NBA = National Blood Authority

The costs directly associated with plasma exchange therapy are listed in Table 72. When provided to MG crisis inpatients (Indication 1), the inpatient hospitalisation cost is based on the AR-DRG code B42 (Nervous System Disorders with Ventilator Support) and do*es not differentiate* between IVIg and PE

[10] As at July 1, 2019

administration methods. Because PE administration equipment is an additional specialised resource, an estimate of the costs associated with specialised consumable tubing and capital equipment amortisation are added to the costing estimates in the Indication 1 analysis to capture genuine resource use differences. This costing detail is not required for Indications 2 and 3, where the outpatient administration cost code B40Z (Plasmapheresis with Neurological Disease, same day) is *specifically associated with apheresis* and therefore captures these specialised costs.

Gajdos 1997 and some other sources[11] describe plasma exchange using albumin diluted (25-50%) with other volume expanders (various types eg normal saline, Hartmann's or Voluven®), which reduces the cost of plasma exchange; however this may be associated with increased risk of adverse events.[12] Paton et al (Paton & Baldwin 2014) describes one Australian ICU practice where albumin is combined with fresh frozen plasma for PE in MG crisis, despite this not being recommended practice. The nature of routine albumin supplementation practice for PE for MG across Australia in other indications is unknown; therefore it is assumed that dilution does not routinely occur in other indications, and that following protocol review, as recommended by Paton et al, dilution with FFP would not routinely occur when administering PE for MG crisis in Australia in the future.

Table 72: Resource prices associated with PE (used in Indication 1, 2 and 3 analyses)

Resource	Cost	Unit cost	Source
Albumin (Albumex 4)	$68.50 / 500mL	$137 /L	NBA product list[1]
Fluid volume expander *(artificial gelatin described in Gajos 1997)*	$44.56 / 3x500mL	$29.71 /L	PBS 9487H Voluven 6%®
Fluid volume expander: FFP (Apheresis clinical FFP)	$263.52 / 295mL	$893.29 /L	NBA product list (https://www.blood.gov.au/national-product-list)
PE specialised consumables + equipment amortisation (Applied in Indication 1 only)	$232 per procedure + $59 per procedure $291 per procedure		Heatwhole 2011 (converted from 2011 US$210 for tubing and US$53 amortisation, per procedure)
Long-term IV access – initial procedure (Indication 3 only)	$1,791		Based on clinical advice; 95% of patients have plasmapheresis compatible port, 5% have AV fistulae (detailed in Table 73 below).

FFP = fresh frozen plasma; NBA = National Blood Authority; PE = plasma exchange; US = United States

The hospitalisation and outpatient treatment administration costs associated with IVIg and PE for the various settings relevant to the different indications under which IVIg is supplied to MG patients according to the NBA BloodSTAR *Criteria V3*, are based on AR-DRG cost estimates[13] shown in Table 73.

[11] https://www.transfusionguidelines.org/transfusion-handbook/11-therapeutic-apheresis/11-1-therapeutic-plasma-exchange-tpe

[12] https://professionaleducation.blood.ca/en/transfusion/guide-clinique/albumin

[13] This costing approach varies from the approach used in Assessment 1565, where a source was identified reporting Australian administration costs for IVIg specifically in the context of acquired hypogammaglobulinaemia (dosed at 0.4g/kg), as $253/administration (predominantly chair and nurse time). Given the dose of IVIg used preoperatively and for maintenance in MG is substantially higher (up to 1g/kg), it is expected to incur significantly longer chair and nursing supervision times, therefore the estimated

Resources associated with adverse events (extended hospitalisation, treatments etc.) and long-term access are also presented in this table.

Table 73 Hospital, administration and adverse event associated resources and cost sources

Resource	Costs	Source
Admission for MG crisis: (Indication 1) Nervous System Disorders W Ventilator Support, Major Complexity	$45,001 per episode	AR-DRG B42A, NHCDC Round 21 2016/17
IVIg administration in hospital outpatient setting (Indication 2 and 3)	$461 per day	NWAU calculator 2019-20 (IHPA)[a]; non-admitted service 10.13
Plasma exchange therapy provided as a same-day admission (Indication 2 and 3)	$1,446.13 per administration day	AR-DRG B40Z, NHCDC Round 21 2016/17
Additional hospitalisation days in ICU due to adverse events (Indication 1)	$6,882.63 per day	Based on 2009 cost reported in (Thompson et al. 2018) (Australian), adjusted to 2018 using annual AIHW Health Price Index.
Additional hospitalisation days in medical ward due to adverse events (Indication 1)	$1,441.45 per day	2018-19 NEP *0.2876 (B42A per diem outlier cost weight)
Placement of an AV Fistula (Indication 3)	$7,549 per surgery	AR-DRG F14C, NHCDC Round 21 2016/17
Long Term Vascular Access with apheresis compatible device (Indication 3) Total:	($297 + $231+ $489 + $471) = $1,488	July 2019 Prostheses List A,[a] 10.09, TX054 + MBS 13318 (CVC/PICC insertion) + same-day surgery facility accommodation (PR420/430) + theatre fees (PRT01)[b]
Red Blood Cells (for RH, Indication 1)	$399.25 per unit (200-250mL)	NBA product list (www.blood.gov.au/national-product-list)
Rivaroxiban 15mg and 20mg (for FT, Indication 1)	$125.60 / 42 tabs $87.56 / 28 tabs	PBS 2160Q PBS 2268J
GP follow-up Level C consult (FT, Indication 1)	$85.30	MBS 5040
Sepsis Admission (Indication 3)	$12,724	Weighted average of AR-DRG T60, A-C

DRG descriptors: B42A = Nervous System Disorders W Ventilator Support, Major Complexity (ALOS 13.2 days); B42B = Nervous System Disorders W Ventilator Support; B40Z = Plasmapheresis with Neurological Disease (same day). F14C = Vascular Procedures, except major reconstruction, W/O CPB pump, minor complexity
ALOS = average length of stay; AR-DRG = Australian Refined Diagnosis Related Groups; FT = femoral thrombosis; IHPA = Independent Hospital Pricing Authority; GP = General Practitioner; IVIg = intravenous immunoglobulin; NBA = National Blood Authority; NEP = National Efficient Price; NHCDC = NWAU = RH = retroperitoneal haematoma;
NWAU service 10.13 = minor medical procedures (using https://www.ihpa.gov.au/what-we-do/pricing/national-weighted-activity-unit-nwau-calculators/nwau-calculators-2019-20
[a] https://www1.health.gov.au/internet/main/publishing.nsf/Content/health-privatehealth-prostheseslist.htm
[b] Return to work SA – Private Hospital Fee Schedule, July 2019 (www.rtwsa.com)

The method of costing additional hospitalisation days attempts to capture real additional resource demands, rather than just the transfer payments between Commonwealth and State which are generally the population average value and therefore insufficient to capture differences in resource use due to adverse events at a patient level. The estimate of the cost per additional day in ICU is based

administration cost of $461, based on Service 10.13 using the NWAU calculator; $461 appears reasonably consistent with the 1565 estimate, despite the different approach.

on a published Australian ICU daily cost for 2009 reported in (Thompson et al. 2018), adjusted to 2018 prices using the annual AIHW Health Price Index. The cost of additional medical ward days is based on the IHPA[14] National Efficient Price for an additional 'per diem' (daily) payment value that is provided to hospitals for patients admitted under the primary diagnosis code AR-DRG B42A; for each day beyond 'inlier' bounds.

The 'per patient' cost of adverse events associated with PE for use in the base case and the sensitivity analysis are calculated in Table 74.

Table 74 Resource use per patient for management of adverse events associated with PE in Indication 1

Adverse event	Resource	# units	Unit cost	Cost per event	Incidence Rate	Cost per patient across population
Retroperitoneal Haematoma	Red Blood Cells	6 units	$399.25	$2,396	2.44%	**$1,914**
	Additional Hospitalisation ICU Ward	10 days 5 days	$6,882 $1,441	$76,034		
	Total			**$78,429**		
Femoral Thrombosis	Additional hospital days	Per day	$1,441.45	$1,441	2.44%	**$49**
	Rivaroxiban 15 mg then 20mg	x 1 pack x 3 packs	$125.60 $87.56	$388		
	Post-discharge GP consultation	2	$85.30	$171		
	Total			**$2,000**		
Systemic Infection	Additional Hospital Days ICU Ward	2.41 days 7.54 days	$6,882.63 $1,441.45	**$27,456**	4.88% or 7.67%	**$1,340** **or** **$2,106**

GP = general practitioner; ICU = intensive care unit
Note: rounding has been applied

Table 75 details costs associated with the observed differences in hospitalisation resource use associated with surgery following administration of either IVIg or PE in Indication 2.

Table 75: Resource use associated with surgery in Indication 2

Resource	Cost	Source
Thymectomy Surgery – Average operating room cost	$11,317 /surgery	AR-DRG D02A, NHCDC Round 21 2016/17, Operating Room Direct Cost
Thymectomy Surgery with 17% reduced operation time for IVIg patients	$9,393 /surgery	Above *0.83, based on Operating time difference identified in Alipour-Faz 2017 (Section C.2)
Remainder of hospitalisation costs associated with thymectomy (including ICU).	$27,518 /episode	DRG D02A, Total Cost less Operating Room Direct Cost ($38,835 - $11,317)

AR-DRG descriptions: D02A = Head and Neck Procedures, Major Complexity.

[14] Independent Hospital Pricing Authority can be accessed at the link: https://www.ihpa.gov.au

Table 76, following, lists the nominated pharmaceutical and surgical therapies which are comparators to supply of immunoglobulin for MG under *Criteria V3*.

Table 76: Resource prices associated with other pharmaceutical and surgical therapy comparators to Ig for MG, supplied under Indication 3

Resource	Published costs	Source	Unit Price
Pyridostigmine 180mg MR tablet	$116.93 / 100 units	PBS 2608G	$1.17 /tab
Prednisolone 25mg tablet	$15.76 / 30 units	PBS 1916W	$0.53 /tab
Azathioprine 50mg tablet	$32.19 / 100 units	PBS 2687K	$0.32 /tab
Methotrexate 10mg tablet	$23.58 / 15 units	PBS 2272N	$1.57 /tab
Methotrexate 2.5mg tablet	$17.31 / 30 units	PBS 1622J	$0.57 /tab
Folic acid 5mg tablet	$17.77 / 200 units	PBS 10573L	$0.09 /tab
Cyclophosphamide 50mg tablet	$153.03 / 50 units	PBS 1266P	$3.06 /tab
Cyclophosphamide 2g injection	$156.76 / supply $197.51 / supply	PBS 4327R (public hospital)	$156.76 /supply
Day stay admission for Cyclophosphamide administration	$1,748 / gross *less*	AR-DRG R63Z *'Pharmacy' component $895*	*administration only:* $853 /day
Ciclosporin 100mg capsule	$309.21 / 60 units	PBS 8660T	$5.15 /cap
Mycophenolate 500mg tablet	$153.28 / 150 units	PBS 8650G	$1.021 /tab
Rituximab 1 x 500mg vial for injection	$1,544.50	Estimated using PBS item 10593M **not PBS funded for MG*	$1,544.50 /vial
Monitoring: Liver function	$17.70	MBS 66512 fee, July 2019	$17.70
Monitoring: Blood disorders	$16.95	MBS 65070 fee, July 2019	$16.95
Monitoring: renal function	$17.70	MBS 66512 fee, July 2019	$17.70
Surgical management			
Thymectomy average hospital episode	$38,835 / episode	AR-DRG D02A, NHCDC Round 21 2016/17	$38,835 surgery in-hospital episode

AR-DRG descriptions: R63Z = Chemotherapy (total cost $1,748; Pharmacy component $895; net of pharmacy); D02A = Head and Neck Procedures, Major Complexity.

HEALTH OUTCOMES

The translation of each adverse event into a utility decrement is described in Table 58, C.4.2.

The overall incremental QALY decrements across the modelled population is calculated by multiplying the QALY decrement per adverse event by the adverse event incidence rate. The estimated incidence rates for the adverse events across a whole population are estimated in Table 56 C.4.1. The modelled overall QALY decrements are presented in Table 77 below.

For Indication 1, the QALY decrements are one-off applications. For Indication 3, the QALY decrement is calculated for each plasma exchange, therefore the QALY decrements accrue with each exchange per year and with each year of analysis.

Table 77 Total QALY decrement calculations per adverse event in the cost-utility analyses

Adverse event description	QALY decrement per event	Incidence rate	Total QALY decrement associated with adverse event(s) across population
Retroperitoneal haematoma	0.02663	2.44%	0.000065
Femoral thrombosis Acute event 3-month anticoagulant Tx Total	0.00641 0.01205	2.44%	0.00016
Systemic Infection (acute ICU setting) lower estimate upper estimate	0.01305	4.88% 7.67%	0.001356 0.002131
Death following sepsis	9.01671	18.4%	At 4.88% sepsis rate: 0.08096 At 7.67% sepsis rate: 0.12725
Morbidity following sepsis	1.50278	81.6%	At 4.88% sepsis rate: 0.05984 At 7.67% sepsis rate: 0.09406
Alternative overall mortality estimate (SA)	9.01671	0.05%	0.00451
Sepsis rate maintenance PE	0.017038	0.2% of exchanges	NA

MG = myasthenia gravis; NA = not applicable; PE = plasma exchange; Ig = immunoglobulin; QALYs = quality adjusted life years; SA = scenario analyses.

D.5/6 RESULTS OF THE ECONOMIC EVALUATION, INCLUDING EXPLORATORY AND SENSITIVITY ANALYSES

For the ease of interpreting the results, all results (base case and sensitivity analyses) for each IVIg indication are presented together. Tables identifying resource use (without prices) are located in Appendix G.

D.5.1 INDICATION 1 ANALYSIS

Trial-based estimate

The overall costs and outcomes, and incremental costs and outcomes as calculated for the intervention and comparator in the model, with the base case assumptions, are shown in Table 78 below. In the trial-based analysis, resource use has been calculated for each of the three trial arms (two arms received IVIg at different doses); however the safety outcomes contributing to the incremental clinical consequences are pooled for the two IVIg study arms (as reported in the publication).

Table 78 Indication 1 Trial based cost consequences analysis (Gajdos 1997)

	IVIg 3 doses	IVIg 5 doses	PE (3 exchanges)	Incremental difference	
Resource costs				**IVIg 3 vs PE**	**IVIg 5 vs PE**
IVig procurement	$5,860	$9,786	$0	$5,860	$9,786
PE replacement Albumin 4%	$0		$925	-$925	-$925
PE replacement diluent (Gelatin)			$201	-$201	-$201
Consumables, equipment depreciation			$873	-$873	-$873
Hospital admission	$45,001	$45,001	$45,001	$0	$0
Total Resource costs	**$50,861**	**$54,787**	**$46,999**	**$3,862**	**$7,788**
Health outcome (safety) consequences					
Patients with adverse events	2.2%		19.5%	-17.3%	
Patients with clinically significant adverse events	0%		4.9%	-4.9%	

IVIg = intravenous immunoglobulin; PE = plasma exchanges

Stepped economic evaluation

The stepped evaluation is shown in Table 79. In step 1, Australian data and estimates for the IVIg and PE dosing are applied. Step 2 adds the assumption that patients who discontinue PE due to adverse events will receive IVIg. Step 3 assumes that the inappropriate use of FFP as a fluid diluent is reversed and PE for MG crisis is conducted with undiluted Albumin 4% as recommended in (Paton & Baldwin

2014). Step 4 adds in the estimated cost of adverse events and the transforms the adverse events outcomes into QALY decrements.

A cost consequences analysis to the timepoint of the direct evidence shows that management of MG crisis using IVIg costs approximately $9,225 more per patient, but 17.3% of patients avoid experiencing an adverse event, including 4.9% of patients avoiding a serious, clinically significant event (based on (Gajdos et al. 1997).

Framed from the health consequences perspective, this is equivalent to identifying that the incremental costs of achieving each consequential outcome is;

- $53,324 per additional adverse event avoided (of which 28% of these are highly clinically significant); or $188,265 per additional highly clinically significant adverse event avoided.

Where the adverse event outcomes are transformed into utility decrements; the total difference in utility is small (as expected given it is only derived from transient adverse events in a small number of patients associated with safety differences, not a treatment effect across all patients as occurs with a treatment effectiveness claim). Therefore where only the direct evidence is used to inform the economic analysis, the ICER is high, at approximately $7 million/QALY.

Steps 5-7 present ongoing modelling incorporating estimates of mortality and morbidity associated with sepsis, based on external data. The accuracy and applicability of this data is more uncertain, and results using a range of alternative inputs are presented. Accepting the estimates of long-term morbidity and mortality associated with rare but serious PE adverse events drastically reduces the ICER to approximately $46 thousand/QALY.

Table 79 Indication 1 Stepped cost consequences analysis to replicate Australian practice

	IVIg	PE	Increment
Resources (disaggregated)	Total Cost	Total Cost	
Step 1 – Australian IVIg doses and PE fluids (4 exchanges)			
IVIg product	$13,894		$13,894
PE tubing and equipment depreciation		$1,164	-$1,164
PE replacement Albumin 4%		$1,096	-$1,096
PE replacement diluent FFP		$7,146	-$7,146
Hospital admission	$45,001	$45,001	$0
Total Step 1	**$58,895**	**$54,407**	**$4,488**
Step 2: Adding cost of treatment failure and re-treatment			
IVIg for 2nd line treatment in 4.88% PE patients	$0	$678	-$678
Total Step 2	**$58,895**	**$55,085**	**$3,810**
Step 3: Assuming updated PE fluid protocol			
Remove FFP		-$7,146	-$7146
Additional Albumin 4% (100% of PE fluid)		$1,096	$1,096
Total Step 3	**$58,895**	**$49,035**	**$9,860**
Step 4: Adding the costs of treating adverse events			
Retroperitoneal Haematoma (in 2.44% of patients)		$586	$586
Femoral Thrombosis (in 2.44% of patients)		$49	$49
Total Step 4	**$58,895**	**$50,998**	**$7,898**
Health outcome (safety) consequences (within trial time)			
Patients with adverse events	2.2%	19.5%	-17.3%
Patients with clinically significant adverse events	0%	4.9%	-4.9%
QALY decrement due to AEs (RH and FT)		-0.001100	0.001100
Step 4 ICER ($/QALY)			**$7,177,933**
Extended Modelling of adverse events			
Step 5: Assuming sepsis at rate of 4.88%: immediate effects only			
Additional sepsis-related resource use		$1,340	**$6,558**
Additional disutility due to acute sepsis episode		-0.001356	**0.002456**
Step 5 ICER ($/QALY)			**$2,670,183**
Step 6: Assuming sepsis mortality implications over 15 years			
Additional disutility due to sepsis-related death		0.08096	0.083419
Step 6 ICER ($/QALY)			**$78,615**
Step 7: Assuming sepsis mortality and morbidity implications over 15 years			
Additional disutility due to sepsis-related morbidity		0.05984	0.143261
Step 7 ICER ($/QALY)			**$45,776**

AE = adverse event; ICER = incremental cost-effectiveness ratio; IVIg = intravenous immunoglobulin; FFP = fresh frozen plasma; FT = femoral thrombosis; PE = plasma exchange; QALY = quality adjusted life years; RH = retroperitoneal haematoma.

