CLINICAL PRIORITIES ADVISORY GROUP
February 2025

Agenda Item No	2.1
National Programme	Trauma
Clinical Reference Group	Neurology
URN	2334

Title
Tocilizumab for Neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) refractory or intolerant to previous lines of therapy (Adults)

Actions Requested	1. Support the adoption of the policy proposition
	2. Recommend its approval as an in year service development

Proposition
Tocilizumab is recommended to be available as a routine commissioning treatment option for neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) refractory or intolerant to previous lines of therapy within the criteria set out in policy proposition document. Tocilizumab is a humanized monoclonal antibody that targets the IL- 6 receptor. It is licensed and NICE Technology Appraisal Guidance approved in rheumatoid arthritis, juvenile Idiopathic arthritis, giant cell arteritis and severe COVID-19 infection. Tocilizumab can be delivered intravenously or subcutaneously. Tocilizumab is not licensed in NMOSD or MOGAD. Tocilizumab is proposed as a treatment for patients with NMOSD or MOGAD who are refractory or intolerant to previous lines of commissioned therapy. This means that patients continue to relapse despite treatment. It can be given as monotherapy or in combination with steroids. It is proposed as an alternative option to immunoglobulin therapy for those eligible. Service delegation status- retained.

Clinical Panel recommendation
The Clinical Panel recommended that the policy proposition progress as a routine commissioning policy.

The committee is asked to receive the following assurance:	
1.	The Deputy Director of Clinical Effectiveness confirms the proposition has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.
2.	The Deputy Director of Acute Programmes confirms the proposition is supported by an: Impact Assessment; Engagement Report; Equality and Health Inequalities Impact Assessment; Clinical Policy Proposition. The relevant National Programme of Care has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Director of Clinical Commissioning (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Engagement Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality and Health Inequalities Impact Assessment

In patients with neuromyelitis optica spectrum disorder (NMOSD) or myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) who are intolerant to, or whose disease is refractory to, previous lines of therapy, what is the clinical effectiveness and safety of tocilizumab compared with current standard of care or best supportive care?

Outcome	Evidence statement
Clinical effectiveness	
Critical outcomes	
Relapse rate in people with NMOSD or MOGAD **Certainty of evidence:** Very low and moderate	This outcome is important to patients because relapse rates contribute to disability progression and may be associated with a significant reduction in quality of life. One open-label randomised trial (Zhang et al. 2020) and 2 retrospective observational studies (Ringelstein et al. 2022; Yang et al. 2023) provided evidence relating to relapse rate.

	In the Zhang et al. 2020 open-label randomised trial (n=118), participants were adults (≥18 years) with highly relapsing NMOSD diagnosed according to 2015 international consensus diagnostic criteria for NMOSD. One hundred and three (87%) participants were AQP4-IgG positive, 15 (13%) were AQP4-IgG negative and of these 15, 3 (3%) were MOG positive. The planned follow up period for this study was 60 weeks, although some participants were followed up for 90 weeks, due to the time taken to recruit the required sample size. In the Yang et al. 2023 retrospective, before and after, observational study (n=65) participants were adults (≥18 years) diagnosed with NMOSD according to 2015 international consensus diagnostic criteria for NMOSD. Fifty-four (83%) participants were AQP4-IgG positive and 11 (17%) were AQP4-IgG negative; people with MOGAD were excluded. The median treatment duration was 34.1 (IQR 25.5 to 39.3) months. In the Ringelstein et al. 2022 retrospective, before and after, observational study (n=57), 3 participants were under 18 years old when switching to tocilizumab, the rest were adults (≥18 years). Thirty-six (63%) were AQP4-IgG positive, 14 (25%) were MOG positive and 7 (12%) were negative for both AQP4-IgG and MOG antibodies (referred to as double-seronegative in the paper and classified as AQP4-IgG negative in this section). The median treatment duration was 23.8 (IQR 13.0 to 51.1) months. **Risk of relapse** At 60 weeks: • One open-label randomised trial (Zhang et al. 2020) showed that risk of relapse was statistically significantly lower in the tocilizumab group compared with the azathioprine group (HR 0.274, 95% CI 0.123 to 0.607; p=0.0006). **(MODERATE)** At up to 90 weeks: • One open-label randomised trial (Zhang et al. 2020) showed a statistically significant reduction in the number of participants who experienced a relapse in the tocilizumab group (8/59, 14%) compared with the azathioprine group (28/59, 47%) (HR 0.236, 95% CI 0.107 to 0.518; p<0.0001). **(MODERATE)** **Percentage relapse free** At up to 90 weeks: • In a per protocol analysis, 1 open-label randomised trial (Zhang et al. 2020) (n=108) showed a statistically significant increase in the proportion of participants who were relapse free in the tocilizumab group (50/56, 89%) compared with the azathioprine group (29/52, 56%) (HR 0.188, 95% CI 0.076 to 0.463; p<0.0001). **(MODERATE)** The per protocol analysis included all participants who used tocilizumab or azathioprine as monotherapy. After a median treatment duration of 23.8 (IQR 13.0 to 51.1) months:

	• One retrospective observational study (Ringelstein et al. 2022) showed that 34/57 (60%) participants receiving tocilizumab were relapse free. **(VERY LOW)** After a median treatment duration of 34.1 (IQR 25.5 to 39.3) months: • One retrospective observational study (Yang et al. 2023) showed that 50/65 (76.9%) participants receiving tocilizumab were relapse free. Twenty relapses (14 myelitis and 6 optic neuritis cases) were reported by 15 participants. **(VERY LOW)** **Time to relapse** • One open-label randomised trial (Zhang et al. 2020) showed that the median time to first relapse was statistically significantly longer in the tocilizumab group (78.9 [IQR 58.3 to 90.6] weeks) than in the azathioprine group (56.7 [IQR 32.9 to 81.7] weeks) (p=0.0026) (primary outcome). **(MODERATE)** • One retrospective observational study (Ringelstein et al. 2022) showed that the median time to first relapse on tocilizumab was 9 months (range 0.5 to 47 months). **(VERY LOW)** • One retrospective observational study (Yang et al. 2023) showed that the median time to first relapse on tocilizumab was 15.5 months (range 4 to 42 months). **(VERY LOW)** **Annualised relapse rate (ARR)** After a median treatment duration of 23.8 (IQR 13.0 to 51.1) months: • One retrospective observational study (Ringelstein et al. 2022) showed a statistically significant reduction in median ARR (0) compared with the 2-year baseline period prior to tocilizumab treatment (1.5) (p<0.001, 95% CI 1.1 to 1.8) (primary outcome). (**VERY LOW)** After a median treatment duration of 34.1 (IQR 25.5 to 39.3) months: • One retrospective observational study (Yang et al. 2023) showed a statistically significantly reduction in median ARR (0.1, range 0 to 1.4) compared with before tocilizumab was started (1.9, range 0.1 to 6.3) (primary outcome) (p<0.0001, 95% CI 1.4 to 2.1). **(VERY LOW)** **One open-label randomised trial and 2 retrospective observational studies provided very low and moderate certainty evidence that tocilizumab reduces relapse rate up to a median treatment duration of about 34 months.** **Moderate certainty evidence from 1 open-label randomised trial showed that relapse rate was statistically significantly reduced, and time to first relapse was statistically significantly longer, with tocilizumab compared with azathioprine at up to 90 weeks. Very low certainty evidence from 2 retrospective observational studies showed statistically significant reductions in median ARR up to a median treatment duration of about 34 months. Although the clinical significance of the reductions in ARR are uncertain, the median ARR after tocilizumab treatment in the 2 observational studies, was (or was close to) 0, indicating a paucity of relapses during the study periods.**

