MANAGEMENT IN CONFIDENCE

CLINICAL PRIORITIES ADVISORY GROUP

Agenda Item No	
National Programme	Trauma
Clinical Reference Group	Neuroscience
URN	1817

Title
Infliximab for Refractory or Progressive Neurosarcoidosis

Actions Requested	Agree the policy proposition

Proposition
Routinely commission infliximab for this indication.

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

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposal has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report
2.	The Head of Acute Programmes confirms the proposal is supported by an: Impact Assessment; Stakeholder Engagement Report; Consultation Report; Equality Impact and Assessment Report; 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 Operational Delivery Director (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.	Consultation Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality Impact and Assessment Report

The Benefits of the Proposition			
No	*Outcome measures*	*Grade of evidence*	*Summary from evidence review*
1.	Survival	Not measured	
2.	Progression free survival	Not measured	
3.	Mobility	Not measured	
4.	Self-care	Not measured	
5.	Usual activities	Not measured	
6.	Pain	Not measured	
7.	Anxiety / Depression	Not measured	
8.	Replacement of more toxic treatment	Not measured	
9.	Dependency on care giver / supporting independence	Not measured	
10.	Safety		This outcome looks at how many people had side effects while they were using infliximab for neurosarcoidosis. In the study by Gelfand et al., 7/66 people (11%) had infections that the investigators considered possibly related to infliximab treatment or the combination of treatments they were taking to suppress their immune system. One person stopped using infliximab because of myositis (inflammation of the muscle), which was considered to be medication-related.

			The results suggest that, when infliximab is used for neurosarcoidosis, the adverse effects seen are similar to those that are seen when it is used for its licensed indications, as listed in the summary of product characteristics; for example, infections are common. These results should be interpreted with caution because the study is small, uncontrolled and retrospective. Weaknesses in the study's design and conduct mean it is subject to bias and confounding, is difficult to interpret and cannot support firm conclusions.
11.	Delivery of intervention	Not measured	

Other health outcome measures determined by the evidence review			
No	Outcome measure	Grade of evidence	Summary from evidence review
1.	Response to treatment on MRI magnetic resonance imaging (MRI)		This outcome looked at whether images of people's brain (obtained using a procedure called MRI) showed that the disease improved, stayed the same or got worse when they were using infliximab. The study by Gelfand et al, (2017) found that, in people using infliximab for 1.5 years on average, neurosarcoidosis resolved completely in 52% (29/56), partially improved in 30% (17/56), stayed the same in 14% (8/56) and got worse in 4% (2/56). A favourable response on MRI (partial or complete improvement) was seen in 82% of people (46/56). This suggests that neurosarcoidosis resolved in the brain in more than half of people using infliximab, and 8 out of 10 people experienced some improvement. These results should be interpreted with caution as per section one metric no. 10.
2.	Clinical response to treatment		This outcome looked at how many people's signs and symptoms of neurosarcoidosis improved, stayed the same or got worse, in the opinion of their specialist, when it was treated with infliximab.

			When people were assessed by their specialist after using infliximab, the study by Gelfand et al, 2017 found that clinical signs and symptoms of neurosarcoidosis resolved completely in 29% (19/66), partially improved in 48% (32/66), stayed the same in 18% (12/66) and got worse in 3% (2/66). A favourable response with complete or partial recovery was seen in 80% of people (45/56) who had evaluations for both clinical response and MRI findings. This suggests that clinical signs and symptoms of neurosarcoidosis resolved in just under a third of people using infliximab, and 8 out of 10 people experienced some improvement in both findings on MRI and clinical signs and symptoms. These results should be interpreted with caution per section one metric no. 10.
3.	Odds of a favourable response to treatment based on duration of disease		This outcome looked at whether the chances of people's signs and symptoms of neurosarcoidosis improving or resolving when they were treated with infliximab was affected by how long they had had the disease. The study by Gelfand et al, (2017) found that the odds of a favourable treatment response were lower in people who had had neurosarcoidosis for a longer time when infliximab was started (adjusted odds ratio 0.79, p=0.02). This suggests that the odds of responding to infliximab were better in people who had had the disease for a shorter period of time. However, the time periods that were compared were not specified in the paper. These results should be interpreted with caution per section one metric no. 10.
4.	Relapse		This outcome looks at the number of people whose signs and symptoms of neurosarcoidosis came back after they stopped using infliximab. Gelfand et al, (2017) found that neurosarcoidosis recurred in 56% of people (9/16) who had experienced remission after

			using infliximab for, on average, 1.5 years. Relapse occurred, on average, about 6 months after treatment was stopped. These results suggest that around half of people with neurosarcoidosis experience relapse when they have been treated with infliximab for about 1.5 years. These results should be interpreted with per section one metric no. 10.
5.	Changes in ePOST scores		This outcome looks at the change in scores obtained using the extrapulmonary physician organ severity tool (ePOST) before and after treatment with infliximab. For the full ePOST score, 17 individual organs (apart from the lungs) are scored on a scale from 0 (meaning not affected) to 6 (meaning very severely affected) and a total score is calculated (0 to 102). For this outcome, just the central nervous system (CNS) organ score is used because this is most relevant in neurosarcoidosis, and the score can range from 0 to 6. In the study by Jamilloux et al, (2017) the average ePOST CNS organ severity score changed from 3.78 to 2.62 after treatment with an anti-TNF (usually infliximab) in 63 people with neurosarcoidosis. This improvement is statistically significant (p=0.001) but it is unclear if it is clinically important. This shows that people's score improved by 1.16 on a 6-point scale, which suggests that, on average, their neurosarcoidosis improved. However, although individual people may feel quite a large benefit, others may experience no benefit, and it is unclear if a 1 point improvement is large enough to be important to the overall population with neurosarcoidosis. These results should be interpreted with caution per section one metric no. 10.
6.	Death		This outcome looks at how many people died while they were using infliximab for neurosarcoidosis. No deaths occurred during the study by Gelfand et al. In Jamilloux et al, (2017), 3

			people died but their deaths were not considered to be related to infliximab. This suggests that death is rare in people using infliximab for neurosarcoidosis. These results should be interpreted with caution because the studies are small, uncontrolled, and did not use standardised treatment and monitoring protocols. Weaknesses in the studies' design and conduct mean they are subject to bias and confounding, are difficult to interpret and cannot support firm conclusions.

Considerations from review by Rare Disease Advisory Group
Not applicable

Pharmaceutical considerations
The policy is recommending infliximab for the treatment of refractory or progressive neurosarcoidosis. This is an off-label use of infliximab. It is recommended that the best value infliximab product is used (likely to be a biosimilar). Infliximab is excluded from tariff.

Considerations from review by National Programme of Care
The Trauma Programme of Care Board supported this policy for routine commissioning on 01 October 2019.