The ICER and cost-effectivenss of IVIg is heavily dependent on the assumption that PE is associated with sepsis, and this in turn has mortality and/or long-term morbidity implications.

Sensitivity analyses were conducted around IVIg pricing and uncertainty in the PE dosing schedules and replacement fluid composition. These are presented in Table 80, below. The ICER for IVIg vs PE is somewhat sensitive to the IVIg price, PE dosing and also mortality rates and morbidity utilities if the extended model is accepted.

Table 80 Sensitivity analyses: Alternative IVIg prices or PE resource use (Indication 1)

	IVIg cost	PE costs	Incremental costs	ICER* $/QALY
Within trial-period results (alternative Step 4 results)				
Analyses based on outcomes estimate of 0.001100 inceremental QALYs, as per Step 4 of base case.				
Base case (IVIg cost $60.41/g, PE 16L,4 exchanges)	$58,895	$49,670	$9,225	$8,386,364
Varying IVIg costs				
Highest IVIg cost ($140.18/g)	$77,242	$51,893	$27,572	$23,039,044
Lowest IVIg cost ($44.94/g)	$55,337	$50,824	$5,667	$4,101,948
Alternative cost (weighted historical cost $94.51)	$66,738	$51,380	$15,358	$13,958,225
Alternative IVIg cost (published price $58.23)	$58,394	$49,670	$8,724	$6,744,472
Varying PE dosing				
Minimum plausible : 9L fluid over 3 exchanges	$58,895	$49,748	$9,148	$8,314,001
Maximum plausible: 40L fluid over 8 exchanges	$58,895	$55,450	$3,446	$3,131,713
Extended modelling to 15 years with morbidity and mortality (alternative Step 7 results)				
All analyses based on outcomes estimate of 0.143261 inceremental QALYs, as per Step 7 of base case.				
Base case (IVIg cost $60.41/g, PE 16L,4 exchanges)	$58,895	$52,388	$6,558	$45,776
Varying IVIg costs				
Highest IVIg cost ($140.18/g)			$24,010	$24,010
Lowest IVIg cost ($44.94/g)			$3,173	$22,152
Alternative cost (weighted historical cost $94.51)			$14,018	$97,851
Alternative IVIg cost (published price $58.23)			$6,081	$42,447
Varying PE dosing				
Minimum plausible : 9L fluid over 3 exchanges			$7,808	$54,502
Maximum plausible: 40L fluid over 8 exchanges			$2,106	$14,700

ICER = incremental cost-effectiveness ratio; IVIg = intravenous immunoglobulin; PE = plasma exchange; QALY = quality adjusted life-years

Table 81 Scenario analyses: alternative sepsis incidence and mortality rates in steps 6 and 7

	Incremental costs	Incremental QALYs	ICER $/QALY
(Step 7 sepsis rate: 4.88%, effective mortality rate of 0.9%, morbidity utility 0.8)	$6,558	0.143261	$45,776
PE-associated sepsis at an incremental rate of 7.67%	$5,792	0.224537	$25,795
PE-associated sepsis morbidity with utility of 0.6	$6,558	0.228750	$28,669
Assuming PE associated mortality is 0.05% (sepsis rate 4.88%)	$6,558	0.079549	$82,439

ICER = incremental cost-effectiveness ratio; IVIg = intravenous immunoglobulin; PE = plasma exchange; QALY = quality adjusted life-years

D.5.2 INDICATION 2 ANALYSIS

Trial-based estimate

Table 82 below, presents the overall costs and outcomes, and incremental costs and outcomes as calculated for the IVIg and PE, based on the information available in the clinical trial.

Table 82 Indication 2 Trial-based cost analysis (Alipour-Faz, 2017)

	IVIg	PE	Incremental cost
Resources (disaggregated)	Costs	Costs	
IVig product	$9,786	$0	$9,786
PE replacement fluid (Albumin 4%)	$0	$685	-$685
All outpatient Tx administration costs (pre-admission)	$922	$7,231	-$6,309
Thymectomy Operating Theatre (surgery time adjusted)	$9,393	$11,317	-$1,924
Other hospitalisation (for surgery) costs	$27,518	$27,518	$0
Total	**$47,619**	**$46,751**	**$868**

IVIg = intravenous immunoglobulin; FFP = fresh frozen plasma; PE = plasma exchange

Stepped economic evaluation

The stepped evaluation uses Australian data to re-estimate the IVIg dose and cost, and is shown in Table 83. No information was identified to suggest changes were required for the PE dosing or other resource use.

Table 83 Indication 2 Stepped analysis to replicate Australian practice (base case)

	IVIg	PE	Incremental cost
Resources (disaggregated)	Total Cost	Total Cost	
IVIg product (156g)	$9,424	$0	$9,424
PE replacement fluid (Albumin 4%)	$0	$685	-$685
All outpatient Tx administration costs (pre-admission)	$922	$7,231	-$6,309
Thymectomy Operating Theatre	$9,393	$11,317	-$1,924
Other hospitalisation (for surgery) costs	$27,518	$27,518	$0
Total	**$47,257**	**$46,751**	**$506**

IVIg = intravenous immunoglobulin; PE = plasma exchange

Overall, the cost analysis suggests PE may be marginally less expensive than IVIg for pre-treatment prior to surgery in MG patients; however, the difference is small in the broader context of the surgery cost.

Sensitivity analyses were conducted around IVIg pricing and an alternative PE dosing schedule. These are presented in Table 84, below.

Table 84 Sensitivity analyses around alternative IVIg pricing and PE dosing in Indication 2

	IVIg cost	PE costs	Cost difference
Base case analysis	$47,257	$46,750	$507
Highest IVIg cost ($140.18/g)	$59,701	$46,750	$12,951
Lowest IVIg cost ($44.94/g)	$44,844	$46,750	-$1,906
Alternative IVIg cost (weighted historical cost $94.51)	$52,577	$46,750	$5,827
Alternative IVIg cost (published price $58.23)	$46,917	$46,750	$167
IVIg dose administered over 5 days	$48,640	$46,750	$1,890
PE exchanges prior to surgery; 2	$47,257	$42,001	$5,256

IVIg = intravenous immunoglobulin; FFP = fresh frozen plasma; PE = plasma exchange

Scenario analysis that assumes operating time does not differ across pre-treatment arms is presented in Table 85 below. The incremental cost of IVIg in this scenario is greater.

Table 85 Scenario analysis Indication 2, assuming no difference in theatre costs

	IVIg	PE	Incremental cost
Resources (disaggregated)	Total Cost	Total Cost	
IVIg product (156g)	$9,424	$0	$9,424
PE replacement fluid (Albumin 4%)	$0	$685	-$685
All outpatient Tx administration costs (pre-admission)	$922	$7,231	-$6,309
Thymectomy Operating Theatre	$11,317	$11,317	$0
Other hospitalisation (for surgery) costs	$27,518	$27,518	$0
Total	**$49,181**	**$46,751**	**$2,430**

IVIg = intravenous immunoglobulin; PE = plasma exchange

D.5.3 INDICATION 3 ANALYSIS

Where IVIg is costed at the estimated average maintenance dose, it is more expensive than a low intensity PE regimen (e.g. 4 weekly), but less expensive than intensive weekly PE, as shown in Table 86.

In this analysis, IVIg is costed with a loading dose in the first year, and then on an ongoing maintenance basis at either minimal or maximal maintenance usage rates based on dose and dosing interval, as described in D.5 Table 66 and Table 67. Year 2 and beyond only cost maintenance doses (also at minimum or maximum levels). Resource use for PE, surgery and pharmaceutical comparators are applied over the time horizon according to the patterns extrapolated in Section C.3. From year 2 onwards, non-fistula IV access costs are repeated at a rate of 33% to account for the routine replacement of these every 3 years on average. A summary of the resource use incurred each year is presented in Appendix G Economic analysis appendices.

The overall costs over varying time horizons for IVIg and nominated comparators for Indication 3 are shown, undiscounted and discounted at 5%pa, in Table 86 (vs Plasma Exchange), Table 88 (surgical and pharmaceutical managements) and Table 88 (IVIg costs with alternative pricing).

Low dose IVIg also appears less expensive than low intensity PE, and high dose IVIg monthly appears less expensive than high intensity PE.

Table 86 Cost comparison for IVIg vs PE over varying time doses and time horizons in Indication 3 (base case – no adverse event costs), undiscounted and discounted.

		Total undiscounted costs (including administration + IV access costs)			
		1 year	**2 years**	**5 years**	**10 years**
IVIg	NBA data annual dose (base case)	$34,516	$69,032	$172,581	$345,161
	minimum dose	$30,055	$51,819	$117,113	$225,936
	maximum dose	$74,959	$144,564	$353,378	$701,402
PE	low intensity (every 8 weeks)	$33,362	$58,102	$132,321	$256,020
	high intensity (every 3 weeks)	$100,219	$197,387	$488,890	$974,729
Undiscounted Cost Difference IVIg vs PE					
	IVIg base case – low intensity PE	$1,154	$10,930	$40,260	$89,142
	IVIg base case – high intensity PE	-$65,703	-$128,354	-$316,309	-$629,568
	IVIg minimum dose – low intensity PE	-$3,308	-$6,283	-$15,208	-$30,084
	IVIg maximum dose – high intensity PE	-$25,260	-$52,823	-$135,512	-$273,327
		Total discounted costs (discounted at 5% pa)			
		1 year	**2 years**	**5 years**	**10 years**
IVIg	NBA data annual dose	$34,516	$67,306	$156,164	$277,001
	minimum dose	$30,055	$50,731	$106,761	$182,956
	maximum dose	$74,959	$141,083	$320,273	$563,950
PE	low intensity (every 8 weeks)	$33,362	$56,865	$120,554	$207,165
	high intensity (every 3 weeks)	$100,219	$192,528	$442,675	$782,848
Discounted Cost Difference IVIg vs PE					
	IVIg base case – low intensity PE	$1,154	$10,441	$35,610	$69,836
	IVIg base case – high intensity PE	-$65,703	-$125,222	-$286,511	-$505,847
	IVIg minimum dose – low intensity PE	-$3,308	-$6,134	-$13,793	-$24,209
	IVIg maximum dose – high intensity PE	-$25,260	-$51,445	-$122,403	-$218,898

IVIg = intravenous immunoglobulin; PE = plasma exchange;

An exploratory analysis including a 0.2% rate of sepsis (based on (Vucic & Davies 1998)) has been presented in Table 87 which may be relevant if superior safety was an accepted claim. This analysis only accounts for short-term sepsis effects (not mortality/long-term morbidity) and does not make a substantial difference to the cost comparison. These estimates should be interpreted caution, as the accuracy and reliability of inputs associated with infection rates, infection utilities and costs are all highly uncertain. The analysis estimates ICERs ranging between 'dominant' (in all cases where the comparison is vs high intensity PE or low dose IVIg is compared to low dose PE), through to $18 million per QALY comparing average NBA doses to low dose PE over the long-term. The broad range of ICERs is consistent with the findings of the cost comparison where cost-savings were demonstrated in all comparisons except average IVIg dosing vs low dose PE. The extreme range in the ICER demonstrates the high sensitivity to relative treatment costs given outcome differences are minimal, and the overall uncertainty in the comparison.

Table 87 Exploratory cost-utility analysis for IVIg vs PE over varying time doses and time horizons, incorporating costs and QALY impacts associated with sepsis in Indication 3, discounted.

	Cumulative total discounted (at 5%) values			
IVIg (Australian dose) vs low intensity PE	**1 year**	**2 years**	**5 years**	**10 years**
Incremental Costs IVIg – low intensity PE (including sepsis)	$721	$9,695	$34,011	$67,079
Incremental QALYs	0.00058	0.00100	0.00214	0.00369
ICER ($/QALY)	**$1,245,044**	**$9,693,386**	**$15,889,120**	**$18,171,894**
IVIg low dose vs low intensity PE	**Dominant**	**Dominant**	**Dominant**	**Dominant**
IVIg (Australian dose) vs high intensity PE	**Dominant**	**Dominant**	**Dominant**	**Dominant**
IVIg high dose vs high intensity PE	**Dominant**	**Dominant**	**Dominant**	**Dominant**

AE = adverse event; ICER = incremental cost-effectiveness ratio; IVIg = intravenous immunoglobulin; PE = plasma exchange; QALY = Quality adjusted life year.

The price of non-PE comparators over varying time-frames is presented in Table 88.

Table 88 Costs of other potential comparators for Indication 3 over varying time horizons (undiscounted and discounted at 5%pa

Note: The following therapies are not assumed to have equivalent effectiveness: – cost analysis provided for information purposes only.				
	Total cumulative undiscounted costs over varying time horizons			
	1 year	**2 years**	**5 years**	**10 years**
Surgery				
Thymectomy – once per lifetime	$47,335	$47,335	$47,335	$47,335
Other Pharmaceuticals				
Prednisolone + Pyridostigmine (P+P)	$1,241	$2,422	$6,205	$12,410
Mycophenolate mofetil added to (P+P)	$3,308	$6,616	$16,540	$33,080
Azathioprine added to (P+P)	$1,964	$3,928	$9,820	$19,640
Methotrexate (+ folic acid) added to (P+P)	$1,574	$3,148	$7,870	$15,740
Cyclophosphamide IV then Azathioprine (and P+P)	$7,283	$9,247	$15,139	$24,959
Ciclosporin 100mg added to (P+P)	$9,111	$18,222	$45,555	$91,110
Rituximab added to (P+P)	$8,341	$9,582	$20,405	$33,710
	Total cumulative discounted costs over varying time horizons			
Surgery				
Thymectomy – once per lifetime	$47,257	$47,257	$47,257	$47,257
Other Pharmaceuticals				
Prednisolone + Pyridostigmine (P+P)	$1,241	$2,420	$5,615	$9,959
Mycophenolate mofetil added to (P+P)	$3,308	$6,450	$14,965	$26,545
Azathioprine added to (P+P)	$1,964	$3,829	$8,884	$15,758
Methotrexate (+ folic acid) added to (P+P)	$1,574	$3,068	$7,119	$12,628
Cyclophosphamide IV then Azathioprine (and P+P)	$7,283	$9,149	$14,205	$21,081
Ciclosporin 100mg added to (P+P)	$9,111	$17,766	$41,222	$73,118
Rituximab added to (P+P)	$8,341	$9,519	$18,810	$28,119

IVIg = intravenous immunoglobulin; FFP = fresh frozen plasma; PE = plasma exchange; P+P = Prednisolone + Pyridostigmine

Although surgery is relatively more expensive than all other therapies (other than high dose IVIg) in the initial year of treatment, it is not particularly expensive compared to long-term blood or pharmaceutical treatments.

Sensitivity analyses around IVIg costs were conducted on the base case (usage based on NBA data, discounted analysis) to identify the extent to which the total costs associated with IVIg use for maintenance therapy in refractory MG were sensitive to the price for IVIg, over different time horizons. These analyses are presented in Table 89, below.

Table 89 Indication 3 Sensitivity analyses; IVIg costs with alternate IVIg prices (discounted analysis)

	1 year	5 years	10 years
Base case (IVIg price $60.41/g)	$34,793	$157,416	$279,221
Highest IVIg cost ($140.18/g)	$74,040	$334,983	$594,187
Lowest IVIg cost ($44.94/g)	$27,181	$122,979	$218,138
Weighted historical IVIg cost ($94.51/g)	$51,570	$233,322	$413,862
Published 2019 IVIg price ($58.23/g)	$33,720	$152,563	$270,613

IVIg = intravenous immunoglobulin;

At the highest nominated price of IVIg, the cumulative cost of IVIg per person at the estimated average Australian maintenance dose remain less than the cost of high intensity PE over all time horizons (1-10 years).

At the lowest nominated price of IVIg, the cumulative cost of IVIg per person at the estimated average Australian maintenance dose becomes less than the cost of low intensity PE over all time horizons (1-10 years).

While the alternative immunoglobulin prices make a large difference to the absolute cost differences between immunoglobulin and each of the surgical or pharmaceutical comparators, the direction of the cost difference does not change in any of the comparisons, with immunoglobulin remaining more costly than pharmaceutical alternatives and only less costly than surgery when considered as a short-term comparison.

SECTION E FINANCIAL IMPLICATIONS

A market-based approach has been used to estimate the financial implications of Ig in Myasthenia Gravis, based on current utilisation of Ig products in patients with Myasthenia Gravis. As data available on utilisation were only available for use under the Version 2 Criteria, the impact of transitioning to the Version 3 Criteria 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 MG are:

- NBA (2019) National reports on the issue and use of immunoglobulin (Ig), which report the number of patients and Ig use, by indication, from 2011-12 to 2015-16.
- The 'HTA Data April2019.xlsx' workbook provided by the NBA - which reports use, by indication, for the full financial year 2017-18 and for the 2018-19 partial year to December 31, 2018 (and so reports some use under the *Criteria V3*).

The full year data available from these sources are summarised in Table 90.

Table 90 Number of patients and grams issued for MG patients who received Ig, 2011-12 to 2017-18

	2011-12	2012-13	2013-14	2014-15	2015-16	2016-17	2017-18
Number of patients	521	609	670	747	818	-	1,174
Ig grams issued	231,064	257,966	313,940	348,336	402,881	-	514,257

MG = myasthenia gravis; NR = not reported
Source: NBA (2019) National Reports on the issue and use of immunoglobulin (Ig), 2012-13, 2013-14, 20114-15 and 2015-16 and the 'HTA Data April2019.xlsx' workbook provided by the NBA.

