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

<table>
<tr><td colspan="2">v2.1 and PUBLIC CONSULTATION CONDITION NAME: Anti-neutrophil cytoplasmic antibody (ANCA) [Proteinase 3 (PR3) or myeloperoxidase (MPO)] - positive systemic necrotising vasculitis
PREVIOUS PUBLIC CONSULTATION NAME: Anti-neutrophil cytoplasmic antibody (ANCA) [Proteinase 3 (PR3) or myeloperoxidase (MPO)]- positive systemic necrotising vasculitis
v3.0 CONDITION NAME: Anti-neutrophil cytoplasmic antibody (ANCA) [Proteinase 3 (PR3) or myeloperoxidase (MPO)]- positive systemic necrotising vasculitis</td></tr>
<tr><td>Anti-neutrophil cytoplasmic antibody (ANCA) [Proteinase 3 (PR3) or myeloperoxidase (MPO)] - positive systemic necrotising vasculitis was endorsed by NIGAC and JBC in 2015 to retain as a condition for which Ig has an Emerging therapeutic role. Since that time, the need for further review has been identified and has now been completed as part of the current Specialist Working Group work program.

PROPOSED APPROACH:

To move Anti-neutrophil cytoplasmic antibody (ANCA) [Proteinase 3 (PR3) or myeloperoxidase (MPO)]- positive systemic necrotising vasculitis from Emerging therapeutic role to Exceptional circumstances only with the changes as outlined.</td><td>SUMMARY OF RATIONALE:

The recommended changes are supported by factors including that:

- The role of Ig therapy in the treatment of ANCA will change and become reduced since Rituximab has been approved on the Pharmaceutical Benefits Schedule for the treatment of ANCA associated systemic vasculitis (AASV). This has occurred since the last NIGAC and JBC submission.
- This change has triggered modification to the eligibility criteria and also the recommendation to designate as a condition for which Ig should be used in exceptional circumstances only.
- While AASV can be potentially life threatening, first, second and third line treatments include potent immunosuppressant therapies in combination with corticosteroids, and when such medications are contra-indicated or side effects become intolerable, Ig therapy has a small but important role to play to achieve remission or treatment of refractory or relapsing disease in these patients.
- The criteria have been developed to ensure that Ig therapy is only accessed after failure to respond to treatment with Corticosteroids, Rituximab and two other immunosuppressant agents unless contra-indicated and or, side effects have become intolerable.
- This condition is included as a ‘grey’ or low priority in the Clinical Guidelines for Ig Use of the United Kingdom (UK Department of Health, 2011) which is equivalent to Chapter 7 in Australia, and is not listed in the Canadian national IVIg Utilisation Management Guidelines (Ontario Regional Blood Coordinating Network, 2016), although it is understood that local provincial funders may still approve rare conditions.</td></tr>
<tr><td colspan="2">v2.1 CONDITION CATEGORY: Condition for which Ig has an emerging therapeutic role (Chapter 6)

v3.0 CONDITION CATEGORY: Condition for which Ig is used in exceptional circumstances only (Chapter 7)</td></tr>
</table>

Role of Ig therapy: Ig is considered to have a limited role in the treatment of ANCA, given that first, second and third line therapy involves treatment with corticosteroids and potent immunosuppressant medications. Given that Rituximab is now available on the PBS in Australia, it is considered that all patients with refractory disease should have undertaken a trial of Rituximab therapy and that three months should have lapsed to confirm non-responsiveness prior to any request being made for Ig therapy. The number of patients expected to not respond to Rituximab is expected to be very low. The ongoing role for Ig therapy will be limited to those patients with refractory AASV failing to respond to available alternative treatments or in whom such treatments are contraindicated or side effects have become intolerable.

Different mechanisms of action have been proposed to explain the benefits of Ig on autoimmune diseases, including neutralisation of circulating antibodies, modulation of Fc receptor expression on leukocytes and endothelial cells, interaction with complement proteins, modulation of the synthesis and release of cytokines and chemokines or interaction with other cell surface molecules expressed on lymphocytes and monocytes. The exact mechanism of action in AASV is unknown.