Measure of disability in people with NMOSD or MOGAD: EDSS score **Certainty of evidence:** Very low to moderate	This outcome is important to patients because a measure of disability progression will likely be associated with a significant reduction in quality of life. One open-label randomised trial (Zhang et al. 2020) and 2 retrospective observational studies (Ringelstein et al. 2022; Yang et al. 2023) provided evidence for disability. The follow up period varied by study from up to 90 weeks for the randomised trial, to a follow up after a tocilizumab median treatment duration of 23.8 (IQR 13.0 to 51.1) months in the Ringelstein et al. 2022 study and 34.1 (IQR 25.5 to 39.3) months in the Yang et al. 2023 study. **Expanded Disability Status Scale (EDSS)** The EDSS is a method of assessing an individual's level of disability and was developed for use in multiple sclerosis. It ranges from 0 (a normal neurological exam) to 10 (death due to multiple sclerosis). Increasing score represents a higher level of disability. A score up to 5 represents normal walking ability with some functional system impairment. A score above 5 represents impairment in mobility. **Disability progression** In Zhang et al. 2020, disability progression was defined as an increase in EDSS score of at least 1.0 point from baseline that was sustained on subsequent visits for at least 12 or 24 weeks if the baseline EDSS score was 5.5 or less. If the baseline EDSS score was greater than 5.5, disability progression was defined as an increase in the EDSS score of at least 0.5 points that was sustained for 12 or 24 weeks. At 12 weeks: • One open-label randomised trial (Zhang et al. 2020) showed that the number of participants with confirmed disability progression was statistically significantly lower in the tocilizumab group (5/59, 8%) compared with the azathioprine group (15/59, 25%) (HR 0.288, 95% CI 0.105 to 0.795, p=0.0087). **(MODERATE)** At 24 weeks: • One open-label randomised trial (Zhang et al. 2020) showed that the number of participants with confirmed disability progression was lower in the tocilizumab group (2/59, 3%) compared with the azathioprine group (6/59, 10%) (HR 0.221, 95% CI 0.047 to 1.042, p=0.0309) (exploratory outcome). **(LOW)** **Change in EDSS score** At up to 90 weeks: • One open-label randomised trial (Zhang et al. 2020) showed that there was no difference in the mean change in EDSS score in the tocilizumab group (−0.32, SD ±0.72) compared with the azathioprine group (−0.13, SD ±1.05) (MD −0.20, 95% CI −0.52 to −0.13; p=0.242). **(MODERATE)** • One open-label randomised trial (Zhang et al. 2020) showed that statistically significantly more participants in the azathioprine group had a worsening EDSS score compared with the tocilizumab group (RR 3.667, 95% CI 1.603 to 8.387; p=0.0005). **(MODERATE)**

	After a median treatment duration of 23.8 (IQR 13.0 to 51.1) months: • One retrospective observational study (Ringelstein et al. 2022) showed a reduction in median EDSS score from 4.5 (IQR 3.0 to 7.0) at the start of tocilizumab treatment to 3.5 (IQR 2.0 to 6.5) at last follow up on tocilizumab treatment. No statistical analyses were reported. **(VERY LOW)** • One retrospective observational study (Ringelstein et al. 2022) showed that 5/57 (9%) participants had a worsening EDSS score from the start of tocilizumab treatment to the last follow up on tocilizumab treatment. **(VERY LOW)** After a median treatment duration of 34.1 (IQR to 25.5 to 39.3) months: • One retrospective observational study (Yang et al. 2023) showed that 5/65 (7.7%) participants had a worsening EDSS score from the start of tocilizumab treatment to the end of the follow up period during tocilizumab treatment. **(VERY LOW)** **One open-label randomised trial and 2 retrospective observational studies provided very low to moderate certainty evidence that although tocilizumab may not improve disability, it may limit disability progression up to about 34 months.** **Moderate certainty evidence from 1 open-label randomised trial showed that tocilizumab reduced disability progression up to 24 weeks compared with azathioprine; this was statistically significant at 12 weeks. Moderate certainty evidence from the same study showed that statistically significantly fewer participants in the tocilizumab group experienced a worsening EDSS score at up to 90 weeks. Very low certainty evidence from 2 retrospective observational studies showed that fewer than 10% of participants had a worsening EDSS score up to a median treatment duration of about 34 months.** **Moderate certainty evidence from 1 open-label randomised trial showed a small reduction in mean EDSS score of 0.32 at up to 90 weeks with tocilizumab, but it is unknown if this is clinically meaningful. There was also no difference between the tocilizumab and azathioprine groups. Very low certainty evidence from 1 retrospective observational study showed a reduction in median EDSS score of 1.0 after about 23 months of tocilizumab, but no statistical analyses were reported.**
Measure of disability in people with NMOSD or MOGAD: Visual acuity **Certainty of evidence:** Very low to moderate	This outcome is important to patients because a measure of disability progression will likely be associated with a significant reduction in quality of life. **Visual acuity** One open-label randomised trial (Zhang et al. 2020) provided evidence for outcomes on visual acuity. Assessments were undertaken of low-contrast letter scores measured with a retro-illuminated 2.5% Sloan letter chart and best corrected high-contrast Logarithm of the Minimum Angle of Resolution (LogMAR) visual acuity measured using a retro-illuminated Early Treatment Diabetic Retinopathy Study chart at 2.52 m. Between baseline and at 60 weeks:

	• One open-label randomised trial (Zhang et al. 2020) showed no significant difference in LogMAR visual acuity between the tocilizumab and azathioprine groups in either affected (MD −0.0095, 95% CI −0.0191 to −0.0002; p=0.0558) or unaffected (MD 0.0012, 95% CI −0.0032 to 0.0056; p=0.5796) eyes. **(MODERATE)** A decrease in LogMAR visual acuity represents recovery of vision. • One open-label randomised trial (Zhang et al. 2020) showed no significant difference in high-contrast letter score between the tocilizumab and azathioprine groups in either affected (MD 0.3553, 95% CI −0.0833 to 0.7938; p=0.1110) **(MODERATE)** or unaffected (MD 0.0034, 95% CI −0.0300 to 0.0367; p=0.8398) eyes (exploratory outcome). **(VERY LOW)** An increase in high-contrast letter score represents recovery of vision. • One open-label randomised trial (Zhang et al. 2020) showed no significant difference in low-contrast letter score between the tocilizumab and azathioprine groups in either affected (MD 0.1113, 95% CI −0.0078 to 0.2304; p=0.0667) **(LOW)** or unaffected (MD 0.0164, 95% CI 0.0292 to 0.1415; p=0.4190) eyes (exploratory outcome). **(MODERATE)** An increase in low-contrast letter score represents recovery of vision. At an unspecified timepoint: • One open-label randomised trial (Zhang et al. 2020) showed a statistically significant lower risk of optic neuritis attacks in the tocilizumab group (1 attack in affected eyes and no attacks in unaffected eyes) compared with the azathioprine group (3 attacks in the affected eyes and 6 attacks in the unaffected eyes) (HR 0.182, 95% CI 0.049 to 0.677; p=0.011). **(MODERATE)** Note, optic neuritis was also one of the criteria that was used to define a relapse. **One open-label randomised trial provided very low to moderate certainty evidence that tocilizumab did not have a beneficial impact on LogMAR, high-contrast or low-contrast visual acuity at 60 weeks, compared with azathioprine. However, moderate certainty evidence from the same trial showed a statistically significant lower risk of optic neuritis with tocilizumab.**
Symptom alleviation in people with NMOSD or MOGAD **Certainty of evidence:** Very low	This outcome is important to patients because reduction in symptoms directly improves the patient's quality of life. This outcome is both a key indicator of the effectiveness of treatment and provides an insight into the patient's perception of the effectiveness of treatment. Two retrospective observational studies provided evidence for symptom alleviation. Both studies provided evidence on the impact of tocilizumab on participant's pain after a median treatment duration of 23.8 (IQR 13.0 to 51.1) months in the Ringelstein et al. 2022 study and 34.1 (IQR 25.5 to 39.3) months in the Yang et al. 2023 study.

	After a median treatment duration of 23.8 (IQR 13.0 to 51.1) months: • One retrospective observational study (Ringelstein et al. 2022) showed that 25/52 (48%) participants on tocilizumab still had chronic pain with a median intensity of 2.0 (IQR 1 to 3, data from 24 participants) and that there was no change from baseline, when 28/51 (55%) reported chronic pain with a median intensity of 2.0 (IQR 1 to 3, data from 27 participants). **(VERY LOW)** Chronic pain was measured as occurrence and intensity and was classified as mild = 1, moderate = 2 and severe = 3. After a median treatment duration of 34.1 (IQR 25.5 to 39.3) months: • One retrospective observational study (Yang et al. 2023) showed that in 34/65 (52%) participants who reported chronic pain before tocilizumab treatment, median pain intensity scores increased to 2.5 (IQR 1.5 to 4.0) from 2 (IQR 1.5 to 3.5) at baseline. No statistical analyses were reported. **(VERY LOW)** Participants were asked to report on NMOSD-related pain (i.e. pain related to myelitis) and it was assessed using a numerical rating scale rated between 0 (no pain) to 10 (worst pain imaginable). **Very low certainty evidence from 2 retrospective observational studies showed that tocilizumab did not improve chronic pain up to a median duration of about 34 months, but no statistical analyses were reported. It is unclear if validated pain tools were used and whether they were sensitive enough to detect change.**
Important outcomes	
Health related quality of life	This outcome is important to patients because it provides a holistic evaluation and indication of the patient's general health and their perceived wellbeing and their ability to participate in activities of daily living. This outcome is both a key indicator of the effectiveness of treatment and provides an insight into the patient's perception of the effectiveness of treatment. No evidence was identified for this outcome.
Hospitalisations / hospital appointments	This outcome is important to patients and their carers because a reduction in number and length of hospitalisations or hospital appointments may indicate that their treatment has been successful. From a service delivery perspective, it reflects the additional demands placed on the health system for the new intervention. No evidence was identified for this outcome.
Steroid reduction	This outcome is important to those patients receiving corticosteroids because corticosteroid treatment is linked with iatrogenic health problems including osteoporosis, diabetes, hypertension, obesity, scarring and electrolyte disorders. No evidence was identified for this outcome.
Safety	

Frequency of adverse events in people with NMOSD or MOGAD **Certainty of evidence:** Very low and moderate	These outcomes are important to patients because they will impact on their treatment choices, recovery and could have long term sequelae if they are irreversible. They reflect the tolerability and adverse effects (AEs) of the treatment. From a service delivery perspective, they reflect the additional demands placed on the health system to manage the adverse consequences of the treatment. One open-label randomised trial **(**Zhang et al. 2020) and 2 retrospective observational studies (Ringelstein et al. 2022; Yang et al. 2023) provided evidence relating to the frequency of adverse events during tocilizumab treatment. The follow up period varied by study from up to 90 weeks for the randomised trial, to a follow up after a tocilizumab median treatment duration of 23.8 (IQR 13.0 to 51.1) months in the Ringelstein et al. 2022 study and 34.1 months (IQR 25.5 to 39.3 months) in the Yang et al. 2023 study. None of the studies reported any statistical analyses. In Zhang et al. 2020: • The incidence of adverse events was similar between the tocilizumab (57/59, 97%) and azathioprine (56/59, 95%) groups, and most were classified as mild. **(MODERATE)** • The most common adverse events were increased alanine transaminase concentrations (18/59, 31% in the tocilizumab group compared with 27/59, 46% in the azathioprine group), upper respiratory tract infection (17/59, 29% in the tocilizumab group compared with 23/59, 39% in the azathioprine group) and urinary tract infections (17/59, 29% in the tocilizumab group compared with 21/59, 36% in the azathioprine group). (**MODERATE**) • Grade 3 (severe) and grade 4 (life-threatening) adverse events were higher in the azathioprine group (21/59, 36%) than in the tocilizumab group (9/59, 15%). (**MODERATE**) • The incidence of serious adverse events was higher in the azathioprine group (9/59, 15%) than in the tocilizumab group (5/59, 8%). (**MODERATE**) In Ringelstein et al. 2022: • Of the selected adverse events reported, the following occurred in at least 10% of participants in the study: transient and mild to moderate liver enzyme change (20/57, 35%), neutropenia (10/57, 17%), upper respiratory tract infections, colds, bronchitis or pneumonia (9/57, 16%), recurrent urinary tract infections (9/57, 16%) and infusion-related reactions (7/57, 12%). **(VERY LOW)** In Yang et al. 2023: • Of the selected adverse events reported, 28/65 (43%) participants had mild to moderate increases in serum alanine transaminase level. Infections occurred in 18/65 (27.7%), including urinary tract (n=11), upper respiratory tract (n=8), zoster virus (n=4), and pneumonia (n=3). Infusion-related reactions occurred in 5/65 (7.7%), including skin rash (n=2), lower limb oedema (n=2), headache (n=1), dizziness (n=1) and hypotension (n=1). Transient fatigue, lasting a mean 3.4 days (range 1 to 9 days), occurred in 15/65 (23.1%) participants and 7/65 (10.7%) had hypercholesterolaemia. **(VERY LOW)**