The 'HTA Data April2019.xlsx' workbook data for IVIg use in MG collates information across the three MG indications; disaggregated data on total Australian usage and patients, specifically for each of these indications was not available. However disaggregated 2017-18 BloodSTAR[15] data (Worksheet 5), which excludes NSW, reports 820 MG patients receiving IVIg distributed across Indications 1, 2 and 3 in proportions of 17.1%, 2.8% and 80.1%. Applying these proportions to the total 1,174 patients for

[15] See https://www.blood.gov.au/bloodstar. The criteria for IVIg supply in MG (as defined in Version 3) are;

1. Patients with, or at risk of, myasthenic crisis.
2. Patients with advanced MG, bulbar symptoms or respiratory involvement, prior to surgery and/or thymectomy.
3. As maintenance therapy in patients with moderate to severe MG when other treatments have been ineffective or caused intolerable side effects.

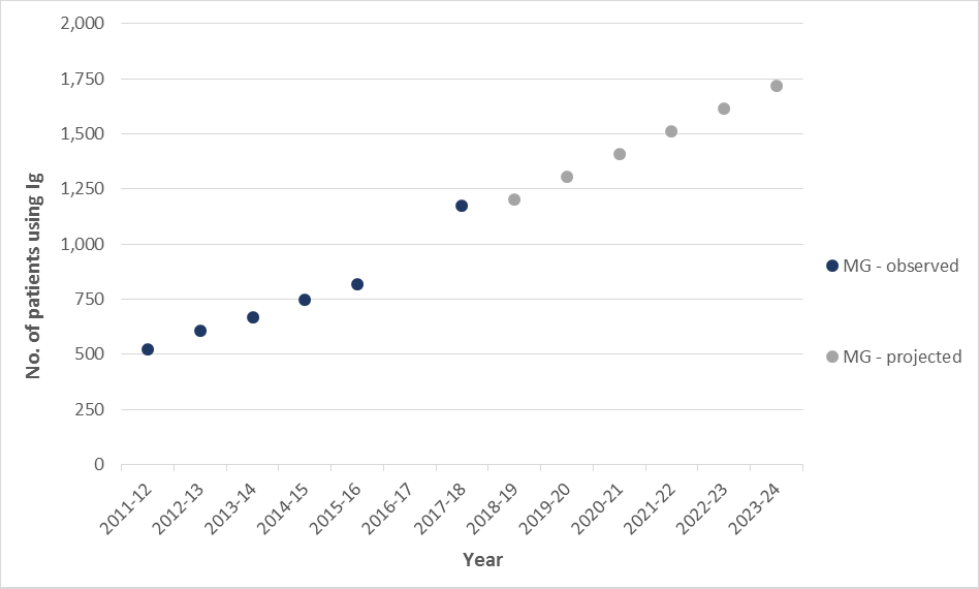
2017-18 estimates disaggregated patient numbers in Indications 1, 2 and 3 to be 201, 33 and 940 patients, respectively, for the most recent year where data is available.

E.2. USE AND COSTS OF IVIG FOR MG

While there is inevitably some uncertainty associated with future projections, the current eligible population and their extent of Ig use is well defined in the BloodSTAR database, and a ground-up epidemiological approach to estimating the size of the relevant population is therefore not required.

Figure 9 presents the patient numbers projected using linear extrapolations fitted to the observed data presented in Table 90. The projected estimated MG patients requesting IVIg are presented in Table 91.

Figure 9 Total MG Patients requiring IVIg; projected patient numbers to 2022-2023



MG = myasthenia gravis.
Source: 'Estimated patient numbers' worksheet in '1566 Financials.xlsx' workbook.

Table 91 Number of MG patients projected to receive Ig by indication, 2019-20 to 2023-24

	2019-20	2020-21	2021-22	2022-23	2023-24
Indication 1: 17.1%	223	241	258	276	294
Indication 2: 2.8%	37	39	42	45	48
Indication 3: 80.1%	1,046	1,128	1,211	1,293	1,376
MG Total	1,306	1,408	1,511	1,614	1,717

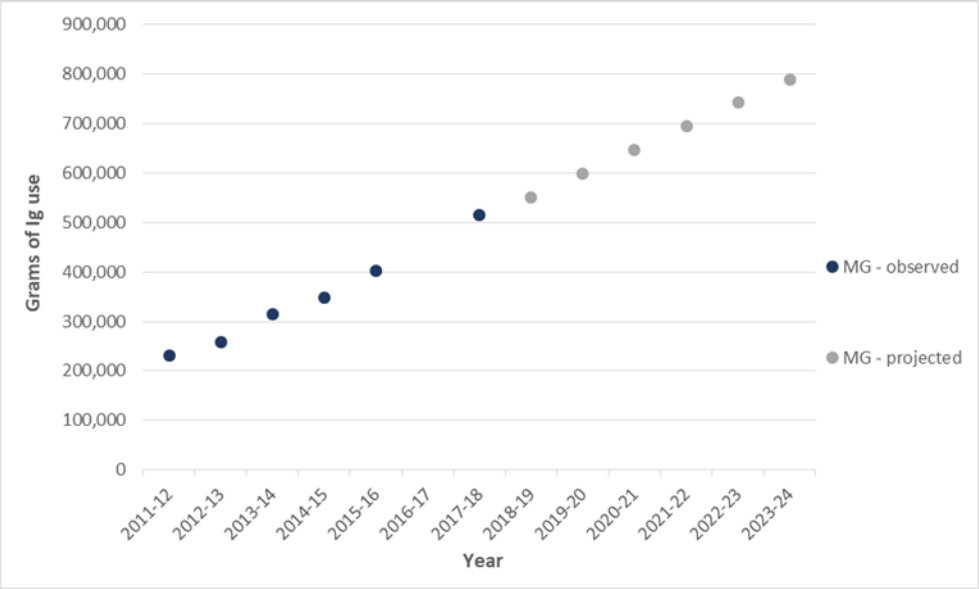
MG = myasthenia gravis.
Source: 'Estimated patient numbers' worksheet in '1566 Financials.xlsx' workbook.

ESTIMATED USE AND COST PER PATIENT WHO RECEIVES IG

Average grams per patient per year

A similar approach is used to estimate Ig use over the projected period, as patient weights and dose may change over time. The projected grams of IVIg use for each indication are presented in Table 922.

Figure 10 IVIg for MG, use projections to 2023-24



MG = myasthenia gravis.
Source: 'Estimated grams issued' worksheet in '1566 Financials.xlsx' workbook.

Data was not available to identify the allocation of IVIg in grams specifically associated with each indication. The National Blood Authority recommended assuming usage of IVIg on a 'grams issued' basis to be allocated in a split across the MG Indications 1, 2 and 3; in proportions of 9%: 1%: 90%, respectively (as presented in Section D.4).[16]

Table 92 Projected number of Ig grams issued by indication, 2019-20 to 2023-24

	2019-20	2020-21	2021-22	2022-23	2023-24
Indication 1: 9% use by g	53,903	58,193	62,482	66,772	71,061
Indication 2: 1% use by g	5,989	6,466	6,942	7,419	7,896
Indication 3: 90% use by g	539,034	581,928	624,822	667,716	710,610
MG Total	598,927	646,587	694,247	741,907	789,567

MG = myasthenia gravis.
Source: and 'Estimated grams issued' worksheet in '1566 Financials.xlsx' workbook.

[16] Department correspondence 12/04/19

In the available data (FY 2011-12-2015-16 and 2017-18), the average IVIg use (g)/patient for MG has varied year to year and while the overall trend is rising, this has not been particularly consistent or predictable (line of best for R^2 = 0.0696). Projecting use per patient using the projected number of grams issued and the projected patient numbers, the average number of grams of Ig issued per patient for MG is estimated to increase only slightly over the projected period (Table 93).

Table 93 Average Ig use (g) per patient per year

	Av 2011-18* [observed]	2019-20	2020-21	2021-22	2022-23	2023-24
MG	455	459	459	459	460	460

MG = myasthenia gravis.
Source: 'Section E1 tables' worksheet in '1566 Financials.xlsx' workbook.

This may be an underestimate as projections of 'IVIg use per patient' show a more rapidly rising trend, but this not consistent with data year on year and is not particularly well correlated (R^2 = 0.07), therefore is not use for the following analysis.

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 (i.e. domestic Ig including plasma, $140.18)

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

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

iv) The weighted average cost of Ig (mixed of domestic and imported product) used for MG in Australia which is $68.75, based on the 'HTA Data April2019.xlsx' workbook

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

Estimated cost of Ig

Projected costs across the MG indications are presented in Table 94.

Table 94 Cost of Ig for MG, 2019-20 to 2023-24

	2019-20	2020-21	2021-22	2022-23	2023-24
Cost per gram of Ig	$60.41				
No. Indication 1 patients	223	241	258	276	294
Ig grams issued for Indication 1	53,903	58,193	62,482	66,772	71,061
Cost of Ig for Indication 1	$3,256,280	$3,515,439	$3,774,538	$4,033,697	$4,292,795
No. Indication 2 patients	37	39	42	45	48
Ig grams issued for Indication 2	5,989	6,466	6,942	7,419	7,896
Cost of Ig for Indication 2	$361,795	$390,611	$419,366	$448,182	$476,997
No. Indication 3 patients	1,046	1,128	1,211	1,293	1,376
Ig grams issued for Indication 3	539,034	581,928	624,822	667,716	710,610
Cost of Ig for Indication 3	$32,563,044	$35,154,270	$37,745,497	$40,336,724	$42,927,950
Total number of patients	**1,306**	**1,408**	**1,511**	**1,614**	**1,718**
Total number of Ig grams issued	**598,926**	**646,587**	**694,246**	**741,907**	**789,567**
Total cost of Ig	**$36,181,120**	**$39,060,321**	**$41,939,401**	**$44,818,602**	**$47,697,742**
Cost of Ig to the Commonwealth[a]	$22,794,105	$24,608,002	$26,421,823	$28,235,719	$30,049,578
Cost of Ig to the States[a]	$13,387,014	$14,452,319	$15,517,578	$16,582,883	$17,648,165

Ig = Immunoglobulin; MG = myasthenia gravis

[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

Use of Ig for MG is currently provided only as an intravenous administration and therefore in some cases there are additional healthcare services and costs associated with administration.

No additional administration costs are assumed for Indication 1 patients as these patients are hospital inpatients, already occupying a hospital bed and receiving medical and nursing care. However patients utilising IVIg for Indications 2 and 3 do 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 adminimistration costs are estimated assuming the infusion is provided in a hospital outpatient setting, under the service cateqory of 10.13 (minor medical procedures), which includes infusions. The NWAU calculator 2019-20 (IHPA)[17] estimated cost of this service is $461 per episode.

The additional healthcare costs associated with IVIg administration are estimated in Table 95.

[17] https://www.ihpa.gov.au/what-we-do/pricing/national-weighted-activity-unit-nwau-calculators/nwau-calculators-2019-20

Table 95 Additional costs associated with IVIg use (administration costs) for Indications 2 and 3

	2019-20	2020-21	2021-22	2022-23	2023-24
Indication 2 patients	37	39	42	45	48
Annual number of IVIg administrations (@ 2 per patient)	74	78	84	90	96
Administration costs (@ $461 per administration)	$34,114	$35,958	$38,724	$41,490	$44,256
Indication 3 patients	1,046	1,128	1,211	1,293	1,376
Annual number of IVIg administrations (@ 11 per patient)	11,506	12,408	13,321	14,223	15,136
Administration costs (@ $461 per administration)	$5,304,266	$5,720,088	$6,140,981	$6,556,803	$6,977,696
Total IVIg administration costs (State Hospital Budgets)	**$5,338,380**	**$5,756,046**	**$6,179,705**	**$6,598,293**	**$7,021,952**

IVIg = intravenous immunoglobulin

For Indications 1 and 2, the use of IVIg is directly in place of the comparator management PE, and the extent of PE treatment that would be required in the absence of IVIg availability, and the associated cost-offsets associated with IVIg availability can be estimated. However in the case of IVIg provided under Indication 3, it is highly uncertain to what extent existing IVIg availability for use in MG replaces the nominated comparator therapies and associated cost offsets. Over nine different potential comparator management strategies were identified, ranging from PE, surgery and numerous pharmacological treatments, and within these dosing was highly variable. 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 IVIg was not available. An estimate of the costs associated with using PE instead of IVIg in Indications 1 and 2 is presented in Table 96. No cost-offsets for PE administration are included given patients are hospital inpatients (likely ICU) receiving medical and nursing care irrespective of the therapy being utilised.

It is not possible to quantify the cost-offsets associated with current availability of IVIg to existing *Criteria V3* patients. There are a broad range of comparator therapies patients would utilise in the absence of IVIg, and in many cases at least some of these are used concurrently with IVIg, but IVIg enables dose-reduction. Where IVIg is used in place of PE, cost offsets are relevant to both Commonwealth and State government budgets, in the case of surgery, predominantly hospital budget cost-offsets would be expected, and in the case of pharmaceuticals (with the exception of rituximab) predominantly Commonwealth PBS expenditure is offset along with some MBS-funded side-effect monitoring. Where IVIg is utilised rather than off-label rituximab, cost offsets associated with rituximab procurement and administration would apply to State hospitals.

Table 96 Cost offsets due to IVIg use (reduced use of PE for Indications 1 and 2, other comparators for Indication 3.

	2019-20	2020-21	2021-22	2022-23	2023-24
Indication 1 Patients [would otherwise receive PE]	223	241	258	276	294
Albumin 4% (L) (4 exchanges x 4 L = 16L /patient)	3,568	3,856	4,128	4,416	4,704
Albumin 4% (at cost: $137/L)	$488,816	$528,272	$565,536	$604,992	$644,448
Indication 2 Patients [would otherwise receive PE]	37	39	42	45	48
Albumin 4% (L) (5 exchanges x1L = 5L/patient)	185	195	210	225	240
Albumin 4% (at cost: $137/L)	$25,345	$26,715	$28,770	$30,825	$32,880
PE administrations (5 per patient)	185	195	210	225	240
Cost of PE administrations: $1,446.13/exchange day	$267,534	$281,995	$303,687	$325,379	$347,071
Indication 3 Patients	1,046	1,128	1,211	1,293	1,376
[would otherwise increase utilisation of PE, surgery, PBS and hospital-supplied pharmaceuticals: in an unknown pattern]	Unknown financial impact *- would impact Commonwealth health budgets (NBA, PBS and MBS expenditures) and State government budgets (health/hospital expenditure).*				
Total costs offsets achieved using IVIg	**>$781,695**	**>$836,982**	**>$897,993**	**>$961,196**	**>$1,024,399**
Offsets to the Commonwealth[a]	>$323,921	>$349,642	>$374,413	>$400,565	>$426,717
Offsets to the States[a,b]	>$457,774	>$487,341	>$523,581	>$560,632	>$597,683

[a] Albumin 4% costs are allocated as 63% Commonwealth, 37% State government.
[b] Outpatient and Day patient therapy administration costs are allocated as 100% State government.
IVIg = intravenous immunoglobulin; MBS = Medicare Benefits Schedule; NBA = National Blood Authority; PBS = Pharmaceutical Benefits Scheme; PE = plasma exchange.

E.4. FINANCIAL IMPLICATIONS FOR GOVERNMENT HEALTH BUDGETS

The net financial implications for government budgets associated with the funding of Ig for MG are presented in Table 97. However, these are likely underestimates as additional cost offsets associated with reduced comparator therapy use in Indication 3 patients is highly likely but cannot be reliably estimated.

Table 97 Net financial implications to government associated with Ig for MG

	2019-20	2020-21	2021-22	2022-23	2023-24
Total cost of Ig	$36,181,120	$39,060,321	$41,939,401	$44,818,602	$47,697,742
Cost of Ig to the Commonwealth	$22,794,105	$24,608,002	$26,421,823	$28,235,719	$30,049,578
Cost of Ig to the States	$13,387,014	$14,452,319	$15,517,578	$16,582,883	$17,648,165
Additional cost to states (administration)	$5,338,380	$5,756,046	$6,179,705	$6,598,293	$7,021,952
Total cost offsets due to a reduction in PE	$781,695	$836,982	$897,993	$961,196	$1,024,399
Offsets to the Commonwealth	$323,921	$349,642	$374,413	$400,565	$426,717
Offsets to the States	$457,774	$487,341	$523,581	$560,632	$597,683
Net cost	**$40,737,805**	**$43,979,384**	**$47,221,113**	**$50,455,699**	**$53,695,295**
Net cost to the Commonwealth	$22,470,184	$24,258,360	$26,047,410	$27,835,154	$29,622,861
Net cost to States	$18,267,621	$19,721,024	$21,173,703	$22,620,544	$24,072,434

Ig = immunogolobulin; PE = plasma exchange

E.5. IDENTIFICATION, ESTIMATION AND REDUCTION OF UNCERTAINTY

Sensitivity analyses exploring uncertainty in the IVIg price used to determine the financial implications are presented in Table 98, with the alternative prices (calculated per g), as described in Section E.2 .

Table 98 Sensitivity analyses around the financial implication estimates, net cost (Commonwealth and states)

	2019-20	2020-21	2021-22	2022-23	2023-24
Base: case $60.41 per gram	$40,737,805	$43,979,384	$47,221,113	$50,455,699	$53,695,295
Varying the cost of Ig					
High cost scenario, $140.18	$88,514,132	$95,557,629	$102,601,116	$109,637,620	$116,679,055
Low cost scenario, $44.94	$31,472,419	$33,976,683	$36,481,127	$38,978,397	$41,480,694
Weighted average, $94.51	$61,161,181	$66,028,001	$70,894,901	$75,754,727	$80,619,530
Published Price 2019, $58.23	$39,432,146	$42,569,825	$45,707,656	$48,838,341	$51,974,039
MG weighted average, $68.75	$45,732,847	$49,371,920	$53,011,124	$56,643,203	$60,280,284

Ig = immunoglobulin; MG = myasthenia gravis.

SECTION F OTHER RELEVANT CONSIDERATIONS

This section includes a brief discussion of the effectiveness and safety of rituximab for MG. Rituximab is a comparator for Indication 3 in the PICO Confirmation for Application 1566, but the evidence identified for this treatment was not comparative and was therefore not included in *Section B Clinical Evaluation*.