ITEM	2015 JBC APPROVED WORDING	PROPOSED REVISIONS TO THE CRITERIA	SPECIALIST WORKING GROUP RATIONALE FOR ADDITIONS/CHANGES
Condition Name	**Anti-neutrophil cytoplasmic antibody (ANCA) [Proteinase 3 (PR3) or myeloperoxidase (MPO)]-positive systemic necrotising vasculitis**	**Anti-neutrophil cytoplasmic antibody (ANCA) [Proteinase 3 (PR3) or myeloperoxidase (MPO)]-positive systemic necrotising vasculitis**	No change
Specialty	Rheumatology, Immunology	Rheumatology ; Immunology	No change
Category	*Emerging therapeutic role*	*Exceptional circumstances only*	
Specific Conditions	Anti-neutrophil cytoplasmic antibody (ANCA) [Proteinase 3 (PR3) or myeloperoxidase (MPO)]- positive systemic necrotising vasculitis ANCA (PR3 or MPO)-positive idiopathic rapidly progressive	Anti-neutrophil cytoplasmic antibody (ANCA) [Proteinase 3 (PR3) or myeloperoxidase (MPO)]- positive systemic necrotising vasculitis ANCA (PR3 or MPO)-positive idiopathic rapidly progressive glomerulonephritis Eosinophilic granulomatosis with polyangiitis (Churg-Strauss Syndrome)	No change

ITEM	2015 JBC APPROVED WORDING	PROPOSED REVISIONS TO THE CRITERIA	SPECIALIST WORKING GROUP RATIONALE FOR ADDITIONS/CHANGES
	glomerulonephritis Eosinophilic granulomatosis with polyangiitis (Churg-Strauss Syndrome) Granulomatosis with polyangiitis (Wegener Granulomatosis) Microscopic polyangiitis	Granulomatosis with polyangiitis (Wegener Granulomatosis) Microscopic polyangiitis	
Level of Evidence	Evidence of probable benefit (Category 2a).	Evidence of probable benefit - more research needed (Category 2a)	No change
Justification for Evidence Category	The Biotext (2004) review found one randomised trial of 34 patients and one case series of 7 patients with ANCA-associated systemic vasculitis (AASV). Different AASVs were represented in the studies. The Biotext (2004) review concluded that there is possible benefit in the treatment of AASV with IVIg if disease activity persists after standard therapy.	The Biotext (2004) review found one randomised trial of 34 patients and one case series of 7 patients with ANCA-associated systemic vasculitis (AASV). Different AASVs were represented in the studies. The Biotext (2004) review concluded that there is possible benefit in the treatment of AASV with IVIg if disease activity persists after standard therapy. However, in recent years, there have been a number of randomised controlled trials demonstrating the effectiveness of immunosuppressants and biologicals in achieving remission and treating relapsing and refractory disease. In particular, Rituximab is now considered a mainstay of treatment, and is now available on the Australian Pharmaceutical Benefits Schedule (PBS). The publication of the evidence based British Guidelines in 2014 for treatment of ANCA in adults, do not include Ig therapy. It is recognized that Rituximab is more effective	Additional paragraph added to incorporate recent literature, recent availability of Rituximab on the PBS and the position of the 2014 British ANCA Guidelines that do not include Ig therapy. These emphasise the increasingly limited role for Ig therapy in the management of ANCA associated vasculitis.