	Moderate certainty evidence from 1 open-label randomised trial showed that most participants (about 95%) experienced adverse events with both tocilizumab and azathioprine, and they were mainly mild. Moderate certainty evidence from the same study and very low certainty evidence from 2 retrospective observational studies showed that the reported adverse events included raised liver enzyme levels, upper respiratory and urinary tract infections, and infusion-related reactions. Serious, severe, and life-threatening events were lower in participants receiving tocilizumab compared with azathioprine, but no statistical analyses were reported.
Adverse events leading to discontinuation in people with NMOSD or MOGAD **Certainty of evidence:** Very low and moderate	These outcomes are important to patients because they will impact on their treatment choices, recovery and could have long term sequelae if they are irreversible. They reflect the tolerability and adverse effects (AEs) of the treatment. From a service delivery perspective, they reflect the additional demands placed on the health system to manage the adverse consequences of the treatment. One open-label randomised trial **(**Zhang et al. 2020) and 1 retrospective observational study (Ringelstein et al. 2022) provided evidence relating to adverse events leading to discontinuation of study drug. The follow up period varied by study from up to 90 weeks for the randomised trial, to a follow up after a tocilizumab median treatment duration of 23.8 (IQR 13.0 to 51.1) months in the Ringelstein et al. 2022 study. Neither study reported any statistical analyses. In Zhang et al. 2020: • Adverse events led to discontinuation of a study drug in 1/59 (2%) of the tocilizumab group (due to an acute haemorrhagic stroke) and 2/59 (3%) of the azathioprine group (due to severe hepatic dysfunction and following severe myelosuppression). **(MODERATE)** In Ringelstein et al. 2022: • Tocilizumab was discontinued in 5/57 (9%) participants, due to suspected side effects. **(VERY LOW)** **Moderate certainty evidence from 1 open-label randomised trial and very low certainty evidence from 1 retrospective observational study showed that adverse events leading to discontinuation of the study drug were low (occurring in less than 10% of participants) and were similar between the tocilizumab and azathioprine groups, but no statistical analyses were reported.**
Mortality in people with NMOSD or MOGAD **Certainty of evidence:** Very low and moderate	One open-label randomised trial **(**Zhang et al. 2020) and 1 retrospective observational study (Ringelstein et al. 2022) provided evidence relating to mortality. The follow up period varied by study from up to 90 weeks for the randomised trial, to a follow up after a tocilizumab median treatment duration of 23.8 (IQR 13.0 to 51.1) months the Ringelstein et al. 2022 study. Neither study reported any statistical analyses. In Zhang et al. 2020, 2 deaths were reported (1 in each of the tocilizumab and azathioprine groups) which occurred during the study; neither was considered treatment or study drug related. In the

	azathioprine group, the death was caused by severe intracranial infection and cerebral oedema. In the tocilizumab group, the death was due to central respiratory failure secondary to myelitis. (**MODERATE**) In Ringelstein et al. 2022, 1 death due to recurrent pneumonia was reported, which occurred 2 months after discontinuation of a 6-month tocilizumab treatment period, it was considered unrelated to tocilizumab treatment. (**VERY LOW**) **Moderate certainty evidence from 1 open-label randomised trial and very low certainty evidence from 1 retrospective observational study suggests that tocilizumab does not have an impact on mortality in participants with NMOSD. However, these studies may have been too small or too short to detect rare events.**

Abbreviations

AQP4-IgG, aquaporin-4 water antibodies; ARR, annualised relapse rate; CI, confidence interval; EDSS, Expanded Disability Status Scale; HR, hazard ratio; IQR, interquartile range; LogMAR, Logarithm of the Minimum Angle of Resolution; MOG, myelin oligodendrocyte glycoprotein; MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease; MD, mean difference; NMOSD, neuromyelitis optica spectrum disorder; RR, relative risk; SD, standard deviation.

In patients with NMOSD or MOGAD who are intolerant to or whose disease is refractory to previous lines of therapy, what is the cost effectiveness of tocilizumab compared with current standard of care or best supportive care?

Outcome	Evidence statement
Cost effectiveness	No evidence was identified for this outcome.

From the evidence selected, are there any subgroups of patients that may benefit from tocilizumab more than the wider population of interest?

Prespecified subgroups

Subgroup	Evidence statement
People with AQP4-IgG positive NMOSD	**Relapse rate** One open-label randomised trial (Zhang et al. 2020, n=103) provided evidence for relapse rate in participants with AQP4-IgG positive NMOSD at up to 90 weeks. Two retrospective observational studies (Ringelstein et al. 2022, n=36; Yang et al. 2023, n=54) provided evidence for relapse rate and disability. Ringelstein et al. 2022 reports the median duration of tocilizumab received by participants with AQP4-IgG positive NMOSD (27.9 months, IQR 12.9 to 53.2 months). Yang et el. 2023 does not report the median treatment duration for their AQP4-IgG positive

	NMOSD population, so the median treatment duration for the entire cohort (34.1 months, IQR 25.5 to 39.3 months) is reported in this section. **Risk of relapse** At up to 90 weeks: One open-label randomised trial (Zhang et al. 2020) showed that the risk of relapse was statistically significantly lower in the tocilizumab group (6/50 relapses, 12%) compared with the azathioprine group (25/53 relapses, 47%) (HR 0.202, 95% CI 0.083 to 0.493; p=0.0004). **Time to relapse** • One retrospective observational study (Ringelstein et al. 2022) showed that the median time to first relapse on tocilizumab was 4.4 (range 0.5 to 47) months. • One retrospective observational study (Yang et al. 2023) showed that the median time to first relapse on tocilizumab was 18.6 months. **Percentage relapse free** After a median treatment duration of 27.9 (IQR 12.9 to 53.2) months: One retrospective observational study (Ringelstein et al. 2022) reported that 20/36 (56%) participants on tocilizumab were relapse free. After a median treatment duration of 34.1 (IQR 25.5 to 39.3) months: One retrospective observational study (Yang et al. 2023) reported that 41/54 (75.9%) participants on tocilizumab were relapse free. **Annualised relapse rate (ARR)** After a median treatment duration of 27.9 (IQR 12.9 to 53.2) months: One retrospective observational study (Ringelstein et al. 2022) showed a statistically significant reduction in median ARR (0, range 0 to 4.2) compared with the 2-year baseline period prior to tocilizumab treatment (1.5, range 0 to 5) (p<0.001, 95% CI 0 to 0.2). After a median treatment duration of 34.1 (IQR 25.5 to 39.3) months: One retrospective observational study (Yang et al. 2023) showed a statistically significant reduction in median ARR (0.14) compared with before tocilizumab treatment (1.89) (p<0.0001, 95% CI 1.38 to 2.12). **One open-label randomised trial and 2 retrospective observational studies showed that in participants with AQP4-IgG positive NMOSD, relapse rate was statistically significantly reduced with tocilizumab compared with azathioprine at up to 90 weeks and compared with before tocilizumab treatment up to a median treatment duration of 34.1 months. However, in 1**