A discussion of the effectiveness of IVIg in two other clinical scenarios of MG is also included in *Section F*. The PICO confirmation for CA 1566 refers to the following sub-populations which are not covered by *Criteria V3* Indications 1, 2 or 3. They are:

- Ocular MG: data not reported separately for those receiving IVIg, therefore not discussed separately; data on pure ocular MG was not included as patients are not eligible for Ig therapy;
- MG with MuSK antibodies: discussed in *Section F*, not covered by NBA Indication 1 to 3;
- Thymectomy: data not reported separately for those receiving IVIg, except for data on preparation for surgery, which is included in *Section B*;
- Impending myasthenic crisis: data not reported separately from crisis, included in *Section B*;
- MG in pregnancy: discussed in *Section F*, not covered by NBA Indications 1 to 3;
- Juvenile MG: discussed in *Section B*, not covered by NBA Indications 1 to 3

SAFETY AND EFFECTIVENESS OF RITUXIMAB FOR PATIENTS WITH MG

Rituximab is a genetically engineered monoclonal antibody therapy designed to target the transmembrane protein CD20, which has been found on the surface of both normal and malignant B-lymphocytes. Following successful trials in B-cell non-Hodgkin's lymphoma, it has been trialled in other cancers and autoimmune conditions including MG (Tandan et al. 2017). In particular, rituximab has been used in clinical settings for refractory MG cases which have not responded to standard therapies, PE or IVIg. Rituximab is a comparator for Indication 3 in the PICO Confirmation for Application 1566, and as a possible alternative to PE and IVIg, it is relevant to provide a discussion of rituximab in the context of MG in this assessment. Rituximab is not PBS funded for use in MG patients.

A significant body of literature was found through the literature review and pearling that discussed the effectiveness of rituximab in MG patients, albeit not in comparison with IVIg. Articles consisted of open label single arm trials, case series and case reports. To summarise the safety and effectiveness of rituximab for MG, two SRs have provided data on the primary studies (Guptill, Sanders & Evoli 2011; Tandan et al. 2017) and in addition to these, two articles based on Australian MG patients provided data on the authors' experience with rituximab (Blum et al. 2011; Chan et al. 2018).

The two SRs had a significant overlap in included case series and case reports, but reported symptom improvement in different ways. The later and more comprehensive review (n = 169 cases) (Tandan et al. 2017) reported symptom improvement based on a modified version of the MGFA post-intervention scale (PIS-m) of minimal manifestations (MM) or better and the QMGS. A PIS-m of MM or better was achieved in 44% of all cases treated with rituximab, with a significantly greater proportion improved in those with MuSK-MG compared to AChRAb-MG (72% versus 30%; p < 0.001). QMGS was only available for 18 cases, and for these there was an absolute score improvement of 8.2 ± 5.1 following treatment or per cent change in score of 52.6 ± 33.11%. Further data is provided in Table 99.

The change from baseline in mean QMGS was statistically significant in the whole group and for both MG serotypes but the improvement was greater in those with MuSK-MG compared to AChRAb-MG in all analyses (difference in mean improvement 8.1 ± 2.1; 95% CI 3.9, 12.3; p = 0.0004 for all 18 cases).

The rate of side effects was lower than that for IVIg or PE reported in other studies (15 AEs reported on 105 patients, 14%). The most common event was flushing (n = 3) and one report each of a range of events including agranulocytosis, pneumonia, bronchitis, dyspnoea and myocardial infarction.

The earlier SR (Iorio et al. 2015) performed a meta-analysis of symptom improvement in articles that reported on two or more cases (K = 15). Improvement was again based on the MGFA PIS (unmodified). The overall response rate was 83.9% for the 15 studies. The response in those with MuSK serotype was better than those with AChRAb-MG but without statistical significance (88.8% versus 80.4%).

Table 99 Improvement following rituximab in patients with MG (Tandan et al. 2017)

Improvement measure	All MG (n = 169)	AChRAb-MG (n = 99)	MuSK-MG (n = 57)	Difference AChRAb vs MuSK (p-value)
MGFA grade before rituximab (median)	IVB	IVA	IVB	0.19
Treatment effect				
PIS-m MM or better (n, %)	75/169 (44%)	30/99 (30%)	41/57 (72%)	<0.0001
PIS-m CSR or PR (n, %)	45/169 (27%)	16/99 (16%)	27/57 (47%)	<0.0001
Any relapse after rituximab (n, %)	26/101 (26%)	21/63 (33%)	4/29 (14%)	0.05
Relapses after rituximab (mean ± SD) (n)	0.4 ± 0.9 (n = 100)	0.5 ± 1.0 (n = 62)	0.2 ± 0.6 (n = 29)	0.04
QMGS (mean ± SD)				
Number of cases	18	15	3	
Pre-rituximab	16.8 ± 5.5	17.7 ± 0.5	12.7 ± 4.5	0.15
Post-rituximab	8.7 ± 6.9	9.9 ± 6.7	2.3 ± 4.0	0.08
Change in score (absolute)	8.2 ± 5.1	7.7 ± 5.4	10.3 ± 2.5	0.44
Change in score (%)	52.6 ± 33.1	45.9 ± 30.9	86.3 ± 23.8	0.05
Pre-post difference in mean (p-value)[a]	0.0004	0.0001	0.04	

AChRAb = acetylcholine receptor antibody; CSR = complete stable remission; MG = myasthenia gravis; MGFA = Myasthenia Gravis Foundation of America; MM = minimal manifestations; MuSK = muscle specific kinase antibody; PIS-m = modified post-intervention scale; PR = pharmacologic remission; QMGS = quantitative myasthenia gravis score; SD = standard deviation

[a] Difference in observed means, MedCalc online calculator

An Australian article published data on 38 MG patients receiving rituximab for reasons of refractory disease, side effects with standard IS therapies or contraindication to IS (Chan et al. 2018). The patients, who were identified retrospectively, were treated between May 2006 and July 2017 in South East Queensland. The article, which was published in a letter format, provided data on 14 patients included in an earlier study by Blum et al (Blum et al. 2011) and an additional 24 patients. The majority of patients were of moderate to severe disease status according to their MGFA score.

The refractory disease and MGFA status met eligibility criteria for IVIg under *Criteria V3* Indication 3. Of the 38 patients treated with rituximab, 22 were also using corticosteroids, 27 were taking steroid-sparing agents (for example azathioprine, methotrexate and ciclosporin), 24 received IVIg infusions, and three patients received PE. Five patients were able to cease IVIg treatment (20.8%) compared to two of the patients receiving PE (66.7%). In addition, of those receiving rituximab and IVIg, six were able to reduce their IVIg dose, and one patient was commenced on IVIg.

The overall response to rituximab was clinical improvement for 28 out of 38 patients (74%) with 10 experiencing clinical remission, 7 with MM and 11 experiencing improvement on the MGFA PIS scale. Five patients were unchanged or worse, and five were deceased. Treatment response is summarised in Figure 11. The data does not show safety or effectiveness for rituximab in comparison to IVIg, but there is potential for rituximab to be used as an alternative in refractory cases or where there are contraindications, or until further comparative evidence becomes available.

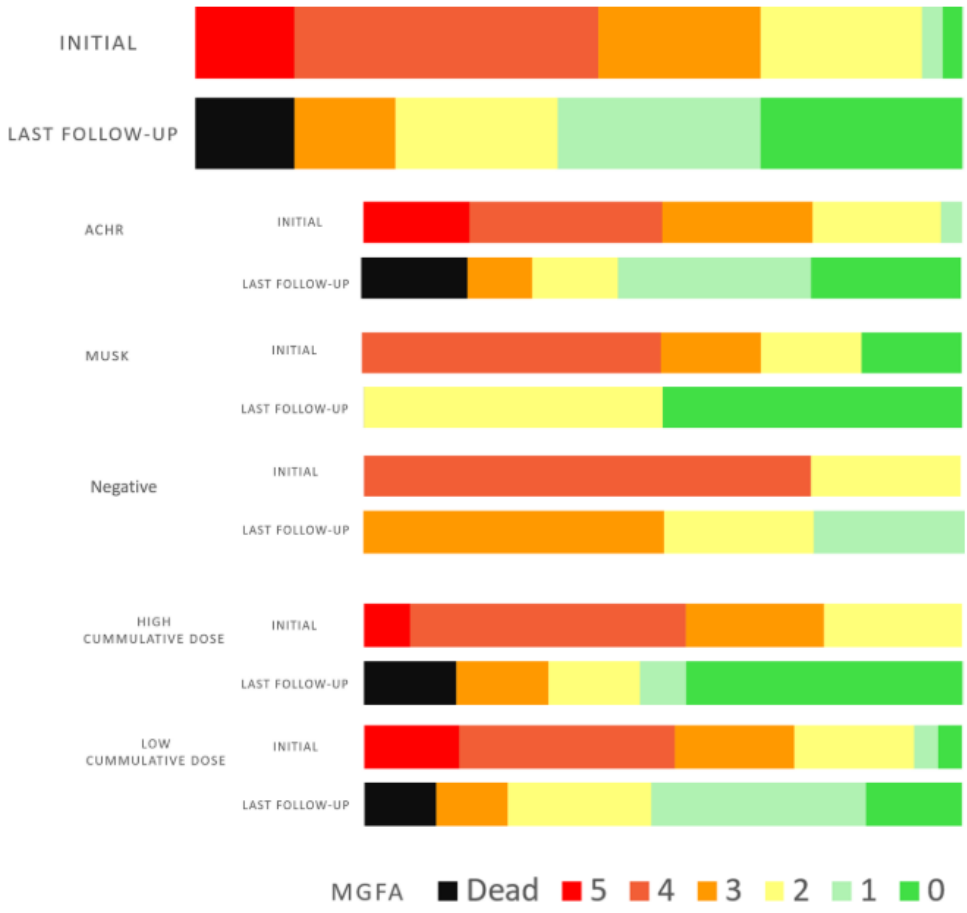


Figure 11 MGFA scores (1-5 and dead) at the time of initial rituximab therapy and last follow-up (Chan et al. 2018)

Relative percentage of patients with different MGFA scores at the time of initial therapy with rituximab versus time of last follow-up. Scores are shown combined for the entire cohort (two top bars) as well as detailed for AChRAb (lines 3 & 4) and MuSK antibody positive patients (lines 5 & 6) and antibody negative (lines 7 & 8) patients. After treatment, there was an increase in the numbers of patients with lower scores in the total cohort as well as in all subgroups. (Chan et al. 2018)

SAFETY AND EFFECTIVENESS OF IVIG COMPARED WITH PE IN PATIENTS WITH ANTI-MUSK MG

Although MuSK-MG and seronegative patients are not specifically excluded from the *Criteria V3* eligible populations, the Ig Reference Group has listed them as a specific sub-population of MG. In the evidence provided on the safety and effectiveness of IVIg for MG, the majority of patients are AChRAb positive, and those that are not (either MuSK antibody positive or seronegative) are rarely analysed separately

To address this gap in the evidence, two retrospective cohort studies, which represented the best evidence identified in the literature search, are presented here. They provided data in MuSK- MG patients comparing the effectiveness of IVIg and PE (Guptill, Sanders & Evoli 2011; Pasnoor et al. 2010). The two studies followed treatments given to MuSK-MG patients. Guptill et al analysed data sourced from two MuSK-MG cohorts (total n = 110). Most patients (98%) were initially treated with

acetylcholinesterase inhibitors (pyridostigmine), followed by PN and IS therapies if required or for those contraindicated. PE and IVIg were given in periods of exacerbation. The proportion of patients who received PE was 66% (n = 73) and IVIg was 28% (n = 31). Average follow-up was 11 years and 5.3 years for the two cohorts. In the second retrospective review (Pasnoor et al. 2010), treatments were followed in 53 MuSK-MG patients whose duration of disease ranged from 1 week to 22 years, with a mean follow-up of 6.7 years. Treatments were similar to those given in the study by Guptill et al, and patients were often receiving concurrent treatments. The proportion who received PE was 62% (n = 33) and IVIg was 47% (n = 25).

Guptill et al found that remission was more common with PE than IVIg (93% versus 61%). This difference was statistically significant using the chi-squared test (difference in proportion: 32%; 95% CI 14.9%, 49.9%; p = 0.0001; MedCalc online calculator). The authors comment was that "the response to PE was generally rapid and gratifying". Interestingly, all six patients who had been previously treated with either PE or IVIg (one patient received both) were given rituximab and achieved improved or MM status with no side effects from the drug (Guptill, Sanders & Evoli 2011). Patient response reported by Pasnoor et al was also greater for those receiving PE compared to IVIg (51% versus 20%) and the difference was statistically significant (difference in proportion: 31%; 95% CI 5.9%, 50.5%; p = 0.02; MedCalc online chi-squared calculator). Pasnoor et al found that IVIg achieved the lowest response (20%) rate while corticosteroids and PE achieved the greatest response rates (51% and 53% respectively) in MuSK-MG patients. Patient response rates to treatments are given in Table 100.

Table 100 Rate of clinical improvement in response to treatment in MuSK-MG patients

Treatment/study	Patients treated N (%)	Patients who responded N/number treated (%)
AChE-I (pyridostigmine)		
Guptll et al 2011	108 (98%)	62/108 (57%)
Pasnoor et al 2010	51 (96%)	27/51 (16%)
IS agents		
Guptill et al 2011	105 (96%)	NR
Pasnoor et al 2010	39 (74%)	16/39 (41%)
Rituximab		
Guptill et al 2011	6 (5%)	6/6 (100%)
Pasnoor et al 2010	NR	NR
Thymectomy		
Guptill et al 2011	40 (36%)	20/40 (50%) (MM or better)
Pasnoor et al 2010	18 (34%)	7/18 (39%)[a]
IVIg		
Guptill et al 2011	31 (28%)	19/31 (61%)
Pasnoor et al 2010	25 (47%)	5/25 (20%)
PE		
Guptill et al 2011	73 (66%)	68/73 (93%)
Pasnoor et al 2010	33 (62%)	17/33 (51%)

AChE-I = acetylcholinesterase inhibitor therapy; IS = immunosuppressive therapy; IVIg = intravenous immunoglobulin therapy; MuSK-MG = muscle specific kinase antibody positive myasthenia gravis; MM = minimal manifestations; NR = not reported; PE plasm exchange

[a] From patients with 3 year follow-up data

IVIG FOR MG IN PREGNANCY

Despite pregnancy being a known trigger of MG exacerbation (Statland & Ciafaloni 2013), there were very limited data on the use of IVIg during pregnancy in MG patients. In two studies, a total of eight patients were treated with IVIg during pregnancy or in the post-partum period. Three pregnant women were treated with IVIg for myasthenic crisis precipitated by infection in one study, but the outcomes of the pregnancies were unclear. In another study, five women transferred from standard therapies to IVIg when they decided to conceive and during their pregnancies. There were no exacerbations during pregnancy, delivery or postpartum in the five women and no symptoms of MG in the neonates. The patient numbers are too small to make conclusions from the outcomes in these studies.

Appendix A Clinical Experts and Assessment Group

IG REVIEW REFERENCE GROUP

ASSESSMENT GROUP

Adelaide Health Technology Assessment

Name	Position
Joanne Milverton	Senior research officer
Camille Schubert	Team leader - health economy
Ben Ellery	Senior research officer
Jaqueline Parsons	Team leader – Special projects

NOTED CONFLICTS OF INTEREST

There were no conflicts of interest.

APPENDIX B SEARCH STRATEGIES

BIBLIOGRAPHIC DATABASES

Database	Period covered
Cochrane Library – including, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials (CENTRAL), the Health Technology Assessment Database, the NHS Economic Evaluation Database	1980 – March 2019
PubMed	1980 – March 2019
Embase.com (including Embase and Medline)	1980 – March 2019

ADDITIONAL SOURCES OF LITERATURE (INCLUDING WEBSITES)

Source	Location
Internet	
NHMRC- National Health and Medical Research Council (Australia)	https://www.nhmrc.gov.au/
US Department of Health and Human Services (reports and publications)	http://www.hhs.gov/
Trip database	http://www.tripdatabase.com
Current Controlled Trials metaRegister	http://controlled-trials.com/
National Library of Medicine Health Services/Technology Assessment Text	https://www.nlm.nih.gov
U.K. National Research Register	https://www.nihr.ac.uk
Google Scholar	http://scholar.google.com/
Australian and New Zealand Clinical Trials Registry	http://www.anzctr.org.au
Pearling	
All included articles will have their reference lists searched for additional relevant source material	

APPENDIX C STUDIES INCLUDED IN THE SYSTEMATIC REVIEW

Table 101 Systematic reviews comparing immunoglobulin with plasma exchange or other therapies for myasthenia gravis included in the assessment

Author, Year Country Quality	K studies N patients (total) Objectives	Population characteristics	Eligibility criteria	Intervention Comparator	Outcomes assessed Duration of follow-up	Statistical analysis Sub-group analysis	Comments Funding source
Indication 1,2 & 3							
(Gajdos, Chevret & Toyka 2012) France Update on (Gajdos, Chevret & Toyka 2008), (Gajdos, Chevret & Toyka 2006) & (Gajdos, Chevret & Toyka 2003) Additional data provided by (Gajdos & Chevret 2008) (Bril et al. 2012) (see also studies listed under the RCT Barth et al, 2011) Level I study (SR of RCTs) Quality: high	K = 7 N = 455 *Objectives* To examine the efficacy of IVIg compared to PE, other treatments or placebo for the treating of exacerbations of MG or the chronic phase	*Barth et al 2011* RCT, N = 84 IVIg vs PE, moderate to severe MG with QMGS > 10.5 and worsening weakness *Zinman, Ng and Bril 2007* RCT, N = 51 IVIg vs placebo, MG with worsening weakness defined as increasing symptoms or signs judged by patients and physician to warrant therapy change *Gajdos et al 2005* RCT, N = 173 IVIg 1g/kg vs IVIg 2g/kg, exacerbation with at least one of difficulty swallowing, acute respiratory failure or major functional disability leading to discontinuation of physical activity *Schuchardt et al 2002* RCT, N = 33 IVIG vs CS (methylprednisolone), increase of one point on the Oosterhuis scale and ≥3 on QMGS scale for worst 2 criteria *Wolfe et al 2002* RCT, N = 15 IVIg vs placebo, patients with mild to moderate MG who have never taken CS or IS or with persistent MG	RCTs or quasi-RCTS of patients with MG NBA Indications 1, 2 or 3. 1. Exacerbation or worsening of MG as described by authors of the trials 2 & 3. Chronic generalised MG (severe but stable) treated for reasons other than exacerbation (pre-operative management, chronic use of PE, refractory to CS or IS drugs	*Intervention* IVIg *Comparator* PE Oral methyl-prednisolone Placebo IVIg (dose comparison)	*Primary outcomes* 1. Change in a specific score from before and 7 to 15 days from treatment start or randomisation 2. Improvement by at least one grade in a functional scale between day before and at least 6 months after treatment start or randomisation *Secondary outcomes* 1. i) improvements by at least one grade in a functional scale (of 5 to 6 grades) from before day 7 to 15 after treatment start; ii) weaning from ventilation from before to day 15 of treatment; iii) absolute mean reduction in circulating concentrations of AChRAbs after treatment 2. i) remission by 12 months after start of treatment; ii)delay of the first relapse 3. AEs related to treatment including haemorrhage requiring blood transfusion or a surgical treatment, hypotension requiring vascular expansion, fever (>38^{o}C), acute renal failure, ascetic meningitis 4. Treatment discontinuation due to AEs	Meta-analysis planned but none performed due to differences in study populations and comparators *Subgroup analyses* Patients becoming worse during the initiation of steroids Patients treated before thymectomy Patients on IVIg or PE alone or who are simultaneously being treated with IVIg or PE and CS or IS drugs	*Assessment scales* Oosterhuis class Osserman class QMGS (range: 0 (no MG findings) to 39 (most severe MG findings)