ITEM	2015 JBC APPROVED WORDING	PROPOSED REVISIONS TO THE CRITERIA	SPECIALIST WORKING GROUP RATIONALE FOR ADDITIONS/CHANGES
		than Cyclosporine in refractory disease and if the patient has not had previous treatment with Rituximab, then it is the first choice. Ig therapy is only indicated in patients who have failed to respond to increased doses of immunosuppressants and a further trial of Rituximab, or in those in whom these therapies are contraindicated.	
Indications	ANCA positive systemic necrotising vasculitis failing to respond to corticosteroids and cytotoxic immunosuppression Relapse in ANCA positive systemic necrotising vasculitis resistant following response to Ig therapy	**ANCA positive systemic necrotising vasculitis failing to respond to corticosteroids and cytotoxic immunosuppression** **Relapse in ANCA positive systemic necrotising vasculitis resistant following response to Ig therapy**	No change
Description and Diagnostic Criteria	ANCA associated systemic necrotising vasculitides are life-threatening immune-mediated inflammatory diseases comprising one of four clinical syndromes: 1. Granulomatosis with polyangiitis (Wegener Granulomatosis); 2. Microscopic polyangiitis; 3. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss Syndrome);	ANCA associated systemic necrotising vasculitides are life-threatening immune-mediated inflammatory diseases comprising one of four clinical syndromes: 1. Granulomatosis with polyangiitis (Wegener Granulomatosis); 2. Microscopic polyangiitis; 3. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss Syndrome); 4. ANCA (PR3 or MPO)-positive idiopathic rapidly progressive glomerulonephritis. In these cases the ANCA specificity is directed against the neutrophil cytoplasmic antigens PR3 and MPO. ANCA that lack MPO or PR3 specificity tend to be non-specific. Biopsy of affected tissue is required to establish the diagnosis.	The revised wording was reviewed and agreed by Specialist Working Group consensus.

ITEM	2015 JBC APPROVED WORDING	PROPOSED REVISIONS TO THE CRITERIA			SPECIALIST WORKING GROUP RATIONALE FOR ADDITIONS/CHANGES
	4. ANCA (PR3 or MPO)-positive idiopathic rapidly progressive glomerulonephritis. In these cases the ANCA specificity is directed against the neutrophil cytoplasmic antigens PR3 and MPO. ANCA that lack MPO or PR3 specificity tend to be non-specific. Biopsy of affected tissue is required to establish the diagnosis. Standard combinations of corticosteroids and cytotoxic immunosuppression are generally effective at controlling disease, but relapses are common. IVIg has a limited role as one of several therapeutic options in relapsing disease	Standard combinations of corticosteroids and cytotoxic immunosuppression are generally effective at controlling disease, but relapses are common.			
Diagnosis is required	Yes : Rheumatologist Immunologist	Yes	By which specialty	Rheumatologist Immunologist Nephrologist	Nephrologist has been added because it is recognised that some patients (with renal manifestations) may be treated by nephrologists.
Diagnosis must be verified	No	No	By which specialty		

ITEM	2015 JBC APPROVED WORDING	PROPOSED REVISIONS TO THE CRITERIA	SPECIALIST WORKING GROUP RATIONALE FOR ADDITIONS/CHANGES
Exclusion Criteria	First line or initial treatment for ANCA.	First line or initial treatment for ANCA.	No change
Qualifying Criteria	**ANCA positive systemic necrotising vasculitis failing to respond to corticosteroids and cytotoxic immunosuppression** • Evidence of active MPO or PR3 positive vasculitis confirmed by serology and an ANCA level above the normal reference range unless negative ANCA level with active vasculitis AND • At least two reactive indicators when assessed by Birmingham Vasculitis Activity Score (BVAS) version 3 (v3) (score > 5), Erythrocyte Sedimentation Rate (ESR) (score >5) and C-reactive protein (CRP) (score >6). AND • Persistent disease despite standard Corticosteroid therapy for 6 months unless steroid therapy is contraindicated AND • A trial of Rituximab has failed to demonstrate a response unless	**ANCA positive systemic necrotising vasculitis failing to respond to corticosteroids and cytotoxic immunosuppression** • Active MPO or PR3 positive vasculitis confirmed by serology and an ANCA level above the normal reference range OR • Negative ANCA level with active vasculitis AND • Persistent active disease as assessed by at least two reactive indicators of: Birmingham Vasculitis Activity Score (BVAS) version 3 (v3), Erythrocyte Sedimentation Rate (ESR) and C-reactive protein (CRP) AND • Persistent disease despite standard Corticosteroid therapy for six months OR • Corticosteroid therapy is contraindicated AND • No response at least three months after a trial of treatment with Rituximab OR • Rituximab is contraindicated AND • At least two other immunosuppressant agents	Given the recent listing on the PBS, a trial of Rituximab is now mandatory for all patients with at least three months from the last dose of Rituximab now required to lapse before assessing that there has been no response to that agent prior to qualifying for Ig therapy.