	retrospective observational study, the range of ARRs reported were wide, indicating high variability in the results. ## Measure of disability After a median treatment duration of 27.9 (IQR 12.9 to 53.2) months: One retrospective observational study (Ringelstein et al. 2022) showed a statistically significant reduction in median EDSS score from 6.25 (IQR 3.0 to 7.6) at the start of tocilizumab treatment to 4.25 (IQR 2.5 to 7.0) at last follow up on tocilizumab treatment ($p<0.003$). One retrospective observational study (Ringelstein et al. 2022) showed that 3/36 (8%) participants had a worsening EDSS score from the start of tocilizumab treatment to the last follow up on tocilizumab treatment. After a median treatment duration of 34.1 (IQR to 25.5 to 39.3) months: One retrospective observational study (Yang et al. 2023) showed a statistically significant reduction in median EDSS score from 5.75 (range 1 to 8.5) at the start of tocilizumab treatment to 3.5 (range 0 to 8) at last follow up on tocilizumab treatment ($p<0.001$). One retrospective observational study (Yang et al. 2023) showed that 4/54 (7.4%) participants had a worsening EDSS score from the start of tocilizumab treatment to the end of the follow up period during tocilizumab treatment. **Two retrospective observational studies showed that in participants with AQP4-IgG positive NMOSD, there were statistically significant reductions in median EDSS score compared with before tocilizumab treatment, up to a median treatment duration of about 34 months. However, it is unknown if these reductions are clinically meaningful. The range of EDSS scores are also very wide in both studies, indicating high variability in the results.** ## Safety One retrospective observational study (Ringelstein et al. 2022) provided evidence for the safety of tocilizumab in participants with AQP4-IgG positive NMOSD (n=36). The follow up period was after a tocilizumab median treatment duration of 27.9 (IQR 12.9 to 53.2) months. No statistical analyses were reported. **Frequency of adverse events** Ringelstein et al. 2022 reported the following selected adverse events (occurring in at least 10% of all participants in the study) in participants with AQP4-IgG positive NMOSD: transient and mild to moderate liver enzyme change (12/36, 33%), neutropenia (8/36, 22%), recurrent urinary tract infections (7/36, 19%), infusion related reactions (6/36, 17%) and upper respiratory tract infections, colds, bronchitis or pneumonia (5/36, 14%).

	Adverse events leading to discontinuation Ringelstein et el. 2022 reported that tocilizumab was discontinued in 5/36 (14%) participants with AQP4-IgG positive NMOSD due to suspected side effects such as ileus (n=1), nephritis and urticaria in the context of systemic lupus erythematosus (n=1), psoriasis exacerbation (n=1) and upper respiratory tract infection (n=3). **Mortality** Ringelstein et al. 2022 reported that 1 death occurred in someone with AQP4-IgG positive NMOSD (1/36, 3%), which was considered unrelated to tocilizumab treatment by the physician. **One retrospective observational study showed that the safety profile of tocilizumab in participants with AQP4-IgG positive NMOSD is comparable to that in the wider study population. However, this study may have been too small or too short to detect rare events, such as death or discontinuations.**
People with AQP4-IgG negative NMOSD	## Relapse rate One open-label randomised trial (Zhang et al. 2020, n=15) provided evidence for relapse rate in participants with AQP4-IgG negative NMOSD at up to 90 weeks. Two retrospective observational studies (Ringelstein et al. 2022, n=7; Yang et al. 2023, n=11) provided evidence for relapse rate and disability in participants with AQP4-IgG negative NMOSD. Ringelstein et al. 2022 reports the median duration of tocilizumab received by participants with AQP4-IgG negative NMOSD (30.4 months, IQR 10.3 to 38.1 months). Yang et el. 2023 does not report the median treatment duration for their AQP4-IgG negative NMOSD population, so the median treatment duration for the entire cohort (30.4 months, IQR 10.3 to 38.1 months) is reported in this section. **Risk of relapse** At up to 90 weeks: One open-label randomised trial (Zhang et al. 2020) showed no significant difference in the risk of relapse between the tocilizumab group (2/9, 22%) and the azathioprine group (3/6, 50%) (HR 0.470, 95% CI 0.078 to 2.821; p=0.408). Note, Zhang et al. 2020 included participants with MOGAD (n=3) in the AQP4-IgG negative NMOSD group. **Time to relapse** One retrospective observational study (Ringelstein et al. 2022) showed that the median time to first relapse was 12.2 (range 2.6 to 18.9) months. One retrospective observational study (Yang et al. 2023) showed that the median time to first relapse was 15.5 months. **Percentage relapse free** After a median treatment duration of 30.4 (IQR 10.3 to 38.1) months:

	One retrospective observational study (Ringelstein et al. 2022) showed that 3/7 (43%) participants were relapse free. After a median treatment duration of 34.1 (IQR 25.5 to 39.3) months: One retrospective observational study (Yang et al. 2023) showed that 9/11 (81.8%) participants were relapse free. **Annualised relapse rate (ARR)** After a median treatment duration of 30.4 (IQR 10.3 to 38.1) months: One retrospective observational study (Ringelstein et al. 2022) showed a statistically significant reduction in median ARR (0.2, range 0 to 2.0) compared with the 2-year baseline period prior to tocilizumab treatment (3.0, range 1.0 to 3.0) (p<0.032, 95% CI 0.3 to 2.8). After a median treatment duration of 34.1 (IQR 25.5 to 39.3) months: One retrospective observational study (Yang et al. 2023) showed a statistically significant reduction in median ARR (0.06) compared with before tocilizumab treatment (1.75) (p<0.0001, 95% CI 1.22 to 2.49). **One open-label randomised trial showed no significant difference in the risk of relapse between tocilizumab and azathioprine in participants with AQP4-IgG negative NMOSD. However, the 2 retrospective observational studies showed statistically significant reductions in median ARR compared with before tocilizumab treatment. The number of participants with AQP4-IgG negative NMOSD in these studies may be too small to draw definitive conclusions.** ## Measure of disability After a median treatment duration of 30.4 (IQR 10.3 to 38.1) months: One retrospective observational study (Ringelstein et al. 2022) showed no significant difference in the median EDSS score at the start of tocilizumab treatment (5.0, IQR 4.5 to 5.8) to the median EDSS score at last follow up on tocilizumab treatment (5.0, IQR 3.5 to 6.8) (p<0.77). One retrospective observational study (Ringelstein et al. 2022) showed that 2/7 (29%) participants had a worsening EDSS score from the start of tocilizumab treatment to the last follow up on tocilizumab treatment. After a median treatment duration of 34.1 (IQR to 25.5 to 39.3) months: One retrospective observational study (Yang et al. 2023) showed a statistically significant reduction in median EDSS score from 5

