2017 (v3.0) Proposed changes to v2.1 of the Criteria for the clinical use of intravenous immunoglobulin in Australia

| **v2.1 CONDITION NAME: Rasmussen syndrome****v3.0 CONDITION NAME: Rasmussen encephalitis** |
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| **PROPOSED APPROACH:****To retain Rasmussen encephalitis in *Exceptional circumstances only* with changes as outlined**  | **SUMMARY OF RATIONALE:** The recommended changes are supported by factors including that:* Evidence supports that immunomodulatory treatment with Ig therapy is associated with improved outcomes (reduces/ delays seizure, motor and cognitive deteriorations), and early treatment has been shown to yield the best results. The role of Ig therapy is to slow the progressive deterioration during the acute phase, if possible, although, some patients may not respond due to the aggressive nature of their disease and hemispherectomy may still be the best option.
* The European Consensus statement (Bien, 2005) defining diagnostic criteria has been applied to the qualifying criteria for access to Ig therapy.
* Ig therapy is used in combination with corticosteroids where there is a significant level of disability
* National Ig usage indicates that usage is increasing in line with recent published evidence (Varadkar, 2014), and given that demand may further increase, appropriate qualifying and review criteria should be applied to determine that a slowing of the rate of deterioration is demonstrated in response to Ig therapy.
* Given that the active inflammatory phase of twelve to eighteen months is followed by a residual phase of disease, a trial of weaning is to be considered once neurological deficits stabilise.
* This condition is listed as a ‘blue’ condition (medium priority for long term use) in the UK NHS immunoglobulin guidelines (UK Department of Health, 2011), and is also listed in the Canadian IVIg Utilisation Management guidelines (Ontario Regional Blood Coordinating Network, 2016).
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| **v2.1 CONDITION CATEGORY:** Condition for which Ig use is inExceptional circumstances only (Chapter 7)**v3.0 CONDITION CATEGORY:** Condition for which Ig use is inExceptional circumstances only (Chapter 7) |
| **Role of Ig therapy:** Most commonlyoccurring in children under ten years old,this condition is associated with intractable unilateral seizures and progressive development of hemiparesis or weakness and intellectual dysfunction. There is an active progressive phase, often lasting years, followed by quiescence with no further progression. Conventional anticonvulsant medication is ineffectual and historical literature reports seizure cessation only after hemispherectomy. However, with the recognition that this is an autoimmune process, evidence supports treatment with more aggressive immune therapies resulting in improved clinical outcomes and avoiding the side effects of surgery in a subgroup of patients (permanent motor deficits and cognitive impairments). It is acknowledged, however that for some patients, surgery is still ultimately required. Early treatment with immunosuppressive medication includes steroids with IVIg concurrently (or plasmapheresis which may not be clinically appropriate) and additional agents including tacrolimus and natulizumab. The role of Ig therapy is to slow the progressive deterioration during the acute phase, if possible. Where patients do not respond due to the aggressive nature of their disease, hemispherectomy may be the best option. |