ITEM	2015 JBC APPROVED WORDING	PROPOSED REVISIONS TO THE CRITERIA	SPECIALIST WORKING GROUP RATIONALE FOR ADDITIONS/CHANGES
	Rituximab is inaccessible or contraindicated AND • At least two other immunosuppressant agents have been trialled in addition to steroids and Rituximab unless immunosuppressant medication is contraindicated **Note:** The initial authorisation period is six months only. The reporting of clinical outcome data after six months treatment is strongly encouraged as a demonstrated clinical response to Ig therapy is required for eligibility for further authorisation, should the patient relapse in the future. **Relapse in ANCA positive systemic necrotising vasculitis resistant following response to Ig therapy** • Patient has previously demonstrated a clinical	have been trialled in addition to corticosteroids and Rituximab OR • Immunosuppressant medication is contraindicated **Note:** The initial authorisation period is six months only. The retention of clinical outcome data following six months treatment is strongly encouraged as the reporting of demonstrated clinical response to Ig therapy is required for eligibility for further authorisation, should the patient relapse in the future. **Relapse in ANCA positive systemic necrotising vasculitis resistant following response to Ig therapy** • Current evidence of active vasculitis as assessed by increased reactivity in at least one of ESR, CRP, ANCA, BVAS or another indicator of active disease AND • Unresponsive to previous Rituximab therapy OR • Rituximab is contraindicated AND • A description of the relapse and current active vasculitis requiring treatment is provided AND • Clinical improvement in response to six months of Ig treatment was demonstrated previously as measured by a reduction in at least one of	

ITEM	2015 JBC APPROVED WORDING	PROPOSED REVISIONS TO THE CRITERIA	SPECIALIST WORKING GROUP RATIONALE FOR ADDITIONS/CHANGES
	response following six months Ig therapy as measured by a reduction in at least one of Erythrocyte Sedimentation Rate (ESR), C-reactive protein (CRP) or ANCA level or Birmingham Vascular Activity Score (BVAS) version 3 (v3) compared to the original qualifying value. AND • A description of the patient's previous response to therapy is provided AND • The patient has evidence of active vasculitis as assessed by increased reactivity in at least one of ESR, CRP, ANCA or BVAS compared to level after Ig therapy. AND • A description of the relapse and active vasculitis requiring treatment is provided	Erythrocyte Sedimentation Rate (ESR), C-reactive protein (CRP) or ANCA level or Birmingham Vascular Activity Score (BVAS) version 3 (v3) or another indicator of active disease compared to pre-treatment levels AND • A description of the patient's clinical response to previous Ig therapy is provided	The criteria wording for the relapse indication has been streamlined and simplified to more clearly explain the requirement for the patient to have already demonstrated a clinical response to the initial Ig therapy, and confirm the patient's non-responsiveness to Rituximab.
Review Criteria	**ANCA positive systemic necrotising vasculitis failing to respond to corticosteroids and cytotoxic immunosuppression**	**ANCA positive systemic necrotising vasculitis failing to respond to corticosteroids and cytotoxic immunosuppression** Six-month's treatment is authorised for patients in the	The review criteria have been simplified and streamlined but content is largely unchanged. Patients will still only receive six month's treatment initially, and will then be required to requalify under the relapse