Author, Year Country Quality	K studies N patients (total) Objectives	Population characteristics	Eligibility criteria	Intervention Comparator	Outcomes assessed Duration of follow-up	Statistical analysis Sub-group analysis	Comments Funding source
		symptoms and on PN >20 mg on alternate days *Rønager et al 2001* RCT, N = 12 IVIg vs PE, moderate to severe but stable MG, *Gajdos et al 1997* RCT, N = 87 IVIg vs PE, exacerbation with at least one of difficulty swallowing, acute respiratory failure or major functional disability leading to discontinuation of physical activity					
(Alabdali et al. 2014) Canada Level 1 study (SR of level II to IV studies) Quality: poor	K = 8 N = 529 *Objective* To assess the efficacy of IVIg compared with placebo or PE in patients myasthenia crisis,	*Barth et al 2011* (See Gajdos, Chevret & Toyka, 2012) *Zinman, Ng and Bril 2007* (See Gajdos, Chevret & Toyka, 2012) *Gajdos et al 2005* (See Gajdos, Chevret & Toyka, 2012) *Rønager et al 2001* (See Gajdos, Chevret & Toyka, 2012) *Gajdos et al 1997* (See Gajdos, Chevret & Toyka, 2012) *Hellmann et al, 2014* Ret, N = 52 IVIg for patients with chronic MG for a minimum of 1 year *Liew et al, 2014* Ret CCoh, N = 54 IVIg vs PE as treatments for chromic MG in children and adolescents *Eienbröker et al, 2014* POb, N = 16 IVIg 2g/kg, then 0.4 g/kg Q4-12 weeks as maintenance therapy	RCTs, controlled cohort studies and retrospective case series for NBA Indications 1 & 3 1. Patients with acute or severe MG disease flare ups (myasthenic crisis) 3. worsening moderate to severe disease or on therapy for chronic disease	*Intervention* IVIg *Comparator* PE Placebo IVIg (dose comparison)	*Primary outcome* Change in MG status at d 7, 14 or 15 post start of treatment (QMGS, MMS, MGFA, clinical evaluation) *Secondary outcome* Change in MG status at d 21 or 28, or at 24 m (SFEMG, PIS QMGS, AChRAb) Adverse events	No meta-analysis was performed *Subgroup analysis* Juveniles with MG	*Assessment scales* QMGS MMS SFEMG AChRAb Clinical status PIS

Author, Year Country Quality	K studies N patients (total) Objectives	Population characteristics	Eligibility criteria	Intervention Comparator	Outcomes assessed Duration of follow-up	Statistical analysis Sub-group analysis	Comments Funding source
(Ortiz-Salas et al. 2016) Level I study (Meta-analysis of RCTs and SR of RCTs and observational studies) Quality: Low	K = 10 N = *Objective* To carry out a meta-analysis to evaluate the existing evidence that compares the efficacy and the side effects over a short time period of PE vs IVIg in the management of MG	*Barth et al 2011* (See Gajdos, Chevret & Toyka, 2012) *Gajdos et al 1997* (See Gajdos, Chevret & Toyka, 2012) *Rønager et al 2001* (See Gajdos, Chevret & Toyka, 2012) *Mandawat et al 2010* Retrospective study, N = 1606 patients hospitalised between 2000 – 2005 with severe stable chronic MG or myasthenic crisis IVIg vs PE: n = 340 vs n=1266, respectively *Liu et al 2009* RCT, N = 30 late-onset MG patients (mean age 53 years) IVIg vs PE: n = 15 both groups *Perez-Nellar et al 2001* Retrospective study; N = 71 MG patients 33 MG patients treated with IVIg (prospective) and 38 medical records of patients managed with PE during the perioperative period before thymectomy *Jensen et al 2008* Retrospective study; N = 43 pre-operative patients with MG of whom 9 received IVIG alone and were matched to 9 who received PE alone *Pittayanoon et al 2009* Retrospective study; N = 33 patients with myasthenic crisis reviewed between 2001 and 2006 IVIg vs PE: n = 10 and n = 23, respectively *Murthy et al 2005*	RCT or observational studies of more than 10 cases that compared management with PE vs IVIg in patients with MG	*Intervention* IVIg *Comparator* PE	*Primary outcome* Efficacy of management according to commonly used methods. No. of patients who improved, not episodes in which changes occurred were taken as the basis of the primary outcome: changes in the MMS, or QMGS between day 1 and 15 days after treatment commenced, or following randomisation *Secondary outcomes* Adverse event frequency Length of hospital stay Ventilator support time	Publications that reported a RR or an OR with CIs, or reported results that enabled calculation of the RR or OR were included for meta-analysis Meta-analysis conducted using Comprehensive Meta-analysis (2004; Biostat, Englewood, NJ) Standardised effect sizes were calculated and log transformation (log OR and SE) was undertaken to enable a pooled result to be reported on effectiveness and adverse event frequency, (but not severity) across studies using different outcome measures Length of hospital stay and ventilator support time were compared using the SMD with 95% CI, accepting $p<0.05$ as a statistically significant difference	*Assessment scales* ORs of standardised effect sizes calculated from the MMS, QMGS and frequency of adverse events Comparisons for length of hospital stay and ventilator support time were measured in days (SMD [95% CI])

Author, Year Country Quality	K studies N patients (total) Objectives	Population characteristics	Eligibility criteria	Intervention Comparator	Outcomes assessed Duration of follow-up	Statistical analysis Sub-group analysis	Comments Funding source
		Retrospective study, N = 21 patients (9 with thymoma) with 23 episodes of myasthenic crisis IVIg vs PE: n = 8 and n = 15 episodes treated, respectively Average age 40 years (range 28 – 75 years) *Qureshi et al 1999*[a] Retrospective, N = 51 patients / 54 episodes of myasthenic crisis IVIg vs PE: n = 24 and n = 27, respectively PE group received 5 to 6 exchanges and the IVIG group a dose of 0,4 gr7Kg/ day for 5 days.					

AChRAb – acetylcholine receptor antibodies; AEs = adverse events; CCoh = comparative cohort study; CS = corticosteroid therapy; GCS = glucocorticosteroid therapy; IM = immunomodulatory therapy; IS = immunosuppressive drugs; MG = myasthenia gravis; MMS = myasthenia muscle score; NBA = National Blood Authority; OR = odds ratio; PE = plasma exchange; PIS = post-intervention status; POb = prospective observational study; QMGS = quantitative myasthenia gravis score; RCT = randomized controlled trial; Ret CS = retrospective case series; RR = risk ratio; SFEMG = single fiber electromyography; SR = systematic review

[a] No details regarding specific designs of the included studies were specified by Ortiz-Salas et al. Further details on the patient populations and designs of included studies in the SR/meta-analysis are reported in the individual study profiles. Exception: Perez-Nellar et al 2001; article in Spanish and not included in our analysis.

Table 102 Profiles of primary studies on immunoglobulin for myasthenia gravis included in the assessment

Study Country	Study design Study objectives	Level of evidence Quality	Study population	Eligibility criteria	Intervention	Comparator	Outcomes assessed Statistical analyses	Comments Funding source
Indication 1 exacerbation/crisis								
(Gajdos et al. 1997) France Additional data from (Gajdos et al. 1998)	RCT (multicentre, unblinded) *Objective* To assess the efficacy and tolerance of IVIg with PE in MG, and to compare two difference dosing schedules of IVIg	Level II moderate risk of bias	N = 47 Mean age ± SD (y): IVIg 49.4 ± 16.6; PE 50.5 ± 20.5 Mean time since onset ± SD (y): IVIg 3.7 3 ± 4.4; PE 4.3 ± 5.9 MG stage prior to exacerbation: IVIg 1-2 11%, 3 22%, 4-5 67%; PE 1-2 15%, 3 24%, 4-5 61%	*Inclusion* Consecutive MG patients with exacerbation defined as the appearance of at least one of difficulty swallowing, acute respiratory failure or major functional disability responsible for the discontinuation of physical activity (grade 4 or 5 on the study's functional score of 1-5) *Exclusion* Known allergy to Ig or with contraindications to PE, ie coagulation disorders, cardiovascular instability, coronary insufficiency, uncontrolled infection or pregnancy	IVIg (0.4 gm/kg/day for either 3 or 5 consecutive days)	PE (3 x 1.5 volumes performed on days 1,3 & 5 after randomisation)	*Primary* Change in MMS *Secondary* Need for mechanical ventilation or nasogastric tube AChRAb Adverse events *Statistical analysis* ITT using the Wilcoxon, Kruskal-Wallis and Fisher exact tests Kaplan-Meier and log rank tests for failure time data SAS and BMDP software were used	Immunosuppressive CS, AC or other drugs were given as required or continued as before the study Follow-up at 0, 2, 4, 6, 9, 12 & 15 days *Funding* Supported by various French research bodies
(Gajdos et al. 2005) France	RCT (multicentre, double-blind) *Objective* To determine the optimal dose of IVIg for treating MG exacerbation	Level II low risk of bias	N = 168 Mean age [range] (y): group 1 55 [43-71]; group 2 55 [37-71] Male: group 1 31 (38.3%); group 2 35 (40.2%) Disease duration [range] (y): group 1 1 [0-6]; group 2 2 [1-7] MG stage prior to exacerbation: Group 1 1-2 51.8%, 3 38.3%, 4 9.9%; Group 2 1-2 40.2%, 3 44.8%, 4 14.9%	*Inclusion* Consecutive MG patients with exacerbation defined as the appearance of at least one of difficulty swallowing, acute respiratory failure or major functional disability responsible for the discontinuation of physical activity *Exclusion* CS medication begun or modified within 1 month prior to treatment, PE within prior 6 weeks, IVIg within prior 3 months, allergy to IVIg, serum creatinine > 1.4 mg/dL	IVIg (1g/kg on day 1 & placebo on day 2)	IVIg (1 g/kg on day 1 and day 2)	*Primary* Change in MMS *Secondary* FVC Need for mechanical ventilation or nasogastric tube AChRAb titre Adverse events *Statistical analysis* ITT using the Wilcoxon rank sum for continuous variables Fisher exact tests for categorical variables	IVIg source: Tegeline; LFB Laboratories, Les Ulis, France) Immunosuppressive CS, AC or other drugs were given as required or continued as before the study Follow-up at 0, 2, 4, 6, 9, 12 & 15 days Patients were at a lower level of

Study Country	Study design Study objectives	Level of evidence Quality	Study population	Eligibility criteria	Intervention	Comparator	Outcomes assessed Statistical analyses	Comments Funding source
				(>120µmol/L or clearance < 60 ml/L), body weight > 100kg, pregnancy, younger than 15 y.			Mixed linear models & linear model with generalised estimating equations for repeated measures over time and treatment response respectively Kaplan-Meier and log rank tests for failure time data SAS version 8.2 & S-PLUS 2000 software were used	severity then Gajdos 1997 *Funding* Supported by LFB Laboratories & the Association Française Contre les Myopathies, Paris, France.
(Mandawat et al. 2010) USA	Retrospective cohort study *Objective* To compare clinical and economic outcomes following PE and IVIg in US hospital patients with primary diagnoses of MG (including crisis)	Level III-2 Moderate risk of bias	N = 1,606 **MG - crisis (n = 698):** Mean age ± SD (y): PE 58.9 ± 18.5; IVIg 56.3 ± 22.0 Male: PE 45.4%; IVIg 29.6% Charlson comorbidity index: PE 49.0% mild, 46.7% moderate, 4.35% severe; IVIg 56.8% mild, 39.6% moderate, 3.6% severe Admitted for acute respiratory failure with endotracheal intubation: PE 28.0%; IVIg 12.4% Admitted for acute respiratory failure with CPAP/BiPAP: PE 7.37%; IVIg 4.7% **MG - not crisis (n = 908)** Mean age ± SD (y): PE 53.2 ± 18.4; IVIg 50.7 ± 23.7 Male: PE 34.3%; IVIg 37.4%	*Inclusion* ICD-9-CM codes for primary diagnoses of MG (358.0) and MG crisis (358.01) to identify initial cohort *Exclusion* Patients who received both PE and IVIg Secondary diagnoses of the following, according to ICD-9-CM criteria: neonatal MG, Lambert-Eaton myasthenic syndrome, chronic inflammatory demyelinating polyneuropathy, critical illness polyneuropathy, polyneuropathy due to other diseases classified elsewhere, acute poliomyelitis (with and without paralysis), acute transverse myelitis, acute alcohol intoxication, and poisoning by drug and biologic substances To avoid double representation of the same patient, patients whose disposition or admission	IVIg, no further details	PE, no further details	Mortality Complications Length of hospital stay Total hospital charges *Statistical analyses* Bivariate analysis of independent variables by outcomes was performed using Fisher's exact test for categorical variables and Wilcoxon signed-rank test and Mood's median test for continuous variables Significance set a priori at $p<0.05$ Stepwise multiple regression models fitted to determine the independent association of significant variables associated with use of IVIg over PE; Length of stay and total hospital charge were log-transformed to reduce skewness and meet normality assumptions.	*Funding* Research partially supported by grant from the National Institute of Neurological Disorders and Stroke Authors reported that they have no potential conflict of interest

Study Country	Study design Study objectives	Level of evidence Quality	Study population	Eligibility criteria	Intervention	Comparator	Outcomes assessed Statistical analyses	Comments Funding source
			Charlson comorbidity index: PE 63.8% mild, 34.6% moderate, 1.6% severe; IVIg 58.5% mild, 39.8% moderate, 1.8% severe; excluded :acute respiratory failure	type indicated a transfer to or from another short-term hospital Patients with a hospital charge less than $100, (as deemed likely to be incorrectly coded) and those with a negative length of stay or a stay exceeding 365 days				
(Pittayanon, Treeprasertsuk & Phanthumchinda 2009)] Thailand	Retrospective cohort study *Objective* To evaluate the efficacy and outcomes of MG crisis treatment with PE or IVIg in King Chulalongkorn Hospital, Thailand	Level III-2 Low-Moderate risk of bias	N = 33 episodes of MG crisis with respiratory failure among 26 patients Mean age ± SD (y): 44.4 ± 15.0 (range 20–75) Male: 9 (35%) Mean duration of MG prior to crisis ± SD (y): 2.9 ± 5.9 First crisis presented within 2 years after the diagnosis of MG in 68% of patients Comorbidities and associated disease: 13 patients (50%)	*Inclusion* Episodes of MG crisis between 1 June 2001 and 30 June 2006 in the study hospital were recruited retrospectively using the hospital database Diagnosis indeces using MG crisis and respiratory failure were searched for cases MG diagnosed by clinical features, electro-diagnostic test and therapeutic response to pyridostigmine Crisis defined as weakness of respiration that required respiratory assistance	IVIg dosed at 400 mg/kg/day for 5 days	PE, 3–5 cycles of volume exchange on alternate days	Duration of intubation Length of hospital stay Complications during hospital stay Discharge status *Statistical analysis* SPSS version 13 was used for data analysis Methods included unpaired t-test, Fisher's exact test, Pearson Chi-square (exact) test and Mann-Whitney U-test, where appropriate Statistical significance accepted at the p<0.05 level	*Funding* No statement regarding the funding of the study or any potential conflicts of interest were provided by the study authors
(Murthy et al. 2005) India	Retrospective cohort study *Objectives* Not stated	Level III-2 High risk of bias	N = 21 patients with 23 episodes of MG crisis Median age crisis onset: 40 years (range 28–75) Ratio of men to women 1.3:1. Median duration of the crisis episode: 11 days (range 7-39 days)	All patients with episodes of MG crisis identified from the case records of the patients with MG seen by the senior author	IVIg	PE	Duration of crisis episode Median intensive care unit stay Time to stabilisation/Median number of days for extubation Complications Mortality, crisis-related and all-cause *Statistical analysis* None reported	*Funding* The study authors reported that there were not sources of support to declare, nor any conflicts of interest

Study Country	Study design Study objectives	Level of evidence Quality	Study population	Eligibility criteria	Intervention	Comparator	Outcomes assessed Statistical analyses	Comments Funding source
(Panda et al. 2004) India	Retrospective cohort study *Objective* To study the demographic, clinical and treatment-related characteristics of patients who developed MG crisis and admitted to a tertiary care centre in India	Level III-2 Low risk of bias	N = 11 patients admitted to hospital with 12 episodes of MG crisis Mean age at presentation ± SD (y) = 39.8 ± 13.2 9 (range 22-66) 3:1 ratio M:F Median disease duration prior to MC: 20.02 + 22.93 months (median of 8 months, range 7 days–5 years) Concomitant medication to intervention/comparator: 100% AC, 75% pyridostigmine, 33% on neostigmine. 60% steroids, 42% azathioprine	*Inclusion* Patients admitted to the neurology ward and ICU with MG crisis from February 1999 to August 2001. Diagnosis of MG was based on evidence of muscle weakness, fatigability and diurnal fluctuation of symptoms, and clinical examination, supplemented by positive decrement response on repetitive nerve stimulation test and improvement with edrophonium or neostigmine testing.	3 (25%) episodes of MG crisis treated with IVIg Mean volume of plasma exchange per cycle was 854 mL(range, 600-980) per day	8 (66.7%) patients treated with PE 1/8 (12.5%) patients also received IVIg	Perceptible improvement of MG crisis (defined as the point of weaning off the ventilator) Proportions of patients able to walk unsupported and feed orally Mortality *Statistical analysis* None reported	*Funding* The study authors did not provide any statement regarding funding or potential conflicts of interest
(Qureshi et al. 1999) USA	Retrospective cohort study *Objective* To compare the efficacy and tolerance of PE and IVIg in the treatment of MG crisis	Level III-2 Moderate risk of bias	N = 54 episodes of MG 26 episodes among 24 patients with primary treatment of IVIg 28 episodes among 27 patients with primary treatment of PE Treatment based on local physician preference	*Inclusion* All patients with MG crisis who were treated with PE or IVIg in 4 US university-affiliated hospitals from January 1990 through December 1997. MG crisis characterised by acute episode of respiratory muscle weakness, defined by forced vital capacity ≤1.0 L, negative inspiratory force ≤20 cm H_2O, or requirement of mechanical ventilation Episodes of respiratory failure 6 months apart in the same patient were considered as separate episodes *Exclusion*	IVIg 400 mg/kg/day for 5 days Preparations included Gamimune N (Bayer, West Haven, CT), Gammagard (Baxter, Glendale, CA) and Sandoglobulin (Sandoz, East Hanover, NJ) Treatment prematurely terminated in 2 patients due to complications (n=2) or lack of response (n=1)	PE 5 or 6 cycles on alternate days 25–45 cc/kg of plasma exchanged per session Treatment prematurely terminated in 3 patients due to early recover (n=1) or complications (n=2)	*Outcomes recorded* 1. Clinical severity of disease graded before and 7 days after initiation of treatment using standard scoring system: MSS 2. Ventilatory status, 2 weeks after initiation of treatment, divided into three categories: a) intubated but unable to extubate after primary treatment; b) intubated but successfully extubated; and c) did not require intubation. 3. Functional outcome, 1 month after initiation of treatment, divided into five categories: a) dead; b) require mechanical ventilation; c) tracheostomy without	*Funding* Study authors reported no sources of funding, nor commented on conflicts of interest