	(range 1.5 to 6.0) at the start of tocilizumab treatment to 2.5 (range 0 to 5.5) at last follow up on tocilizumab treatment (p=0.043). One retrospective observational study (Yang et al. 2023) showed that 1/11 (9.1%) participants had a worsening EDSS score from the start of tocilizumab treatment to the end of the follow up period during tocilizumab treatment. **Two retrospective observational studies provided evidence on the outcome of disability in participants with AQP4-IgG negative NMOSD, but the results are inconsistent. The number of participants with AQP4-IgG negative NMOSD in these studies may be too small to draw definitive conclusions.** ## Safety One retrospective observational study (Ringelstein et al. 2022) provided evidence for the safety of tocilizumab in participants with AQP4-IgG negative NMOSD (n=7). The overall follow up period was after a tocilizumab median treatment duration of 30.4 (IQR 10.3 to 38.1) months. No statistical analyses were reported. **Frequency of adverse events** Ringelstein et al. 2022 reported the following selected adverse events (occurring in at least 10% of all participants in the study) in participants with AQP4-IgG negative NMOSD: transient and mild to moderate liver enzyme change (6/7, 86%), upper respiratory tract infections, colds, bronchitis or pneumonia (2/7, 29%), recurrent urinary tract infections (1/7, 14%). There were no reports of infusion related reactions or neutropenia in participants with AQP4-IgG negative NMOSD. **Adverse events leading to discontinuation** Ringelstein et al. 2022 reported that tocilizumab was not discontinued due to side effects in any participants with AQP4-IgG negative NMOSD. **Mortality** Ringelstein et al. 2022 reported that no deaths occurred in participants with AQP4-IgG negative NMOSD. **One retrospective observational study showed that the safety profile of tocilizumab in participants with AQP4-IgG negative NMOSD is comparable to that in the wider study population. However, this study may have been too small or too short to detect rare events, such as death or discontinuations.**
People with MOGAD	## Relapse rate One open-label randomised trial (Zhang et al. 2020, n=3) provided evidence for relapse rate in participants with MOGAD at up to 90 weeks. One retrospective observational study (Ringelstein et al. 2022, n=14) provided evidence for relapse rate and disability in participants with MOGAD at up to a median treatment duration of 16.3 (IQR 14.2 to 44.6) months. **Time to relapse**

	One retrospective observational study (Ringelstein et al. 2022) showed that the median time to first relapse on tocilizumab was 9.4 months (range 9 to 15 months). **Percentage relapse free** At up to 90 weeks: One open-label randomised trial (Zhang et al. 2020) showed that 1/1 (100%) participant in the tocilizumab group was relapse free compared with 1/2 (50%) in the azathioprine group. No statistical analyses were reported. After a median treatment duration of 16.3 (IQR 14.2 to 44.6) months: One retrospective observational study (Ringelstein et al. 2022) showed that 11/14 (79%) participants on tocilizumab were relapse free. **Annualised relapse rate (ARR)** After a median treatment duration of 16.3 (IQR 14.2 to 44.6) months: One retrospective observational study (Ringelstein et al. 2022) showed a statistically significant reduction in median ARR (0, range 0 to 0.9) compared with the 2-year baseline period prior to tocilizumab treatment (1.75, range 0.5 to 5) ($p<0.0011$, 95% CI 1.3 to 2.6). **One open-label randomised trial provided evidence for relapse rate in participants with MOGAD but no statistical analyses were carried out. Very low certainty evidence from 1 retrospective observational study showed a statistically significant reduction in ARR with tocilizumab. The number of participants in these studies may be too small to draw meaningful conclusions.** ## Measure of disability One retrospective observational study (Ringelstein et al. 2022) provided evidence for disability in participants with MOGAD, measured after a median treatment duration of 16.3 months. After a median treatment duration of 16.3 (IQR 14.2 to 44.6) months: One retrospective observational study (Ringelstein et al. 2022) showed a statistically significant reduction in median EDSS score from 2.75 (IQR 2.0 to 3.5) at the start of tocilizumab treatment to 2.0 (IQR 1.2 to 2.9) at last follow up on tocilizumab treatment ($p<0.031$). One retrospective observational study (Ringelstein et al. 2022) showed that 0/14 (0%) participants had a worsening EDSS score from the start of tocilizumab treatment to the last follow up on tocilizumab treatment. **One retrospective observational study showed that in participants with MOGAD, there was a statistically significant**

	reduction in median EDSS score compared with before tocilizumab treatment, up to a median treatment duration of about 16 months. However, it is unknown if this reduction is clinically meaningful. The same study also showed that none of the participants with MOGAD experienced a worsening EDSS score, but the number of participants with MOGAD included in this study may be too small to draw definitive conclusions. **Safety** One retrospective observational study (Ringelstein et al. 2022) provided evidence for the safety of tocilizumab in participants with MOGAD (n=14). The overall follow up period was after a tocilizumab median treatment duration of 16.3 (IQR 14.2 to 44.6) months. No statistical analyses were reported. **Frequency of adverse events** Ringelstein et al. 2022 reported the following selected adverse events (occurring in at least 10% of all participants in the study) in participants with MOGAD: transient and mild to moderate liver enzyme change (2/14, 14%), upper respiratory tract infections, colds, bronchitis or pneumonia (2/14, 14%); neutropenia (2/14, 14%), infusion related reactions (1/14, 7%); recurrent urinary tract infections (1/14, 7%). **Adverse events leading to discontinuation** Ringelstein et al. 2022 reported that tocilizumab was not discontinued due to side effects in any participants with MOGAD. **Mortality** Ringelstein et al. 2022 reported that no deaths occurred in anyone with MOGAD. **One retrospective observational study showed that the safety profile of tocilizumab in participants with MOGAD is comparable to that in the wider study population. However, this study may have been too small or too short to detect rare events, such as death or discontinuations.**
Comparing people with AQP4-IgG positive NMOSD and AQP4-IgG negative NMOSD	One retrospective observational study (Yang et al. 2023) included some direct comparisons between participants with positive (n=54) and negative (n=11) AQP4-IgG NMOSD, after a median treatment duration of 34.1 (IQR 25.5 to 39.3) months. There was no significant difference in the median ARR after treatment between participants with AQP4-IgG positive NMOSD (0.14) and AQP4-IgG negative NMOSD (0.06) p=0.3618. There was no significant difference in the median times to first relapse between participants with AQP4-IgG positive NMOSD (18.6 months) and AQP4-IgG negative NMOSD (15.5 months) p=0.7210. One retrospective observational study (Ringelstein et al. 2022) included some direct comparisons between participants with positive (n=36) and negative (n=7) AQP4-IgG NMOSD, after a median treatment duration of 23.8 (IQR 13.0 to 51.1) months.