ITEM	2015 JBC APPROVED WORDING	PROPOSED REVISIONS TO THE CRITERIA	SPECIALIST WORKING GROUP RATIONALE FOR ADDITIONS/CHANGES
	Six-month's treatment is authorised for patients in the first instance, and no review is required. The reporting of clinical outcome data is encouraged as demonstrated clinical response to Ig therapy is required for eligibility for further authorisation, should the patient relapse in the future. **Outcome measures** Evidence of clinical benefit and response to treatment is assessed by a reduction in at least one indicator of: • Erythrocyte Sedimentation Rate (ESR) • C-reactive protein (CRP) level • ANCA Level or Birmingham Vasculitis Activity Score (BVAS) (<50% **Relapse in ANCA positive systemic necrotising vasculitis resistant following response to Ig therapy** Six monthly review by rheumatologist or clinical immunologist is required to assess	first instance. The reporting of clinical outcome data is encouraged as demonstrated clinical response to Ig therapy is required for eligibility for further authorisation, should the patient relapse in the future. Clinical effectiveness of Ig therapy may be demonstrated by: • Reduction in at least one indicator of Erythrocyte Sedimentation Rate(ESR) C-reactive protein (CRP) level, ANCA Level or Birmingham Vasculitis Activity Score (BVAS) (<50%) or other indicator of active disease compared to the qualifying value **Relapse in ANCA positive systemic necrotising vasculitis resistant following response to Ig therapy** Six monthly review by a rheumatologist or clinical immunologist or nephrologist is required to assess evidence of clinical benefit. Once the patient has been in clinical remission for two years after relapse, cessation of Ig therapy should be considered **On review of an initial authorisation period** Clinical effectiveness of Ig therapy may be demonstrated by: • Reduction in at least one indicator of Erythrocyte Sedimentation Rate (ESR), C-reactive protein (CRP) level, ANCA level or Birmingham Vasculitis Activity (BVAS) Score or other indicator of active disease compared to the qualifying value	indication if more treatment is required.

ITEM	2015 JBC APPROVED WORDING	PROPOSED REVISIONS TO THE CRITERIA	SPECIALIST WORKING GROUP RATIONALE FOR ADDITIONS/CHANGES
	evidence of clinical benefit. Once the patient has been in clinical remission for two years after relapse, cessation of Ig therapy should be considered **On review of an initial authorisation period** • Patients demonstrate evidence of clinical benefit and response to treatment as assessed by reduction in at least one indicator of Erythrocyte Sedimentation Rate (ESR), C-reactive protein (CRP) level, ANCA level or Birmingham Vasculitis Activity (BVAS) Score compared to the original qualifying value. **On review of a continuing authorisation period** Once the patient has been in clinical remission for two years, a trial off therapy should be considered. • Patients demonstrate evidence of clinical benefit and response to Ig treatment as assessed by	AND • Improvement in clinical symptoms in response to Ig treatment **On review of a continuing authorisation period** Once the patient has been in clinical remission for two years, a trial off therapy should be considered. Clinical effectiveness of Ig therapy may be demonstrated by: • Stabilisation of at least one indicator of Erythrocyte Sedimentation Rate (ESR), C-reactive protein (CRP) level, ANCA level or Birmingham Vasculitis Activity (BVAS) Score or other indicator of active disease compared to the previous review score AND • A trial off Ig therapy is planned following two years in remission unless a valid reason is provided	

ITEM	2015 JBC APPROVED WORDING	PROPOSED REVISIONS TO THE CRITERIA	SPECIALIST WORKING GROUP RATIONALE FOR ADDITIONS/CHANGES
	stabilisation of at least one indicator of Erythrocyte Sedimentation Rate (ESR), C-reactive protein (CRP) level, ANCA level or Birmingham Vasculitis Activity (BVAS) Score compared to the previous review score AND • A trial off Ig therapy is planned unless a valid reason is provided.		
Dose	Induction Dose - 2 g/kg in divided doses Maintenance 0.4-1g/Kg 4 to 6 weekly **Dosing above 1 g/kg per day is contraindicated for some IVIg products.** **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.**	**ANCA positive systemic necrotising vasculitis failing to respond to corticosteroids and cytotoxic immunosuppression** **Induction Dose –** 2 g/kg in divided doses **Maintenance Dose -** 0.4-1g/Kg 4 to 6 weekly 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. **Relapse in ANCA positive systemic necrotising vasculitis resistant following response to Ig therapy** **Induction Dose -** 2 g/kg in divided doses	Dosing is unchanged from the previous submission. The script "Dosing above 1 g/kg per day is contraindicated for some IVIg products" has been removed as it does not apply to Immunoglobulin current products and prescribers should be encouraged to review the product insert regarding infusion instructions and patient safety precautions**.**

ITEM	2015 JBC APPROVED WORDING	PROPOSED REVISIONS TO THE CRITERIA	SPECIALIST WORKING GROUP RATIONALE FOR ADDITIONS/CHANGES
		Maintenance Dose: 0.4-1g/Kg 4 to 6 weekly 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.	