Study Country	Study design Study objectives	Level of evidence Quality	Study population	Eligibility criteria	Intervention	Comparator	Outcomes assessed Statistical analyses	Comments Funding source
				Patients with perioperative respiratory crisis associated with thymectomy			mechanical ventilation; d) spontaneous breathing without tracheostomy but functional impairment (unable to resume baseline level of activity); e) spontaneous breathing without tracheostomy or functional impairment (complete resolution of admission symptoms). 4. Requirement for second treatment of IVIg or PE as determined by the primary physician because of complications, lack of response, or secondary worsening of symptoms.	
Indication 2 surgery preparation								
(Alipour-Faz et al. 2017) Iran	RCT (single centre, unblinded) *Objectives* To investigate the effectiveness of PE and IVIg in patients undergoing thymectomy	Level II moderate risk of bias	N = 24 Mean age ± SD (y): 36 ± 9.89 Female: 12 (50%)	*Inclusion* Adults with generalised MG & thymoma, positive AChRAb *Exclusion* Ocular MG, exacerbation due to current medications, infection, irregular medical treatment or dosage alterations, history of IVIg or albumin anaphylaxis, surgical contraindication	IVIg (1 g/kg/day for 2 consecutive days)	PE (1 L plasma 5 x with 5% albumin replacement fluid every other day)	Length of hospital stay Length of ICU stay Intubation period Duration of surgery Dose of steroid administered Incidence of myasthenic crisis *Statistical analysis* SPSS version 2.0 Comparison of independent variables with t test or Mann-Whitney U test. Chi-square used for some categorical variables	*Funding* No funding received
(Jensen & Bril 2008)	Comparative retrospective matched cohort *Objectives*	Level III-2 Low risk of bias	N = 18 Mean age ± SD (y): IVIg 46.0 ± 17.9; PE 44.5 ± 19.1 Female: 10 (56%)	*Inclusion* MG patients who underwent thymectomy between 2001 and 2006, requiring preoperative immunomodulation	IVIg	PE	Post-operative Osserman grade (determined at first post-operative neuromuscular clinic) Operative complications	Patients of the PE cohort were matched to the IVIg cohort of 9 identified in the

Study Country	Study design Study objectives	Level of evidence Quality	Study population	Eligibility criteria	Intervention	Comparator	Outcomes assessed Statistical analyses	Comments Funding source
	To compare the efficacy of IVIg and PE in thymectomy patients		Baseline Osserman grade 2: 56%; grade 3: 44%	*Exclusion* Osserman Grade 4, patients who received both IVIg and PE			Patients perceived treatment effect Side effects Length of hospital stay *Statistical analysis* Comparison of Osserman grade ordinal values using contingency table analysis	chart review of 105 MG patients referred for thymectomy *Funding* Unrestricted educational grant from Talecris Therapeutics
(Leuzzi et al. 2014) Italy	Retrospective cohort study *Objectives* To analyse factors affecting perioperative course, and predictors of post-thymectomy myasthenic crisis	Level III-2 Moderate risk of bias	N = 177 Mean age ± SD (y): 45.8 ±16.8 Osserman stage: I-IIA 29%, IIB 39%, III-IV: 11%	MG patients who underwent thymectomy identified in clinical records in the Department of Thoracic surgery at 'Agostino Gemelli' General Hospital	IVIg	PE Immunosuppressive therapy	Post thymectomy myasthenic crisis	*Funding* NR
Indication 3 maintenance								
(Barth et al. 2011) Additional data from (Barnett et al. 2013)	RCT (single centre, single blind with masked evaluators) *Objectives* To determine whether IVIg was comparable to PE for patients with worsening moderate to severe MG	Level II Low risk of bias	N = 84 LTF = 4 Mean age ± SD (y): IVIg 57 ± 18; PE 58 ± 17 Female: IVIg 24 (58%); PE 24 (55%) Baseline mean QMGS ± SD: IVIg 14.26 ± 4.0; PE 14.44 ± 3.88	*Inclusion* Adults (>18 y) with moderate to severe MG with QMGS >10.5 and worsening weakness sufficient to warrant change in treatment *Exclusion* Worsening secondary to concurrent medications (eg aminoglycosides) or infection, change in CS dosage in 2 weeks prior to treatment, Ig A deficiency, active renal or hepatic disease, significant cardiac disease, history of severe allergic response to IVIg or albumin, refractory to	IVIg (Gamunex®, Talecris Biotherapeutics) 1g/kg/day for 2 days	PE (Caridian Spectra) 1.0 plasma volume exchanges x 5	*Primary* Change in QMGS *Secondary* Change in QMGS at day 14, 21 &28 Clinical parameters SFEMG RNS Change in AChRAb titre Need for ICU Need for ventilation, intubation or hospitalisation MG-QOL-60 Adverse events Cost analysis	Follow-up: 14 days after treatment for primary, and 14, 21, 28 & 60 days for secondary outcomes *Funding* Talecris Biotherapeutics provided an unrestricted educational grant but had no role in developing the protocol,

Study Country	Study design Study objectives	Level of evidence Quality	Study population	Eligibility criteria	Intervention	Comparator	Outcomes assessed Statistical analyses	Comments Funding source
				IVIg or PE, poorly controlled hypertension, pregnancy, breastfeeding			Immunomodulation response predictors *Statistical analysis* JMP SAS version 5 ANOVA for repeated measures, ANCOVA and χ^2 for covariance and multi-variance analyses	evaluation or writing the results Drs Barth and Bril receive research support from Talecris Biotherapeutics
(Eienbröker et al. 2014) Germany	Retrospective case series with pre and post-treatment outcomes *Objectives* To observe clinical endpoints in MG patients in response to IVIg therapy	Level IV Low risk of bias	N = 16	*Inclusion* Incomplete response to standard long-term , high-dose IP therapy	IVIg	NA	*Primary* Change in QMG score	*Funding* NR
(Griffin et al. 2017b)	Abstract for an RCT with some data reported on clinicaltrials.gov NCT02473952	Level II Quality unknown	N = 62	MG patients who are symptomatic on standard of care treatment with a QMGS > 10 points at screening.	IVIg	placebo	Adverse events Mortality	Include data if necessary?? *Funding* Sponsor: Grifols Therapeutics LLC
(Hellmann et al. 2014) Israel	Case series with pre and post-treatment outcomes (retrospective cohort study of cases identified on a database) *Objectives* To assess the impact of IVIg on disease severity and course, to identify indications for IVIg	Level IV Low risk of bias	N = 52 Average age at start of IVIg (y): 46.0 Average age at onset (y): 43.1 Disease duration (y): 2.9 Females: 31 (60%)	*Inclusion* Patients of any MG class attending a single medical centre between Jan 1995 and 2012, failed to respond to other therapies or were contraindicated for them and therefore offered maintenance treatment with IVIg *Exclusion* NR	IVIg 2 g/kg over 5 days, followed by a maintenance dose of 0.4 g/kg every 3 to 6 weeks	NA	*Primary* Change in MGFA class Adverse events *Secondary* Change in concurrent drug therapy dose from before to after IVIG therapy *Statistical analysis* Bootstrapping to estimate the sample distribution	Follow-up: treatment period range was 1-17 years *Funding* NR

Study Country	Study design Study objectives	Level of evidence Quality	Study population	Eligibility criteria	Intervention	Comparator	Outcomes assessed Statistical analyses	Comments Funding source
(Liu et al. 2010) China	RCT (single centre, single blind) *Objectives* To compare IA and PE with IVIg for clinical efficacy in late onset MG, and determine whether AChRAb levels are correlated with QMGS	Level II Quality: moderate risk of bias	N = 40 Mean age ± SD (y): IVIg 53.2 ± 1.7; PE 55.2 ± 1.4; IA 57.2 ± 2.4 Mean age at onset ± SD (y): IVIg 52.7 ± 2.3; PE 51.8 ± 2.1; IA 54.5 ± 3.5 Female: IVIg 47%; PE 40%; IA 40% Baseline QMGS ± SD: IVIg 16.5 ± 1.7; PE 19.4 ± 2.2; IA 16.3 ± 2.0	*Inclusion* Patients with late-onset MG attending the Huashan hospital *Exclusion* NR	IVIg (0.4 g/kg/day for 5 days)	PE (3 x volume exchange of 2500-3000 mL, every 24-48 hours) IA (protein A column HWT-52/65)	*Primary* Change in AChRAb titre Change in QMGS Adverse effects Remission time Number of respiratory supports Length of hospital stay *Statistical analysis* Paired t-test for pre and post treatment outcomes Kruskal-Wallis test for changes between groups Pearson's correlation for relationship between AChRAb and QMGS	Late onset population All groups received concurrent PN treatment (0.6-0.8 mg/kg/d) Follow-up at 14 days *Funding* NR
(Liew et al. 2014) USA	Comparative retrospective cohort study *Objectives* To compare the efficacy of PE and IVIg for maintenance therapy in children and adolescents with MG	Level III-2 Moderate risk of bias	N = 33 Mean age at onset [Q1, Q3] (y): 8 [2,13] Female: 38 (70%) Treatments received: IVIg 26 (48%); PE 19 (35%); CS 17 (31%); PD 51 (94%)	*Inclusion* Children and adolescents with a diagnosis of juvenile MG who were seen in 3 Boston clinics between 1979 and 2012 and underwent medical treatments *Exclusion* NR	IVIg (1 g/kg for 1-2 daily treatments, every 2-3 weeks followed by a taper to complete withdrawal)	PE (3-5 plasma exchanges over 1-2 weeks, every 2-3 weeks followed by a taper to complete withdrawal)	*Primary* Objective physical exam (eg fatigability, MMT) Patient reported improvement Recovery per treatment Adverse events	Juvenile population Patients with ocular MG and generalised MG were separated for analysis Some patients receiving IVIg and PE treatments also received CS, PD, and/or thymectomy *Funding* Athena Diagnostics
(Nosadini et al. 2016) Australia	Case series with before and after treatment data	Level IV Moderate risk of bias	N = 12 Children who received IVIg for MG at a single hospital	*Inclusion* Given IVIg at the Children's Westmead hospital between	IVIg	NA	Change in disease severity (modified Rankin Scale, mRS)	*Funding* Post-graduate NHMRC

Study Country	Study design Study objectives	Level of evidence Quality	Study population	Eligibility criteria	Intervention	Comparator	Outcomes assessed Statistical analyses	Comments Funding source
	Objective To review current clinical practice in use of IVIg and paediatric neurology		Mean age at onset (for196 children with neuroimmunological conditions: 6y 5 mo Mean length of follow-up (range): 37.7 (4.5-123) mo	Jan 2000 and June 2014 for any paediatric indication *Exclusion* Non-neurological indications				scholarships & from Petre Foundation (Australia). Research funding from NHMRC, MS Research Australia, Star Scientific Assoc, University of Sydney & the Petre Foundation.
(Rønager et al. 2001) Denmark	RCT (crossover study) *Objective* To compare the efficacy of high-does IVIg treatment with PE in patients with moderate to severe, but stable, MG	Level II High risk of bias	N = 12 Mean age not reported, age range included 18–75 years	*Inclusion* Generalised moderate to severe MG on immunosuppressive treatment for at least 12 months Only patients in Osserman Classes 3 to 5 and with functional status 4 to 5 were include *Exclusion criteria* Known or suspected allergy against IVIg; hypogammaglobinemia; HIV antibody positive; impaired renal function; pregnancy; lactating or fertile women without use of acceptable contraception; psychosis; other major diseases	IVIg (Gammagard S/D from Baxter, Glendale, CA) 400 mg/kg body weight administered as 5% solution on 5 subsequent days Minimum duration of each infusion was 4 hours	PE Total of 5 treatments, with 1 given every other day Plasma volume exchanged during 3 hours equivalent to 5% body weight	*Primary outcomes* QMGS before and at follow-up visits after each treatment *Secondary* Adverse events *Statistical analysis* Time course of clinical effect assessed at 4, 8 and 16 weeks after each treatment course. Wilcoxon's sign test was used. 2-sided testing was performed denoting statistical significance only with p-values of 0.05 or less. The SPPSS 7.5.2 was used for analysis.	QMGS was assessed by one person who was blinded to treatment regimens *Funding* The study authors acknowledged that Baxter A/S supplied the blood products (Gammagard and albumin) and gave financial support
(Selcen et al. 2000) USA	Case series with before and after treatment data *Objective* To evaluate juvenile patients for	Level IV Moderate risk of bias	N = 10 Juvenile patients refractory to cholinesterase inhibitors, incomplete response to PE or	*Inclusion* Juvenile MG patients refractory to other treatments *Exclusion* NR	IVIg	NA	Change in functional status (University of Virginia modification of Osserman classification)	*Funding* NR

Study Country	Study design Study objectives	Level of evidence Quality	Study population	Eligibility criteria	Intervention	Comparator	Outcomes assessed Statistical analyses	Comments Funding source
	responses to and complications from IVIg		complications from or failure of steroids Age range: 2-18 y MG duration range: 1-180 mo					
(VanderPluym et al. 2013) Canada	Case series with before and after treatment data *Objective* To evaluate the incidence, clinical features, diagnostic and treatment trends of paediatric myasthenia in Canada	Level IV Moderate risk of bias	N = 34 Cases of PM identified through the Canadian paediatric Surveillance Program from Jan 2010 to Dec 2011 Age of onset: <3y 8; 3-6y 2; >6-9y 4; >9-12y 7; >12y 10; unknown 3	*Inclusion* Cases of generalised juvenile MG <18y, ≥1 of typical clinical features, or positive for other diagnostic testing *Exclusion* Underlying primary muscle, nerve or metabolic disease, transient neonatal myasthenia	IVIg	NA	Improvement	PM includes juvenile MG, congenital myasthenic syndromes and transient neonatal MG, Juvenile MG being the most common. *Funding* Tara and Bobby Disenhouse Fund, Myasthenia Gravis Ontario Chapter-Muscular Dystrophy Canada, Talecris Biotherapeutics, University of Alberta
(Wang et al. 2016) China	Case-control study *Objective* To analyse the comparative clinical effects of: Methylprednisolone + IVIg (observation group) Methylprednisolone (control group)	Level III-2 High risk of bias	N = 70 (35 patients per group) Mean age ± SD (y): observation 4 ± 1.5 (range 1–12) ; control 4.1 ± 1.7 (range 1.2–13) Male: observation 18 (5.14%); control 19 (54.3%) Disease duration: observation 1.5 months to	*Inclusion* Diagnostic basis for inclusion: Pathological fatigue and daily unstable manifestation of myasthenia as well as positive neostigmine test result At baseline all patients had AC for symptomatic treatment. The most frequently used AC at the study hospital was pyridostigmine, most commonly dosed at 5	MPN + IVIg (observation group) IV MPN 15-20 mg/kg/day (to max 1000 mg/day) for 3 to 5 days Oral PN 1.5-2 mg/kg/day for 1-2 months, reduced every 0.5-1 month IVIg (Chengdu Institute of Biological	IV MPN 15-20 mg/kg/day (to max 1000 mg/day) for 3 to 5 days Oral PN at 1.5–2 mg/kg/day for 1–2 months, reduced every 0.5–1 month according to patient condition until the minimum effective maintenance dose	*Primary effectiveness* Total effective rate (%) based on no. of patients showing a clinical improvement vs no clinical effect Improvement categories: 'Recovery', 'Basically cured', 'Evident effects', 'Improved' Total effective rate was calculated from composite measures of mean ± SD absolute (severity) scores	Children with MG *Assessment scales* The metric for determination of clinical absolute scores was not stated *Funding* NR Authors state that they have no

Study Country	Study design Study objectives	Level of evidence Quality	Study population	Eligibility criteria	Intervention	Comparator	Outcomes assessed Statistical analyses	Comments Funding source
			1 year; control 3 months to 1.5 years Juvenile MG Types: observation Type I = 15 (42.9%), Type II = 16 (45.7%), Type III = 4 (11.4%); control Type I = 16 (45.7%), Type II = 15 (42.9%), Type III = 4 (11.4%)	mg/kg/day (age <5 years) or 7 mg/kg/day (age ≥5 years), and 3 to 4 times per day for both groups Study authors state all patients were treated the same in all other respects, excepting the intervention and comparator treatments	Products) 0.4 g/kg/day, slow infusion, increasing over 5 days		before and after treatment *Other effectiveness outcomes* Duration of symptom relief (days) Length of hospital stay (days) *Safety* Adverse events No. patients requiring breathing machine/ventilator *Statistical analysis* Analysis using SPSS 17.0 statistical software (SPSS Inc., Chicago, IL, USA) Comparison between the groups tested by paired t test Enumeration data were tested by $\chi 2$	conflicts of interest
(Zinman, Ng & Bril 2007) Canada	Double blind, single centre RCT *Objective* To determine the effectiveness of IVIg compared with placebo in MG patients	Level II Low risk of bias	N = 51 Mean age ± SD: IVIg 56.0 ± 17.20, PE 55.0 ± 17.12 Baseline QMGS: IVIg < 10.5 45.8%, > 10.5 54.2%; PE < 10.5 44.4%, > 10.5 55.6%	*Inclusion* Adults with worsening weakness *Exclusion* Respiratory distress requiring ICU admission, severe swallowing difficulties, vital capacity < 1 L, change in corticosteroid dosage in 2 weeks prior to screening	IVIg (2g/kg over 2 days)	Placebo (IV dextrose 5% in water over 2 days)	*Primary* Change in QMGS *Secondary* SFEMG RNS AChRAb titre *Statistical analysis* X^2 or Fisher's exact test for categorical variables ANCOVA for covariance	Separate analysis performed in the moderate to high severity sub-population *Funding* Bayer/Talecris provided an unrestricted education grant for this study
Maintenance – Subcutaneous delivery								
(Beecher, Anderson & Siddiqi 2017) Canada	Case series with before and after data (prospective, open-label single-arm phase 3 pilot trial) *Objective*	Level IV Low risk of bias	N = 22 Age range (y): 22-83 Female: 16 (73%) Disease duration (mo): 1-480	*Inclusion* 18 y or older, mild to moderate MG, worsening symptoms (MGFA class I to II/III or class II to III) *Exclusion*	SCIg (2 g/kg infused sub-cutaneously at weekly intervals over 4 weeks in a dose escalating manner (Hizentra, CSL	NA	*Primary* QMGS *Secondary* Adverse events MMT MG-ADL	Follow-up weekly for 6 weeks *Funding* CSL Behring AG (Berne, Switzerland)