| **ITEM** | **CRITERIA v2.1**  | **PROPOSED REVISIONS TO THE CRITERIA** | **SPECIALIST WORKING GROUP RATIONALE FOR ADDITIONS/CLARIFICATIONS** |
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| **Condition Name** | Rasmussen syndrome | Rasmussen encephalitis | Amendment to the condition name to more accurately reflect the inflammatory nature of the disease. |
| **Specialty** | Neurology | Neurology | No change |
| **Category** | *Exceptional circumstances only*  | *Exceptional circumstances only*  | No change |
| **Specific Conditions** |  |  | No change |
| **Level of Evidence** | Evidence of probable benefit – more research needed (Category 2a) |  Evidence of probable benefit – more research needed (Category 2a) | No change |
| **Justification for Evidence Category** |   | A number of retrospective case series, open label studies and one randomized controlled study (Bien et al, 2012) between 1996 and 2013. Hart YM et al (1996), Granata et al (2003) and Takahashi (2013) have reported benefit from immunomodulatory treatments including pulse steroids, IVIg, PE and tacrolimus. Benefit was seen in regard to reduced tissue and function loss and reduced chance of intractable epilepsy. A single case report described a good outcome with natulizumab (Bittner S et al, 2013). Early therapies may yield the best outcomes. Varadkar et al (2014) reported that immunomodulatory treatments seem to slow rather than halt disease progression without changing the eventual outcome. Patients are often left with intractable epilepsy for which functional hemispherectomy remains the only effective cure. | Justification of evidence section has been drafted in line with the literature. |
| **Indications** |   | **Rasmussen encephalitis with concurrent steroid therapy unless contra-indicated** | The indication has been agreed by Specialist Working Group consensus after consulting the literature.  |
| **Description and Diagnostic Criteria** | Rasmussen syndrome is a chronic, progressive, focal encephalitis that is commonly accompanied by focal seizures, hemiparesis and cognitive decline. It is generally considered to be a disease of childhood, with most cases occurring in children younger than 10 years, although adult onset cases do occur. Conventional anticonvulsant therapy is usually ineffective and hemispherectomy may be helpful in the correct setting.Immunomodulatory therapy may be useful and, of the different therapies, intravenous immunoglobulin (IVIg) may be most useful. Other therapies to consider include methylprednisolone and rituximab.Ongoing supply of IVIg would be based on evidence of stabilisation of either seizure frequency or cognitive decline. |  Rasmussen encephalitis is a chronic, progressive, focal encephalitis that is commonly accompanied by focal seizures, hemiparesis and cognitive decline. It is generally considered to be a disease of childhood, with most cases occurring in children younger than 10 years, although adult onset cases do occur. Conventional anticonvulsant therapy is usually ineffective and hemispherectomy may be helpful in the correct setting.Generally there is an active progressive phase of the disease, often lasting some years, followed by quiescence and no further progression of disease. (Varadkar et al, 2014). Although historical data has generally reported seizure freedom only after functional hemispherectomy, some centres practise more aggressive immune therapies and report improved outcomes. Functional hemispherectomy provides the best opportunity of seizure freedom, however there will inevitably be post-surgical motor deficits, and often cognitive impairments post-hemispherectomy. Therefore it can be argued that aggressive early immune therapy may reduce the surgical sequelae of motor and cognitive deficits (The decision regarding when and if to perform hemispherectomy is challenging and discussed in Figure 4 of Varadkar et al (2014). | The description and diagnostic criteria section has been updated to reflect the findings of more recently published evidence on disease presentation, progression and management. |
| **Diagnosis is required** |   | Yes | By which specialty | Neurology  | The Specialist Working Group recommends that the diagnosis should be limited to Neurologists as this rare neurological condition is usually managed by neurologists.  |
| **Diagnosis must be verified** |  | By which specialty |  |
| **Exclusion Criteria** |   |  |  |
| **Qualifying Criteria** |  | * Clinical features, EEG and MRI findings consistent with a diagnosis of Rasmussen encephalitis per the European Consensus Statement (Bien, 2005)

OR* Two of typical clinical features, MRI changes or histopathology findings consistent with a diagnosis of Rasmussen encephalitis per the European Consensus Statement (Bien, 2005)

AND * Significant level of disability as measured by a Modified Rankin Score of at least 3 points

AND * Concurrent steroid therapy

OR* Steroid therapy is contraindicated.
 | Qualifying criteria have been based on the European Consensus Statement (Bien, 2005) and Specialist Working Group consensus. Supporting evidence items include relevant objective measures to confirm that the criteria have been met. The modified Rankin Scale has been adapted to provide a standard method of assessment for disability. Ig therapy should be given concurrently with steroid therapy unless contraindicated. |
| **Review Criteria** |   | Review by a Neurologist is required within 6 months of treatment and annually thereafter. It is recognised that the acute phase of Rasmussen encephalitis can last for at least 12 months followed by stabilisation of symptoms and residual disease. The aim of Ig therapy is to reduce the trajectory of deterioration in a progressive disease. (Varadkar et al, 2014). Some patients will have aggressive and refractory disease, and in these cases hemispherectomy may be the preferred option (discussed in figure 4, Varadkar et al, 2014). For patients on maintenance treatment, review by a Neurologist is required at least annually. It is recognised that patients will typically reach a stabilisation phase eighteen months to two years from onset, at which time, a trial of weaning should be considered. Documentation of clinical effectiveness is necessary for continuation of IVIg therapy. **On review of the initial authorisation period**Clinical effectiveness of Ig therapy can be demonstrated by: * Reduction in the rate of deterioration or stabilisation of symptoms and disability compared to the qualifying assessment