References

(most recent update: May 2016)

Biotext (2004). Summary data on conditions and papers: A systematic literature review and report on the efficacy of intravenous immunoglobulin therapy and its risks. Commissioned by the National Blood Authority on behalf of all Australian Governments, pp. 248–50. Available at: http://www.nba.gov.au/pubs/pdf/report-lit-rev.pdf.

Foster R, Rosenthal E, Marques S, Vounotrypidis P, Sangle S and D'Cruz D (2006). Primary systemic vasculitis: treatment of difficult cases. *Lupus*, 15(3):143–7.

https://www.ncbi.nlm.nih.gov/pubmed/16634367

Jayne DR and Rasmussen N (1997). Treatment of antineutrophil cytoplasm autoantibody-associated systemic vasculitis: initiatives of the European Community Systemic Vasculitis Clinical Trials Study Group. *Mayo Clinic Proceedings*, 72(8):737–47.

http://www.mayoclinicproceedings.org/article/S0025-6196(11)63594-5/abstract

Jayne DR, Chapel H, Adu D, Misbah S, O'Donoghue D, Scott D et al. (2000). Intravenous immunoglobulin for ANCA-associated systemic vasculitis with persistent disease activity. *Quarterly Journal of Medicine*, 93(7):433–9.

https://www.ncbi.nlm.nih.gov/pubmed/10874052

Jayne DR, Davies MJ, Fox CJ, Black CM and Lockwood CM (1991). Treatment of systemic vasculitis with pooled intravenous immunoglobulin. *Lancet*, 337(8750):1137–9.

https://www.ncbi.nlm.nih.gov/pubmed/1674023

Jennette JC, Falk RJ, Andrassy K, Bacon PA, Churg J, Gross WL, et al. (2004). Nomenclature of systemic vasculitides: proposal of an international consensus

conference. *Arthritis & Rheumatism*, 37(2): 187–92 (Chapel Hill Consensus criteria).

https://www.ncbi.nlm.nih.gov/pubmed/8129773

Ntatsaki E, Carruthers D, Chakravarty K, D'Cruz D, Harper L, Jayne D, et al. on behalf of the British Society for Rheumatology and British Health Professionals in Rheumatology Standards, Guidelines and Audit Working Group (2014). BSR and BHPR guideline for the management of adults with ANCA-associated vasculitis. *Rheumatology*, 53: 2306-2309.

https://www.ncbi.nlm.nih.gov/pubmed/24729399

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/.

Orange JS, Hossny EM, Weiler CR, Ballow M, Berger, M, Bonilla, FA, et al. (2006). Use of intravenous immunoglobulin in human disease: A review of primary evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. *Journal of Allergy and Clinical Immunology*, 117(4):S525–53.

https://www.ncbi.nlm.nih.gov/pubmed/16580469

Smith RM, Jones RB and Jayne DRW (2012). Progress in treatment of ANCA-associated vasculitis. *Arthritis Research & Therapy*, 410:210.