	The AQP4-IgG negative NMOSD group had on average 2.6 times the relapse counts compared with the AQP4-IgG positive NMOSD group (p<0.03). **Two retrospective observational studies provided evidence on the difference in relapse rates between participants with AQP4-IgG positive and AQP4-IgG negative NMOSD treated with up to a median duration of about 34 months tocilizumab. However, the results are inconsistent, and no conclusions can be drawn.**
Comparing people with MOGAD and AQP4-IgG positive NMOSD	One retrospective observational study (Ringelstein et al. 2022) included some direct comparisons between participants with AQP4-IgG positive NMOSD (n=36) and participants with MOGAD (n=14), after a median treatment duration of 23.8 (IQR 13.0 to 51.1) months. Relapses occurred 8% less in MOGAD participants compared with participants with AQP4-IgG positive NMOSD, but this was not statistically significant (p=0.86). **One retrospective observational study showed no statistically significant difference in the relapse rate between participants with MOGAD and AQP4-IgG positive NMOSD treated with a median duration of about 23 months tocilizumab.**

Abbreviations

AQP4-IgG, aquaporin-4 water antibodies; ARR, annualised relapse rate; CI, confidence interval; EDSS, Expanded Disability Status Scale; EMA, European Medicines Agency; HR, hazard ratio; IQR, interquartile range; MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease; NMOSD, neuromyelitis optica spectrum disorder.

Additional subgroups

Subgroup	Evidence statement
People with NMOSD or MOGAD who used concomitant immunosuppressants, including corticosteroids	In 1 retrospective observational study (Yang et al. 2023), 59/65 (90.7%) participants were taking oral prednisone at a median dose of 25 mg (range 15 to 40 mg) when starting tocilizumab. The prednisone was tapered and discontinued within a median of 4.2 (range 3 to 8) months. Tocilizumab was used as monotherapy from the start in 6/65 (9.2%) participants. After a median treatment duration of 34.1 (IQR 25.5 to 39.3) months: Of 59 participants receiving concomitant corticosteroids when starting tocilizumab, 48 (81%) were relapse free, compared with 2/6 (33%) participants who were given tocilizumab as monotherapy at initiation. No statistical analyses were reported. Median ARR decreased from 1.95 to 0.09 (p<0.0001, 95% CI 1.51 to 2.21) in those receiving concomitant corticosteroids, compared with from 1.48 to 0.49 (p=0.0495, 95% CI 0.05 to 2.02) in the monotherapy group. The ARR after treatment was statistically

	significantly lower in those receiving concomitant corticosteroids (p=0.0005). In 1 retrospective observational study (Ringelstein et al. 2022), 20/57 (35%) participants received tocilizumab as an add-on treatment with other immunosuppressants. In 2 participants, this was due to comorbidities. Additional medicines included low dose corticosteroids (n=10), methotrexate (n=4), mycophenolate mofetil (n=2), azathioprine (n=1), IVIG (n=1), rituximab (n=1) and monthly high dose corticosteroids (n=1). These were administered for less than 6 months in 3 participants and more than 6 months in 17 participants during tocilizumab treatment. After a median treatment duration of 23.8 (IQR 13.0 to 51.5) months: Of 37 participants given tocilizumab as monotherapy, 29 (78%) were relapse free during treatment, compared with 8/20 (40%) participants receiving add-on treatment. No statistical analyses were reported. Median ARR decreased in participants who were given tocilizumab as monotherapy (n=37), from 1.5 (IQR 1 to 2.5) to 0 (IQR 0 to 0) compared with the 2-year baseline period prior to tocilizumab treatment. In the add-on group, median ARR reduced from 2.0 (IQR 1 to 3) to 0.2 (IQR 0 to 0.8). No statistical analyses were reported. **One retrospective observational study showed that taking tocilizumab with concomitant corticosteroids statistically significantly decreased median ARR, compared with taking tocilizumab as monotherapy. However, the number of participants receiving tocilizumab monotherapy was low and this finding is very uncertain. Another retrospective observational study, which grouped corticosteroids with other immunosuppressants, showed that 78% of those receiving tocilizumab monotherapy were relapse free compared with 40% of those receiving concomitant immunosuppressants, but no statistical analyses were undertaken.**
Treatment infusion interval in people with NMOSD	One retrospective observational study (Yang et al. 2023) compared different treatment intervals, during a median treatment duration of 34.1 (IQR 25.5 to 39.3) months. In 38/65 (58.5%) participants, infusions were administered every 4 weeks, in 18/65 (27.7%) every 6 weeks and in 7/65 (10.8%) every 8 weeks. After a median treatment duration of 34.1 (IQR 25.5 to 39.3) months: Median ARR statistically significantly decreased in all groups after treatment (4 weeks from 2.00 to 0.09, p<0.0001, 95% CI 1.59 to 2.23; 6 weeks from 1.55 to 0.18, p=0.0004, 95% CI 0.66 to 2.07; 8 weeks from 2.69 to 0.24, p=0.0225, 95% CI 0.42 to 4.47). Median times to the first relapse in each group were comparable and not statistically significantly different (4 weeks 17.3 months; 6 weeks 18.8 months; 8 weeks 14 months) p=0.8779. A logistic regression analysis indicated that an infusion interval of more than 4 weeks increased the relapse risk (OR 10.7, 95% CI 1.6 to 71.4, p=0.014). **One retrospective observational study showed that receiving IV tocilizumab statistically significantly decreased median ARR,**