**On review of a continuing authorisation period** Clinical effectiveness of Ig therapy can be demonstrated by: * Reduction in the rate of deterioration or stabilisation of symptoms and disability compared to the previous review assessment

AND * A trial of Ig weaning is planned for patients who have entered the residual stage of disease (permanent and stable neurologic deficits and continuing seizures) or a valid reason provided as to why a trial is not being planned or is contra-indicated at this time.
 | Review criteria have been developed to ensure appropriate use of immunoglobulin and to support a reduction in the rate of deterioration. The Specialist Working Group noted that the usual approach of assessing measurable benefit by improvement may not apply to all patients during the acute phase. While a number of patients may improve in the acute phase, it is recognised that some will continue to deteriorate however, Ig will slow the rate of deterioration. A drop down list of relevant values will allow the Neurologist to report the clinical outcome as well as a description of current symptoms being reported.  |
| **Dose** | Refer to the current product information sheet for further information.The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient. | **Induction Dose – 2 g/kg in divided doses over 2 to 5 days** **Maintenance Dose -1 g/kg monthly as a single dose**The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**Refer to the current product information sheet for further information on dose, administration and contraindications.** | Dosing has been defined.  |

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| **References****(most recent update: March 2016)** |
| Bien CG, Granata T, Antozzi C, et al (2005) Pathogenesis, diagnosis and treatment of Rasmussen encephalitis: a European consensus statement. *Brain*, 128:454–71. <https://www.ncbi.nlm.nih.gov/pubmed/15689357>Bien CG, Tiemeier H, Sassen R, Kuczaty S, Urbach H, von Lehe M, et al (2013) Rasmussen encephalitis: incidence and course under randomized therapy with tacrolimus or intravenous immunoglobulins. *Epilepsia*, 54(3):543-50.<https://www.ncbi.nlm.nih.gov/pubmed/23216622>Bittner S, Simon OJ, Gobel K, Bien CG, Meuth SG, Wiendl H (2013) Rasmussen encephalitis treated with natalizumab. *Neurology,* 81:395–397.<https://www.ncbi.nlm.nih.gov/pubmed/23794679>Caraballo RH, Fortini S, Cersósimo R, Monges S, Pasteris MC, Gomez M, et al (2013) Rasmussen syndrome: an Argentinean experience in 32 patients. *Seizure*, 22(5):360-7. <https://www.ncbi.nlm.nih.gov/pubmed/23466213>Feasby T, Barnwell B, Benstead T, et al (2007) Guidelines on the Use of Intravenous Immune Globulin for Neurologic Conditions Transfusion Medicine Reviews, 21(2):S57-S107.Hart YM, Andermann F, Fish DR, Dubeau F, Robitaille Y, Rasmussen T, et al (1997) Chronic encephalitis and epilepsy in adults and adolescents: a variant of Rasmussen's syndrome? *Neurology*, 48(2):418-24.<https://www.ncbi.nlm.nih.gov/pubmed/9040732>Ontario Regional Blood Coordinating Network (2016). Ontario Intravenous Immune Globulin (IVIG) Utilization Management Guidelines, Version 3.0. [online]. Available at: http://transfusionontario.org/en/download/ontario-intravenous-immune-globulin-IVIg-utilization-management-guidelines-2/.Takahashi Y, Yamazaki E, Mine J, Kubota Y, Imai K, Mogami Y, et al (2013) Immunomodulatory therapy versus surgery for Rasmussen syndrome in early childhood. *Brain Dev*, 35(8):778-85. <https://www.ncbi.nlm.nih.gov/pubmed/23433490>UK Department of Health (2011) Clinical Guidelines for Immunoglobulin Use: Second Edition Update. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment\_data/file/216671/dh\_131107.pdfUK Department of Health (2011) Clinical Guidelines for Immunoglobulin Use: Second Edition Update: Summary Poster. Available at: https://www.igd.nhs.uk/wp-content/uploads/2016/04/DemandManagementPoster\_v4\_February2016.pdfVaradkar S, Bien CG, Kruse CA, Jensen FE, Bauer J, Pardo CA, et al (2014) Rasmussen's encephalitis: clinical features, pathobiology, and treatment advances. *Lancet Neurol*ogy, 13(2):195-205. <https://www.ncbi.nlm.nih.gov/pubmed/24457189> |