https://www.ncbi.nlm.nih.gov/pubmed/22569190

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.pdf

UK 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.pdf

POTENTIAL OPERATIONAL IMPACT	
The investigations used to assess active inflammation in these criteria are routinely performed on this group of patients and should not be an additional burden or cost. While there will be a burden to the data entry required in requesting Ig therapy for this condition, it is considered important in the assessment of eligibility. It is recognised that BVAS is complex to use and largely a measure applied to clinical trials, so it has been introduced as one option for the assessment of clinical response. A communication plan will be developed to support the transition process to the revised criteria. For example, • All patients will need to have failed a trial of Rituximab (unless contraindicated) and three months must have lapsed since the last dose to determine non- responsiveness prior to becoming eligible for Ig therapy. • Patients will only receive six month's treatment initially, and will then be required to requalify under the relapse indication if more treatment is required. • After two years in remission, patients will be required to trial off Ig therapy. • Both Induction and maintenance dosing levels have now been defined with the upper limit of maintenance dose being 1 g/kg rather than the 2 g/kg currently. Any patients receiving 2 g/kg monthly will be identifiable and will need to be weaned to the lower dose by the prescriber prior to implementation.	
POTENTIAL IMPACT ON PATIENTS, DEMAND AND EXPENDITURE	
Description of impact on patients:	Since the revised criteria were proposed, a superior alternative treatment (Rituximab) has become available to treat all patients with AASV. While most patients will respond to Rituximab, and/or the other available alternative therapies, if patients don't respond, or these medications are contra-indicated or side effects become intolerable, Ig therapy has a small but important role to play to help achieve remission or treat refractory or relapsing disease. As a result, while fewer patients will need to receive Ig therapy, it will remain available to those that do need it. While most patients will be treated by clinical immunologists or rheumatologists, nephrologists (kidney doctors) have been added to the diagnosing and treating specialists as this condition may involve the kidney. If existing patients receiving Ig therapy have not already been treated with Rituximab (and Rituximab treatment is not contraindicated), a trial with Rituximab should be undertaken, as it has been proven to achieve superior clinical outcomes in patients and is a more cost effective therapy that has been made available under the Pharmaceutical benefits Scheme (PBS). Patients already on Ig maintenance therapy that have been unresponsive to Rituximab, will already be undergoing regular review by their treating specialist and six monthly checks will be required to confirm that Ig therapy continues to be an effective treatment. If Ig therapy is not effective in controlling the disease, Ig therapy will be stopped and substituted with an alternative treatment approach. The reviews of how well Ig therapy is treating the disease can be done as part of the specialist's usual monitoring process so will not place an added burden on patients. A trial of

	reducing dose and then stopping Ig therapy will be considered by doctors after patients have been in remission for at least two years. If those patients relapse after Ig therapy has been stopped, a further request for treatment can be made. For new patients authorised to receive Ig therapy, an initial six months Ig treatment will be given and most will respond with improvement in disease. If new patients do not show improvement after the first six months Ig therapy, a different treatment approach will be required. After the first six months treatment, there will be a period without Ig treatment to test whether patients are in remission. If new patients initially improve and then relapse once Ig treatment has been stopped, a further request to restart ongoing Ig therapy can be made. Patients will qualify for maintenance Ig therapy provided improvement in disease had been confirmed after the initial six months Ig therapy, and the arrangements for maintenance therapy will be the same as outlined above for existing patients on Ig therapy.
Impact on demand	Given that Rituximab is already approved on the PBS and is considered to be a superior alternative therapy to Ig, it is anticipated that Ig therapy will only be used for patients where Rituximab treatment has failed and/or immunosuppressant medication is contraindicated. While the revised criteria will enforce this practice (which would lead to a reduction in use for this condition compared to the data below), the trend to lower use is likely to have already commenced prior to v3.0 being implemented. However, it is acknowledged that currently under v2.1, there is no limitation to six month's treatment and few barriers to eligibility.

	2011-12	2012-13	2013-14	2014-15	2015-16	The Specialist Working Group estimated magnitude of effect:
Patient number	**23**	**30**	**20**	**20**	**24**	
Total Grams issued	**4,156**	**5,707**	**5,552**	**3,461**	**5,416**	Marginal: <$500K reduction against projected demand
% Total Grams issued	**0.13%**	**0.16%**	**0.14%**	**0.08%**	**0.11%**	

Specialist Working Group knowledge development opportunities and recommendations
None identified at this time.

END OF PUBLIC CONSULTATION DOCUMENT

Next review: One year from BloodSTAR v3.0 implementation (Once sufficient data on inflammatory markers is available from BloodSTAR v2.1)