Study Country	Study design Study objectives	Level of evidence Quality	Study population	Eligibility criteria	Intervention	Comparator	Outcomes assessed Statistical analyses	Comments Funding source
	To assess the efficacy, safety and tolerability of SCIg in patients with mild to moderate MG			Respiratory distress requiring ICU admission or VC < 1L, severe swallowing difficulties with high risk of aspiration, change in CS in the 4 weeks prior to screening, IgA deficiency, pregnancy, breastfeeding, active renal or hepatic insufficiency, significant cardiac disease, worsening associated with infection, previous unresponsiveness to IVIg, MG crisis within last year	Behring AG, Berne Switzerland)		TSQM *Statistical analysis* X^2 or Fisher's exact test for categorical variables ANCOVA for covariance	Sponsors were not involved in the study design, data collection or analysis or publication preparation
(Bourque et al. 2016) Canada	Case series with before and after data (retrospective cohort study of cases identified on a database) *Objectives* To compare clinical response before and after initiation of SCIg, and Ig dosage between SCIg and IVIg	Level IV Low risk of bias	N = 9 Age range (y): 21-83 Female: 7 (78%) Disease duration prior to SCIg (y): 1.7-17	*Inclusion* Consecutive cases identified on The Ottawa Hospital Neuromuscular Disease Database between Jan and Dec 2015 *Exclusion* Renal insufficiency, abnormal liver function, history of thrombotic event or at high risk of thrombosis	SCIg (20 g/100 ml Hizentra, CSL Behring AG, Berne Switzerland)	IVIg (dosage comparison in 6 patients)	*Primary* MGFA class MG-ADL MG-QOL-15 *Secondary* VAS for overall subjective responsiveness Adverse events bases on hospital files	Disease status was MGFA class II for 3 patients and class III for 6 patients at baseline *Funding* The authors report there was no funding support

AC = anticholinesterase therapy; AChRAb = acetylcholine receptor antibodies; ANOVA = analysis of variance modelling; ANCOVA = analysis of covariance modelling CS = corticosteroid therapy; FVC = forced vital capacity; IA = immunoadsorption; IgA = immunoglobulin A; IVIg = intravenous immunoglobulin; LTF = lost to follow-up; MG-ADL = MG activities of daily living; MG-QOL-15/60 = myasthenia gravis quality of life 15 or 60 item score; MGFA = myasthenia gravis foundation of America clinical classification score; MMS = myasthenic muscular score (range 0 to 100 where 100 is normal); MMT = manual muscle test; mo = month; MPN = methylprednisolone therapy; mRS = modified Rankin Scale; MSS = myasthenia severity scale (total score range 0-16, where 16 is normal and 0 is most severe); NA = not applicable; NR = not reported; QMGS = quantitative myasthenia gravis score; PD = pyridostigmine therapy; PE = plasma exchange; PM = paediatric myasthenia; PN = prednisone therapy; RCT =randomised controlled trial; RNS = repetitive nerve stimulation; SCIg = sub-cutaneous immunoglobulin therapy; SD = standard deviation; TSQM = treatment satisfaction questionnaire for medication; VAS = subjective patient visual analogue scale; VC = vital capacity

APPENDIX D EVIDENCE PROFILE TABLES

Table 103 Safety evidence profile table for IVIg in MG patients in or at risk of crisis (*Criteria V3* Indication 1)

Question: How safe is IVIg for patients with MG?
Patient or population: Patients with moderate to severe MG in or at risk of myasthenic crisis
Intervention: IVIg; IVIg 1g/kg
Comparison: PE; IVIg, 2g/kg
Author(s): (Gajdos et al. 1997; Gajdos et al. 2005; Mandawat et al. 2010; Murthy et al. 2005; Panda et al. 2004; Pittayanon, Treeprasertsuk & Phanthumchinda 2009; Qureshi et al. 1999)

Quality assessment			Effect				GRADE	Importance
Outcome Comparison	**Participants Studies**	**Quality of evidence** Key: 0=not serious; -1=serious; -2=very serious	**Intervention result**	**Comparator result**	**Difference**	**Interpretation**		
Adverse events (% patients with an event) IVIg v PE	n=897 k=1 RCT, 5 Ret CoH	Risk of bias: -1[a] Inconsistency: 0 Indirectness: 0 Imprecision: 0 Other: confounding likely to give spurious effect	0%-19.2%	12.5%-46.4%	NA	Overall there were fewer AEs occurring in patients who received IVIg compared to PE	⊕⊕⊕⊖	CRITICAL
Adverse events (cumulative incidence) IVIg 1g/kg v IVIg 2g/kg	n=172 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Other: 0	40.48 ± 5.36	46.59 ± 5.32	P = 0.39	There was no difference in the number of AEs occurring between groups	⊕⊕⊕⊕	IMPORTANT

GRADE Working Group grades of evidence
⊕⊕⊕⊕ **High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
⊕⊕⊕⊖ **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
⊕⊕⊖⊖ **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
⊕⊖⊖⊖ **Very low quality:** We are very uncertain about the estimate.

AE = adverse event; IVIg = intravenous immunoglobulin therapy; MG = myasthenia gravis; NA = not applicable; PE = plasma exchange therapy; Ret CoH = retrospective cohort study; RCT = randomised controlled trial;

[a] Selection bias could not be ruled out

Table 104 Safety evidence profile table for IVIg in MG patients preparing for surgery (*Criteria V3* Indication 2)

Question: How safe is IVIg for patients with MG?
Patient or population: Patients with moderate to severe MG preparing for surgery
Intervention: IVIg
Comparison: PE
Author(s): (Alipour-Faz et al. 2017; Leuzzi et al. 2014)

Quality assessment			Effect				GRADE	Importance
Outcome **Comparison**	**Participants** **Studies**	**Quality of evidence** **Key: 0=not serious; -1=serious; -2=very serious**	**Intervention result**	**Comparator result**	**Difference**	**Interpretation**		
Adverse events (% patients intubated) IVIg v PE	n=24 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: -1[a] Other: confounding likely to give spurious effect	16.7%	58.3%	41.6% P = 0.04 95% CI 3.03, 67.0	Overall there were fewer AEs occurring in patients who received IVIg compared to PE	⊕⊕⊖⊖	CRITICAL
POMC IVIg v PE	n=78 k=1 Ret CoH	Risk of bias: -1[b] Inconsistency: 0 Indirectness: 0 Imprecision: 0 Other: confounding likely to give spurious effect	14.7%	22.7%	8.0% P = 0.38 95% CI -10.3, 24.5	There was no difference in the frequency of POMC occurring between groups	⊕⊕⊖⊖	IMPORTANT

GRADE Working Group grades of evidence
⊕⊕⊕⊕ **High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
⊕⊕⊕⊖ **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
⊕⊕⊖⊖ **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
⊕⊖⊖⊖ **Very low quality:** We are very uncertain about the estimate.

AE = adverse event; IVIg = intravenous immunoglobulin therapy; MG = myasthenia gravis; PE = plasma exchange therapy; POMC = postoperative myasthenic crisis; Ret CoH = retrospective cohort study; RCT = randomised controlled trial;

[a] Participant numbers were too small to make an accurate comparison
[b] Selection bias could not be ruled out

Table 105 Safety evidence profile table for IVIg in MG patients on maintenance therapy (*Criteria V3* Indication 3)

Question: How safe is IVIg for patients with MG?
Patient or population: Patients with moderate to severe MG needing to change maintenance therapy
Intervention: IVIg
Comparison: PE; placebo (standard therapies alone); no comparator
Author(s): (Barth et al. 2011; Beecher, Anderson & Siddiqi 2017; Bourque et al. 2016; Griffin et al. 2017b; Liew et al. 2014; Liu et al. 2010; Mandawat et al. 2010; Rønager et al. 2001)

Quality assessment			Effect				GRADE	Importance
Outcome Comparison	**Participants Studies**	**Quality of evidence** Key: 0=not serious; -1=serious; -2=very serious	**Intervention result**	**Comparator result**	**Difference**	**Interpretation**		
Adverse events (% patients with any event) IVIg v PE	n=1,034 k=3 RCTs, 1 Ret CoH	Risk of bias: -1[a] Inconsistency: 0 Indirectness: 0 Imprecision: 0 Other: confounding is likely to give spurious effect	6.67%-66.7%	11.4%-49%	NA	There was no difference in frequency between groups	⊕⊕⊕⊖	CRITICAL
Adverse events (% patients with any event) IVIg v placebo	n=62 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: -1[b] Imprecision: 0 Other: publication bias -1[c]	16.67%	12.5%	4.17% P = 0.64 95% CI -13.0, 22.7	There was no difference in frequency between groups	⊕⊕⊖⊖	CRITICAL
Adverse events (% patients with event) IVIg v PE in children	n=17 k=1 Ret CoH	Risk of bias: -1[d] Inconsistency: 0 Indirectness: 0 Imprecision: -1[c] Other: confounding is likely to reduce effect	20%	14.2%	-5.8% P = 0.64 95% CI -13.0%, 22.7%	There was no difference in frequency between groups. The participant numbers were too small to make any conclusions.	⊕⊕⊖⊖	CRITICAL
Adverse events (% patients with specific event) SCIg (no comparator)	n=62 k=2 CS	Risk of bias: -1[e] Inconsistency: 0 Indirectness: 0 Imprecision: 0	4.5%-77.3%	NA	NA	The least frequent event was dry cough, parathesias, tinnitus and fatigue. The most frequent event was headache.	⊕⊖⊖⊖	IMPORTANT

		Other: 0						

GRADE Working Group grades of evidence
⊕⊕⊕⊕ **High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
⊕⊕⊕⊖ **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
⊕⊕⊖⊖ **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
⊕⊖⊖⊖ **Very low quality:** We are very uncertain about the estimate.

CS = case series with before and after treatment data; IVIg = intravenous immunoglobulin therapy; MG = myasthenia gravis; NA = not applicable; PE = plasma exchange therapy; Ret CoH = retrospective cohort study; RCT = randomised controlled trial;

[a] Selection bias could not be ruled out in the cohort study
[b] Comparator may not be applicable
[c] Data available online only; no publication available yet
[d] The participant numbers were too small for an accurate comparison
[e] There was no valid comparator

Table 106 Effectiveness evidence profile table for IVIg in MG patients in or at risk of crisis (*Criteria V3* Indication 1)

Question: How effective is IVIg for patients with MG?
Patient or population: Patients with moderate to severe MG in or at risk of myasthenic crisis
Intervention: IVIg; IVIg 1g/kg
Comparison: PE; IVIg, 2g/kg
Author(s): (Gajdos et al. 1997; Gajdos, Chevret & Toyka 2012; Gajdos et al. 2005; Mandawat et al. 2010; Murthy et al. 2005; Pittayanon, Treeprasertsuk & Phanthumchinda 2009; Qureshi et al. 1999)

Quality assessment			Effect				GRADE	Importance
Outcome Comparison	**Participants Studies**	**Quality of evidence** **Key: 0=not serious; -1=serious; -2=very serious**	**Intervention result**	**Comparator result**	**Difference**	**Interpretation**		
Mortality (% patients) IVIg v PE	n=773 k=3 Ret CoH	Risk of bias: -1[a] Inconsistency: -1[b] Indirectness: 0 Imprecision: 0 Other: confounding is likely to give spurious effect	0.59%-12.5%	3.6%-6.7%	NA	Overall there were fewer deaths occurring in patients who received IVIg compared to PE, but suspicion of selection bias in one large cohort study prevents this result from being reliable	⊕⊕⊖⊖	CRITICAL
Infection rate (% patients with event)	n=778 k=3 Ret CoH	Risk of bias: -1[a] Inconsistency: 0	1.18%-11.1%	9.45%-21.4%	NA	Overall there were fewer infections occurring in patients	⊕⊕⊖⊖	CRITICAL

IVIg v PE		Indirectness: 0 Imprecision: -1[c] Other: confounding is likely to give spurious effect				who received IVIg compared to PE, but suspicion of selection bias in one large cohort study prevents this result from being reliable		
Change in MMS (change in score at 15 days from baseline) IVIg v PE	n=87 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Other: 0	15.6 ± 16.0	16.6 ± 16.0	Mean difference -1 95% CI -7.72, 5.72 P = 0 77	There was no difference in the change in MMS occurring between groups	⊕⊕⊕⊖	CRITICAL
Change in MMS (change in score at 15 days from baseline) IVIg 1g/kg v IVIg 2g/kg	n=168 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Other: 0	19.33 ± 16.48	15.49 ± 15.4	Mean difference 3.84 95% CI -0.98, 8.66 P = 0.12	There was no difference in the change in MMS occurring between groups	⊕⊕⊕⊕	IMPORTANT
Change in MSS (change in score at 14 days from baseline) IVIg v PE	n=54 k=1 Ret CoH	Risk of bias: -1[a] Inconsistency: 0 Indirectness: 0 Imprecision: 0 Other: confounding is likely to give spurious effect	2.8 ± 0.71	4.2 ± 0.57	NA	Improvement in symptoms from baseline was only statistically significant in the PE group although there was improvement in both groups	⊕⊕⊖⊖	IMPORTANT
Disease stability (mean days of intubation) IVIg v PE	n=54 k=2 Ret CoH	Risk of bias: -1[a] Inconsistency: 0 Indirectness: 0 Imprecision: 0 Other: 0	10 (range 7-39) – 10.3 ± 4.6	8 (range 7-12) – 12 ± 11.1	NA	There was no difference in the disease stability measured between groups	⊕⊕⊖⊖	IMPORTANT
Time to treatment response (median days to response) IVIg v PE	n=87 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Other: 0	15	9	RR = 0.67 95% CI 0.38, 1.18 P = 0.14	Time to treatment favoured PE but the difference was not statistically significant	⊕⊕⊕⊖	IMPORTANT

GRADE Working Group grades of evidence
⊕⊕⊕⊕ **High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
⊕⊕⊕⊖ **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
⊕⊕⊖⊖ **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
⊕⊖⊖⊖ **Very low quality:** We are very uncertain about the estimate.

IVIg = intravenous immunoglobulin therapy; MG = myasthenia gravis; MMS = myasthenia muscle score; MSS = myasthenia severity scale; NA = not applicable; PE = plasma exchange therapy; Ret CoH = retrospective cohort study; RCT = randomised controlled trial; RR = relative risk

[a] Selection bias could not be ruled out
[b] Direction of results was inconsistent across studies
[c] Description of event varied between studies

Table 107 Effectiveness evidence profile table for IVIg in MG patients preparing for surgery (*Criteria V3* Indication 2)

Question: How effective is IVIg for patients with MG?
Patient or population: Patients with moderate to severe MG preparing for surgery
Intervention: IVIg
Comparison: PE
Author(s): (Alipour-Faz et al. 2017; Jensen & Bril 2008)

Quality assessment			Effect				GRADE	Importance
Outcome Comparison	**Participants Studies**	**Quality of evidence** **Key: 0=not serious; -1=serious; -2=very serious**	**Intervention result**	**Comparator result**	**Difference**	**Interpretation**		
Change in Osserman grade (mean change in grade from baseline) IVIg v PE	n=18 k=1 Ret CoH	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: -1[a] Other: 0	0.78 ± 0.83	1.00 ± 0.71	P = 0.55	There was no difference detected between groups	⊕⊖⊖⊖	IMPORTANT
Change in QoL (% patients with perceived benefit from treatment) IVIg v PE	n=18 k=1 Ret CoH	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: -1[a] Other: 0	56%	100%	-46% P = 0.029 95% CI 4.75%, 73.0%	More patients perceived a benefit following PE treatment. Small patient numbers make this result unreliable.	⊕⊖⊖⊖	IMPORTANT
Intubation period (median hours) IVIg v PE	n=24 k=1 RCT	Risk of bias: -1[b] Inconsistency: 0 Indirectness: 0 Imprecision: 0	0 (2-22)	13 (2-216)	P = 0.01	Intubation period was significantly longer in the PE group. This result may be influenced by selection bias	⊕⊕⊖⊖	IMPORTANT

		Other: confounding likely to give spurious effect						
Rate of intubation (% patients intubated post-operatively) IVIg v PE	n=24 k=1 RCT	Risk of bias: -1[b] Inconsistency: 0 Indirectness: 0 Imprecision: 0 Other: confounding likely to give spurious effect	16.7%	58.3%	41.6% P = 0.039 95% CI 3.03%, 667%	Post-operative intubation was more likely to be required in the PE group. This result may be influenced by selection bias	⊕⊕⊖⊖	IMPORTANT

GRADE Working Group grades of evidence
⊕⊕⊕⊕ **High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
⊕⊕⊕⊖ **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
⊕⊕⊖⊖ **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
⊕⊖⊖⊖ **Very low quality:** We are very uncertain about the estimate.