	regardless of the interval between infusions (4, 6 or 8 weeks), up to a median treatment duration of about 34 months in participants with NMOSD. However, a logistic regression analysis showed that receiving IV tocilizumab at intervals greater than 4 weeks may increase the relapse risk, although the wide confidence intervals around this estimate suggest high variability in this result.
People with NMOSD or MOGAD who had concomitant autoimmune diseases	One open-label randomised trial (Zhang et al. 2020) carried out a prespecified subgroup analysis of participants with (n=47) and without (n=71) concomitant autoimmune diseases at up to 90 weeks follow up. Direct comparison between participants with and without concomitant diseases, in the full analysis set: In the tocilizumab group, there was no difference in the risk of relapse between participants with and without concomitant autoimmune diseases (HR 0.419, 95% CI 0.100 to 1.755, p=0.2134), whereas in the azathioprine group, the risk of relapse was higher in participants with concomitant autoimmune disease (HR 0.349, 95% CI 0.1640 to 0.742, p=0.0058). The median time to first relapse suggested a treatment effect consistent with that of the overall study population, in participants with and without concomitant diseases. One retrospective observational study (Yang et al. 2023) compared participants (with NMOSD) with (n=36) and without (n=29) concomitant autoimmune diseases, over a median treatment duration of 34.1 (IQR 25.5 to 39.3) months. Of participants with concomitant autoimmune diseases, 7/36 (19.4%) relapsed, compared with 8/29 (27.6%) participants without concomitant autoimmune diseases. No statistical analyses were reported. The median ARR decreased after treatment from 1.73 to 0.17 (p<0.0001, 95% CI 1.05 to 2.06) for participants with concomitant autoimmune diseases and from 2.05 to 0.09 (p<0.0001, 95% CI 1.52 to 2.39) for participants without concomitant autoimmune diseases. The median ARR after treatment did not differ between the 2 groups (p=0.2586). The median time to first relapse in participants with concomitant autoimmune disease was 20.1 months, and in participants without concomitant autoimmune diseases was 15.8 months. There was no difference between the 2 groups (p=0.5028). **One open-label randomised trial and 1 retrospective observational study showed that concomitant autoimmune diseases do not affect relapse rates on tocilizumab treatment and the time to first relapse in participants with and without concomitant autoimmune diseases were similar to the wider study population.**
Abbreviations	

AQP4-IgG, aquaporin-4 water antibodies; ARR, annualised relapse rate; CI, confidence interval; HR, hazard ratio; IQR, interquartile range; IV, intravenous; IVIG, intravenous immunoglobulin; MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease; NMOSD, neuromyelitis optica spectrum disorder; OR, odds ratio.

From the evidence selected, what dose and route of administration of tocilizumab was used?

Study	Dose and route of administration of tocilizumab
Ringelstein et al. 2022	IV tocilizumab at a mean interval of 31.6 (range 26.1 to 44.2) days and with a median dose of 8.0 (range 6.0 to 12.0) mg/kg (in 56 participants). SC tocilizumab given as weekly injections of 162 mg (in 1 participant).
Yang et al. 2023	IV tocilizumab 8 mg/kg at a mean interval of 37.5 (range 27 to 61) days. In 38/65 (58.5%) participants, tocilizumab was administered every 4 weeks at a median interval of 29.5 (range 27 to 31) days; 18/65 (27.7%) received tocilizumab every 6 weeks at a median interval of 45 (range 43 to 47) days; 7/65 (10.8%) received tocilizumab every 8 weeks at a median interval of 58 (range 56 to 61) days.
Zhang et al. 2020	IV tocilizumab 8 mg/kg every 4 weeks.

Abbreviations

SC, subcutaneous; IV, intravenous; mg/kg, milligrams per kilogram.

From the evidence selected, how was NMOSD or MOGAD defined?

Outcome	Evidence statement
Ringelstein et al. 2022	The study included all people with AQP4-IgG positive NMOSD, MOGAD and double-seronegative NMOSD (diagnostic criteria for inclusion was not defined). Baseline characteristics report that 36/57 (63%) fulfilled 2006 diagnostic criteria for neuromyelitis optica (4/14 MOGAD, 27/36 AQP4-IgG positive NMOSD, 5/7 double-seronegative NMOSD). All NMOSD participants (both AQP4-IgG positive and double-seronegative) and 7/14 MOGAD participants fulfilled the 2015 international consensus diagnostic criteria for neuromyelitis optica spectrum disorders at baseline.
Yang et al. 2023	The inclusion criteria for the study were adults diagnosed with NMOSD according to 2015 international consensus diagnostic criteria for neuromyelitis optica spectrum disorder.
Zhang et al. 2020	Eligible people were adults with highly relapsing NMOSD diagnosed according to 2015 international consensus diagnostic criteria for neuromyelitis optica spectrum disorder.

Abbreviations

AQP4-IgG, aquaporin-4 water antibodies; MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease; NMOSD, neuromyelitis optica spectrum disorder.

The condition has the following impacts on the patient's everyday life:

- **mobility:** Patients can have moderate to severe problems in walking about or are unable to walk about.
- **ability to provide self-care:** Patients can have moderate to severe problems in washing or dressing or are unable to wash or dress.
- **undertaking usual activities:** Patients can have moderate to severe problems in doing their usual activities or are unable to do their daily activities
- **experience of pain/discomfort:** Patients can have moderate to extreme pain or discomfort.
- **experience of anxiety/depression:** Patients may be moderately to severely anxious or depressed

Further details of impact upon patients:

Patients present with physical disabilities such as weakness / paralysis together with loss of sight and /or with severe neuropathic pain and /or intractable itching. Prompt recognition of this disease together with treatment can dramatically improve and may completely reverse these disabilities allowing the person to lead a normal active life and being able to work. Relapses particularly in the brain stem and brain can cause death. Patients continue to live in the shadow of the risk of a severe/catastrophic relapse which may not respond to or be reversible with current treatments. Patients are on continuous immunosuppression which requires care avoiding exposure to infections such as Covid-19. Many patients have bladder, bowel and sexual dysfunction resultant from attacks if the disease is not adequately controlled and need catheters and anal irrigation.

Further details of impact upon carers:

The impact of loss of sight and difficulties with walking, due to delays in treatment or relapses not responding to current treatments, increases the burden on carers. Treatments used to supress the immune system also put patients into the high-risk COVID-19 group which can impact on carers.

Considerations from review by Rare Disease Advisory Group

RDAG was supportive of this policy proposition highlighting it will provide additional treatment options for this rare disease population.

RDAG noted that the stopping criterion around lack of response to treatment could be strengthened. They also noted that there should be flexibility in interpreting the criteria for eligibility for the drug.

Pharmaceutical considerations
This clinical commissioning policy proposition is for the use of tocilizumab for the treatment of patients with NMOSD or MOGAD which is refractory or intolerant to previous lines of therapy, including rituximab and immunosuppressants. The recommendation is outside of the marketing authorisation for tocilizumab, so use is off-label and Trust policy regarding unlicensed medicines should apply. Tocilizumab is listed on the NHS Payment Scheme Annex A, that is, it is a high-cost drug. The policy proposition covers use in adults aged 18 years and over, in line with the findings from the evidence review. Tocilizumab may be used in children aged two years and over by application of the NHS England's Policy 170001/P Commissioning Medicines for Children in Specialised Services (commissioning medicines children), as it is listed in the BNF Children with a recommended dosage schedule relative to the age of the child.

Considerations from review by National Programme of Care
The proposal received the full support of theTrauma PoC on Wednesday 13th November 2024