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| **POTENTIAL OPERATIONAL IMPACT** |
| The revised criteria provide significantly greater guidance for access to Ig therapy and patient management and neurologists will be required to diagnose and manage patient treatment. There will be increased data entry required (e.g. compliance with the international consensus diagnostic criteria) compared to the previous Ig request process. Patients will be required to be assessed at qualifying and review using a Modified Rankin Scale, however, the scale will be presented as ‘drop-down’ menu options within BloodSTAR v3.0 and will be simple to apply. A trial of weaning from Ig therapy will be considered after eighteen months and once patients have stabilised symptoms.  |
| **POTENTIAL IMPACT ON PATIENTS, DEMAND AND EXPENDITURE** |
| **Description of impact on patients:** | There is not anticipated to be any significant impact on patients as a result of these criteria given that they are based on how neurologists already diagnose and manage patients with Rasmussen encephalitis. The formal access criteria now proposed for this condition require that a neurologist makes the diagnosis and manages the patient treatment. This is because this disease is very rare, can be misdiagnosed and it is important that the correct treatment is given. It is now recognised that an immune process may be causing inflammation of the brain and that early treatment with strong anti-immune medications can result in better long term outcomes in some patients. Ig therapy is one of a number of treatments that can be used, and when prescribed, is given with other treatment concurrently. For existing patients on Ig maintenance therapy, annual reviews are required to assess the effectiveness of the treatment to stabilise symptoms, and the degree of disability. Given that patients will already require regular review by their neurologist, this requirement will not place an added burden on patients. If Ig therapy has not been effective, it will be ceased as a different treatment should be used. A trial of reducing dose and then stopping Ig therapy will be considered by doctors after eighteen months of treatment and when patients are well and stable as it is recognised that the acute (immune) phase of disease lessens after this time and other ongoing treatments will be more effective. New patients authorised to receive ongoing Ig therapy will require an initial check after the first six months of Ig treatment to confirm that Ig therapy is effective. If improvement has been demonstrated after six months ongoing treatment, Ig therapy will be continued; otherwise a different treatment would be required. The ongoing arrangements for maintenance therapy are as outlined above for existing patients. |
| **Impact on demand** | The slight increase in demand over the last few years may be in response to the recognition of the important role of immune therapies in this rare and devastating condition. The revised criteria will better ensure that future use is controlled and clinically appropriate. Demand for this condition is expected to continue to follow the current trend.There is not expected to be any material impact on overall demand as a result of these recommended changes.  |
|  | **2011-12** | **2012-13** | **2013-14** | **2014-15** | **2015-16** | The Specialist Working Group estimated magnitude of effect:No impact against projected demand |
| **Patient number** | **0** | **11** | **10** | **16** | **19** |
| **Total Grams issued** | **0** | **3,443** | **3,724** | **5,249** | **7,131** |
| **% Total Grams issued** | **0.00%** | **0.1%** | **0.09%** | **0.12%** | **0.14%** |
| **Specialist Working Group knowledge development opportunities and recommendations relevant to the transition to v3.0** |
| None identified at this stage.  |

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| **END OF PUBLIC CONSULTATION DOCUMENT****Next review: Twelve to eighteen months from BloodSTAR v3.0 implementation** |