IVIg = intravenous immunoglobulin therapy; MG = myasthenia gravis; PE = plasma exchange therapy; QoL = quality of life; Ret CoH = retrospective cohort study; RCT = randomised controlled trial;

[a] Participant numbers were too small for an accurate comparison
[b] Selection bias could not be ruled out

Table 108 Effectiveness evidence profile table for IVIg in MG patients on maintenance therapy (*Criteria V3* Indication 3)

Question: How effective is IVIg for patients with MG?
Patient or population: Patients with moderate to severe MG needing to change maintenance therapy
Intervention: IVIg
Comparison: PE; placebo (standard therapies alone)
Author(s): (Barnett et al. 2013; Barth et al. 2011; Beecher, Anderson & Siddiqi 2017; Bourque et al. 2016; Griffin et al. 2017b; Liew et al. 2014; Liu et al. 2010; Mandawat et al. 2010; Rønager et al. 2001; Wang et al. 2016; Zinman, Ng & Bril 2007)

Quality assessment			Effect				GRADE	Importance
Outcome **Comparison**	**Participants (n)** **Studies (k)**	**Quality of evidence** **Key: 0=not serious; -1=serious; -2=very serious**	**Intervention result**	**Comparator result**	**Difference**	**Interpretation**		
Mortality (% patients with event) IVIg v placebo	n=62 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: -1[a]	3.33%	0	3.33% P = 0.30 95% CI -7.7, 16.7	There was no difference in frequency between groups	⊕⊕⊖⊖	CRITICAL

		Imprecision: 0 Other: publication bias: -1[b]						
Infection rate (% patients with event) IVIg v PE	n=920 k=1 RCT, 1 Ret CoH	Risk of bias: -1[c] Inconsistency: 0 Indirectness: 0 Imprecision: 0 Other: confounding likely to give spurious effect	10-1.7%	1.63% - 8.3%-1	NA	There was no difference in frequency between groups	⊕⊕⊖⊖	CRITICAL
Change in QMGS (mean change in score from baseline to 14 days or % change from baseline) IVIg v PE	n=124 k=2 RCTs	Risk of bias: 0 Inconsistency: -1 Indirectness: 0 Imprecision: -1[d] Other: 0	3.2 ± 4.1 23.8 ± 3.7%	4.7 ± 4.9 60.8 ± 3.5%	P = 0.13 P < 0.01	The RCTs were inconsistent with their findings. One result appeared to favour PE but was not reliable.	⊕⊕⊖⊖	CRITICAL
Change in QMGS (mean change in score from baseline to 21 days) IVIg v PE	n=84 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Other: 0	3.3 ± 3.6	5.3 ± 5.5	P = 0.07	Symptom improvement favoured PE at 21 days but was not statistically significant.	⊕⊕⊕⊖	CRITICAL
Change in QMGS (mean change in score from baseline to 28 days) IVIg v PE	n=84 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Other: 0	2.6 ± 4.0	4.7 ± 5.7	P = 0.08	Symptom improvement favoured PE at 28 days but was not statistically significant.	⊕⊕⊕⊖	CRITICAL
Change in QMGS (change in score from baseline to day 14) IVIg v placebo	n=51 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: -1[a] Imprecision: 0[d] Other: 0	-2.54	-0.89	P = 0.03	There was greater symptom improvement in the IVIg group at 14 days. This outcome may show an incremental benefit of IVIg over standard therapies.	⊕⊕⊖⊖	IMPORTANT
Change in QMGS (change in score from baseline to day 28) IVIg v placebo	n=51 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: -1[a] Imprecision: -1[d] Other: 0	-3.00	-1.19	P = 0.055	The symptom improvement in the IVIg group at 28 days was not statistically significant. This outcome may show an incremental benefit of IVIg over standard therapies.	⊕⊕⊖⊖	IMPORTANT

Change in QoL (change in MG-QoL-60 from baseline to day 28) IVIg v PE	n=62 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Other: 0	-23 ± 32	-17 ± 23	P = 0.4	Improvement in QoL favoured IVIg but there was no statistical difference between groups	⊕⊕⊕⊖	CRITICAL
Rate of remission (days) IVIg v PE	n=30 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: -1[d] Other: 0	8.4 ± 1.54	6.7 ± 0.34	P < 0.01	Rate of remission favoured PE, but the participant number was small, making the result unreliable	⊕⊕⊖⊖	IMPORTANT
Rate of ventilation (% patients using assisted ventilation) IVIg v PE	n=30 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: -1[d] Other: 0	40%	13%	P < 0.05	Rate of ventilation favoured PE, but the participant number was small, making the result unreliable	⊕⊕⊖⊖	IMPORTANT
Response to treatment in children (% children who responded measured with non-standardised tools) IVIg v PE	n=17 k=1 Ret CoH	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: -1[d] Other: 0	50%	100%	P = 0.04	Response in children was better for those given PE. This result may be unreliable due to non-standardised tools and small participant numbers	⊕⊕⊖⊖	CRITICAL
Change in absolute score in children (mean change from baseline) IVIg + MPN v MPN alone	n=70 k=1 Ret CoH	Risk of bias: -1[e] Inconsistency: 0 Indirectness: -1[a] Imprecision: 0 Other: 0	12.98 ± 7.33	8.84 ± 7.27	P < 0.05	Symptom improvement favoured IVIg in this outcome but may be unreliable due to poor study quality This outcome may show incremental benefit of IVIg over standard therapy.	⊕⊕⊖⊖	IMPORTANT
Rate of remission in children (% children recovered) IVIg v placebo	n=70 k=1 Ret CoH	Risk of bias: -1[e] Inconsistency: 0 Indirectness: -1[a] Imprecision: -1c Other: 0	25.7%	14.3%	P = 0.23	There was no difference in frequency between groups. The result may be unreliable due to poor study quality This outcome may show incremental benefit of IVIg over standard therapy	⊕⊕⊖⊖	IMPORTANT
Need for life support systems in children (% children needing breathing support)	n=70 k=1 Ret CoH	Risk of bias: -1[e] Inconsistency: 0 Indirectness: -1[a] Imprecision: 0	5.71%	8.57%	P = 0.67	There was no difference in frequency between groups. The result may be unreliable due to poor study quality This outcome	⊕⊕⊖⊖	IMPORTANT

IVIg v placebo		Other: 0				may show incremental benefit of IVIg over standard therapy		
Change in QMGS (change from baseline to week 6) SCIg (no comparator)	n=22 k=1 CS	Risk of bias: -2[f] Inconsistency: 0 Indirectness: 0 Imprecision: 0 Other: 0	5.1	NA	NA	There was improvement at week 6 but no conclusion can be made from this result	⊕⊖⊖⊖	IMPORTANT
Change in MMT (change from baseline to week 6) SCIg (no comparator)	n=22 k=1 CS	Risk of bias: -2[f] Inconsistency: 0 Indirectness: 0 Imprecision: 0 Other: 0	12.6	NA	NA	There was improvement at week 6 but no conclusion can be made from this result	⊕⊖⊖⊖	IMPORTANT
Change in MGC (change from baseline to week 6) SCIg (no comparator)	n=22 k=1 CS	Risk of bias: -2[f] Inconsistency: 0 Indirectness: 0 Imprecision: 0 Other: 0	3.9	NA	NA	There was improvement at week 6 but no conclusion can be made from this result	⊕⊖⊖⊖	IMPORTANT
Change in QoL (change in MG-ADL from baseline to week 4) SCIg (no comparator)	n=31 k=2 CS	Risk of bias: -2[f] Inconsistency: 0 Indirectness: 0 Imprecision: 0 Other: 0	2.1-3.6	NA	NA	There was improvement at week 4 but no conclusion can be made from this result	⊕⊖⊖⊖	IMPORTANT

GRADE Working Group grades of evidence
⊕⊕⊕⊕ **High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
⊕⊕⊕⊖ **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
⊕⊕⊖⊖ **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
⊕⊖⊖⊖ **Very low quality:** We are very uncertain about the estimate.

CS = case series; IVIg = intravenous immunoglobulin therapy; MG = myasthenia gravis; MG-ADL = myasthenia gravis activities of daily living score; MGC = myasthenia gravis composite score; MG-QoL-60 = myasthenia quality of life score – 60 questions; MMS = myasthenia muscle score; MMT = manual muscle test; MPN = methylprednisolone; PE = plasma exchange therapy; NA = not applicable; QMGS = quantitative myasthenia gravid score; QoL = quality of life; Ret CoH = retrospective cohort study; RCT = randomised controlled trial; SCIg = subcutaneous immunoglobulin therapy

[a] Comparator may not be applicable
[b] Data available online only; no publication available yet
[c] Selection bias could not be ruled out in the cohort study
[d] The participant numbers were too small for an accurate comparison
[e] Poor study design
[f] This outcome had no comparator

APPENDIX E EXCLUDED STUDIES

Studies that met the inclusion criteria on full text analysis, but were subsequently excluded are listed under reason for exclusion.

Duplicated data

Bril, V, Barnett-Tapia, C, Barth, D & Katzberg, HD 2012, 'IVIG and PLEX in the treatment of myasthenia gravis', Article, vol. 1275, no. (Bril V., vera.bril@utoronto.ca; Barnett-Tapia C.; Katzberg H.D.) Department of Medicine (Neurology), University Health Network, University of Toronto, Toronto, ON, Canada, pp. 1-6, DOI: 10.1111/j.1749-6632.2012.06767.x,<http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L366344246

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APPENDIX F CRITERIA FOR MG INDICATIONS 1-3 (NBA CRITERIA, VERSION 3)

Indication 1: Myasthenic crisis as an alternative treatment to plasma exchange

Initial Qualifying Criteria:

Myasthenic crisis with respiratory insufficiency requiring intubation and assisted ventilation.

OR

Patient at risk of myasthenic crisis displaying symptoms of respiratory insufficiency such as persistent difficulty with speech, difficulty chewing or swallowing and/or shortness of breath on minimal activity.

AND

Clinical assessment confirms severe disability as measured by a Myasthenia Gravis Composite (MGC) score of at least four points.

Indication 2: MG prior to surgery and/or thymectomy in patients with advanced disease, bulbar symptoms or respiratory involvement, as an alternative treatment to plasma exchange

Initial Qualifying Criteria:

Surgery is planned.

AND

The patient has advanced MG disease, bulbar symptoms and/or respiratory involvement.

Indication 3: As maintenance therapy for moderate to severe MG when other treatments have been ineffective or caused intolerable side effects.

Initial Qualifying Criteria:

The patient has moderate to severe MG as assessed by a Myasthenia Gravis Composite (MGC) score of at least four points.

AND

At least two other treatments are ineffective, are contraindicated, unavailable or caused intolerable side effects.

Qualifying postscript

IVIg should be regarded as a stopgap treatment while using short-term drugs such as pyridostigmine and while introducing effective immunotherapy.

IVIg should be used for 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.

Documentation of clinical effectiveness is necessary for continuation of IVIg therapy.

Source: National Blood Authority (National Blood Authority, . 2018)

For Indications 1 and 3, a clinical assessment must confirm a moderate to severe disability using the Myasthenia Gravis Composite (MGC) score, of at least four points. The MGC score is calculated from a 10 question clinical assessment questionnaire (seen in Appendix A).

For access to ongoing Ig treatment for patients using it as maintenance therapy (indication 3), the criteria are listed below.

On review of the initial authorisation period

Improvement in fatigability and weakness as measured by a Myasthenia Gravis Composite (MGC) score of at least three points less than the qualifying score

OR

The patient with severe disease continues to report improvement in symptoms and disability post infusion, with end-of-cycle deterioration

AND

At least two other treatments are being prescribed concurrently

OR

Unable to be prescribed two other treatments concurrently, including:

- Anticholinesterases
- Corticosteroids
- Azathioprine
- Methotrexate
- Cyclophosphamide
- Cyclosporin
- Mycoplenolate mofetil
- Monoclonal antibodies
- Plasma exchange
- Thymectomy

On review of a continuing authorisation period

Stability in fatigability and weakness as measured by a Myasthenia Gravis Composite (MGC) score compared to the previous review and less than the qualifying score

OR

The patient with severe disease continues to report improvement in symptoms and disability post infusion, with end-of-cycle deterioration

AND

At least two other treatments being prescribed concurrently

OR

Unable to be prescribed two other treatments concurrently, including:

- Anticholinesterases
- Corticosteroids
- Azathioprine
- Methotrexate
- Cyclophosphamide
- Cyclosporin
- Mycoplenolate mofetil

- Monoclonal antibodies
- Plasma exchange
- Thymectomy

AND

A trial of weaning/cessation of Ig therapy is planned for patients who are clinically stable to identify those in remission or a reason provided as to why a trial is not planned

Source: National Blood Authority (National Blood Authority, . 2018)

Table 109 Estimation of Ig costs

2017/18 Ig Report	Price in $(m)	Grams (weight,%)	Price/gram in $	Reference to Ig report 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 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: Calculation for price: Total domestic price – Evogam price Calculation for grams: Total domestic grams – Evogam grams
Imported IVIg Flebogamma Privigen	124	2,759,266 (45.0%)	44.94	Table 6: Calculation for price: Total imported price – Hizentra price 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: NBA (2019)

RESULTS CALCULATION TABLES

A table of the dissagregated resource use (uncosted) for each of the cost analyses, including trial-based and stepped analyses is presented below.

Table 110 Indication 1 Trial based resource use (Gajdos 1997)

Resources	IVIg 3 doses	IVIg 5 doses	PE
IVig procurement	97g	162g	-
PE replacement Albumin 4%	-	-	6.75L
PE replacement diluent (Gelatin)			6.75L
Hospital admission	1	1	1

*hospital admission cost captures medical/nursing staffing, consumables, co-administered therapies and management of adverse effects

Table 111 Indication 1 Stepped resource use to replicate Australian practice

Resources (disaggregated)	IVIg	PE
Step 1: Australian doses and fluids (historical)		
IVIg product	230g	
PE tubing and equipment depreciation		4 administrations
PE replacement Albumin 4%		8L
PE replacement diluent FFP		8L
Hospital admission	1	1
Step 2: Assuming retreatment in treatment failure		
IVIg Retreatment (4.88% of PE patients)		11.22g (=0.0488*230g)
Step 3: Assuming updated PE fluid protocol		
100% PE replacement fluid: Albumin 4%		Add 8L
Remove FFP		Remove 8L
Step 4: Adding the costs of treating adverse events		
Retroperitoneal Haematoma (in 2.44% of patients)		2.44% x $22,576 (Table 74)
Femoral Thrombosis (in 2.44% of patients)		2.44% x $2,427 (Table 74)

Table 112 Indication 2 Trial-based resource use (Alipour-Faz, 2017)

Resources	IVIg	PE
IVIg product	162g	
PE replacement fluid (Albumin 4%)		5L
Outpatient Tx administrations (pre-admission)	2	5
Thymectomy Operating Theatre costs	1	1.17
Other hospitalisation (for surgery) costs	1	1

Table 113 Indication 2 Stepped analysis resource use (base case)

Resources	IVIg	PE
IVIg product	156g	
PE replacement fluid (Albumin 4%)		5L
Outpatient Tx administrations (pre-admission)	2	5
Thymectomy Operating Theatre costs	1	1.17
Other hospitalisation (for surgery) costs	1	1

Table 114 Indication 3 Stepped analysis resource use (base case)

Year	Resource Type	IVIg			PE		Surgery	Cyclophosphamide	Rituximab	All other pharmaceuticals
		NBA usage	Low dose	High dose	Low intensity maintenance	High intensity maintenance				
Yr 1 Induction	Administration	-	2	2	5 exchanges	5 exchanges	Pre-surgery IVIg or PE (av)	6 chemo admin (4 weekly x 6 months)	2 OPD administrations	
	Procurement	-	2 x 81g = 162g IVIg	2 x 81g = 162g IVIg	3L x 5 exchanges = 15L Albumin 4%	3L x 5 exchanges = 15L Albumin 4%		6 x 2g vials	1g x2	Annual dose*
	Procedures	-	-	-	5% Fistula placement, 95% Port placement	5% Fistula placement, 95% Port placement	1 Episode			
	Monitoring	-	-	-	-	-		CBE, LFT x 7		Annual monitoring pattern*
Yr 1 Remainder	Administration	-	8	12	6 exchanges (≈ 1 every 6 weeks)	17 exchanges (≈ 1 every 3 weeks)		6mths oral immunosuppressant (eg azathioprine)	-	
	Procurement	-	8 x 32.4g = 259.2g	12 x 81g = 972g	6x 3L Albumin 4%	17x 3L Albumin 4%			-	
	Monitoring	-	-	-	-	-			-	
Ongoing years of maintenance	Administration	11 (≈ every 4-6 weeks)	9 (≈ every 6 weeks)	13 (≈ every 4 weeks)	8 (≈ 1 every 6 weeks)	18 (≈ 1 every 3 weeks)			1 OPD administrations	
	Procurement	492g IVIg	9x 32.4g = 291.6g	13x 81g =1,053g	24 L Albumin 4%	105L Albumin 4%		oral immunosuppressant (eg azathioprine)	1g	Annual dose*
	Procedures or Monitoring	-	-	-	32% of patients replace vascular access device	32% of patients replace vascular access device				Annual monitoring pattern*
Pattern	-	Distribution of NBA patients assumed to represent long-term average	Years 2+ all costed as maintenance	Years 2+ all costed as maintenance	Years 2+ all costed as maintenance	Years 2+ all costed as maintenance	All costs are incurred year 1	Years 2+ all costed as maintenance	Maintenance dosing every 2 years	Identical resource use each year

Table 115 Indication 3 Stepped analysis resource costs (base case)

Year	Resource Type	IVIg			PE		Surgery	Cyclophosphamide	Rituximab	All other pharmaceuticals
		NBA usage	Low dose	High dose	Low intensity maintenance	High intensity maintenance				
Yr 1 Induction	Administration	-	$922	$922	$6,210	$6,210	$8,500	$5,118	$922	
	Procurement	-	$9,786	$9,786	$2,055	$2,055		$940.56	$6,178	Annual dose*
	Procedures	-	-	-	$1,791	$1,791	$38,835			
	Monitoring	-	-	-				$242.55		Annual monitoring pattern*
Yr 1 Remainder	Administration	-	$3,688	$5,532	$7,452	$21,114		$982	-	
	Procurement	-	$15,658	$58,718	$2,466	$6,987			-	
Maintenance Years	Administration	$5,071	$4,149.00	$5,993	$9,936	$22,356		$1,964	$461	
	Procurement	$29,722	$17,615	$63,611	$3,288	$7,398			$3,089	Annual dose*
	Monitoring or procedures	-	-	-	$471	$471				Annual monitoring pattern*
Total Year 1		$0.00	$30,054.69	$74,958.52	$19,974	$38,157	$47,335.00	$6,301.11	$7,100.00	
Total Other		$34,792.72	$21,764.56	$69,604.73	$13,695	$30,225	$0	$0	$3,550	
Pattern	-	NBA usage represents ongoing average	Years 2+ all costed as maintenance	Years 2+ all costed as maintenance	Years 2+ all costed as maintenance	Years 2+ all costed as maintenance	All costs are incurred year 1.	Years 2+ all costed as maintenance	Maintenance dosing every 2 years	Identical resource use each year

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