CLINICAL PRIORITIES ADVISORY GROUP
10 July 2023

Agenda Item No	
National Programme	Internal Medicine
Clinical Reference Group	Specialised Rheumatology
URN	2204

Title
Infliximab for refractory sarcoidosis (excluding neurosarcoidosis) (Adults)

Actions Requested	1. Support the adoption of the policy proposition
	2. Recommend its relative prioritisation.

Proposition
Infliximab is recommended to be available off-label as a routine commissioning treatment option for refractory sarcoidosis (excluding neurosarcoidosis) within the criteria set out in the Clinical Policy Proposition. The policy proposition is restricted to adults in line with the findings from the evidence review. Infliximab may be used in children aged six years and older via NHS England's Policy 170001/P Commissioning Medicines for Children in Specialised Services (commissioning medicines children). Note that infliximab is not licenced in adults for sarcoidosis and therefore this is an off-label use.

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

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposition has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.
2.	The Head 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 Clinical Programmes 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.	Engagement Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality and Health Inequalities Impact Assessment

In people with refractory sarcoidosis[1], excluding neurosarcoidosis, what is the clinical effectiveness and safety of infliximab combined with current standard care (topical or systemic corticosteroids and /or at least one DMARD) compared with current standard care alone?

In people with progressive sarcoidosis[2], excluding neurosarcoidosis, what is the clinical effectiveness and safety of infliximab with or without steroids compared with steroids alone or no treatment?

Outcome	**Evidence statement**
Clinical Effectiveness	
Critical outcomes	
Mortality **Certainty of evidence:** Very low	Mortality is important to patients because it reflects how long people live after treatment, although it does not provide information about patients' health and wellbeing during that time.
	Refractory In total, one RCT and six case series reported mortality, with mean follow-up ranging from six weeks to 12 months. Mortality at six weeks • 1 RCT (Rossman et al 2006) of people with refractory pulmonary sarcoidosis reported mortality at six weeks. 1/13 (7.7%) people in

[1] Refractory sarcoidosis is defined as sarcoid disease that has failed to respond to corticosteroids and/or at least one disease modifying anti-rheumatic drug (DMARD) as current standard care for sarcoidosis or where there is contra-indication or intolerance in treatment with those agents as current standard care for sarcoidosis. This also includes patients with stable disease that is maintained on unsustainable prolonged doses of steroids.
[2] Progressive disease is defined as aggressive disease that manifests with risk of loss of organ function and/or risk to life and/or significant impairment of quality of life. Studies of patients with any form of chronic sarcoidosis treated with tumour necrosis factor alpha (TNF-α), where there was no indication that their disease was refractory to standard treatment, or that standard treatment is contraindicated were considered for inclusion.

	the IFX group died, compared with 0/6 (0%) in the placebo (PB) group. Statistical significance was not reported. **(VERY LOW)** Mortality at 18 weeks • 1 case series of 45 people with refractory mixed sarcoidosis (van Rijswijk et al 2013) reported mortality at 18 weeks. 0/45 (0%) people in the study died. **(VERY LOW)** Mortality at six months • 1 case series of 56 people with refractory mixed sarcoidosis (Vorselaars et al 2015) reported mortality at six months. 1/56 (1.8%) died during the study and 1/56 died several months after treatment discontinuation (1.8%). **(VERY LOW)** Mortality at 12 months • Four case series of people with refractory cardiac sarcoidosis (Gilotra et al 2021, Harper et al 2019), cutaneous sarcoidosis (Heidelberger et al 2017) and mixed sarcoidosis (Sakkat et al 2022) reported mortality at up to 12 months. There were no deaths in the two cardiac sarcoidosis case series (0/38: Gilotra et al 2021; 0/36: Harper et al 2019), one death (1/46; 2.2%) in the cutaneous sarcoidosis case series, although it is not clear whether this person had IFX or another anti-TNF, and one death in the mixed sarcoidosis case series (1/33; 3.0%, Sakkat et al 2022). **(VERY LOW)** **These studies provide very low certainty evidence that the mortality rate in people treated with IFX for refractory sarcoidosis is 7.7% at six weeks (based on one death in a very small RCT); none of the six patients being treated with placebo died during this period. Six case series provided very low certainty evidence that the mortality rate for patients being treated with IFX for refractory sarcoidosis is 0% to 2% at up to six months and 0% to 3% at 12 months.**
Certainty of evidence: Not applicable	**Progressive** No evidence was identified for this outcome.
Health-related quality of life (HRQL) **Certainty of evidence:** Very low to low	HRQL score is important to patients as it provides a holistic evaluation and indication of the patient's general health and perceived wellbeing.
	Refractory One RCT and two case series reported HRQL, with follow-up ranging from six weeks to six months. Studies used the SF-36, the fatigue severity domain of the CIS, and the PGA score to measure HRQL[a]. HRQL at six weeks • 1 RCT (Rossman et al 2006) of 19 people with refractory pulmonary sarcoidosis reported HRQL at six weeks using the SF-36. There was a very small improvement in mean score from baseline (26.72±0.45) to six-week follow-up (27.11±0.46) in the IFX group; statistical significance was not reported. There was no change from baseline in the PB group (26.43±0.83 to 26.4±0.81). No between group comparison was reported. **(LOW)** HRQL at 18 weeks

	• One case series of 45 people with refractory mixed sarcoidosis (van Rijswijk et al 2013) reported:
	  ○ a decrease of 5.3±8.5 points on the fatigue severity dimension of the CIS, indicating statistically significant improvement in fatigue (P= 0.003) **(VERY LOW)**
	  ○ an increase of 12.6±23.9 points on the physical functioning domain of the SF-36, indicating improvement; P= 0.011. **(VERY LOW)**
	HRQL at six months
	• One case series of 56 people with refractory mixed sarcoidosis (Vorselaars et al 2015) reported:
	  ○ a decrease of 14.6 points on the PGA score, indicating an improvement from baseline (P<0.0001). **(VERY LOW)**
	  ○ an increase of 8.2 points on the physical functioning domain of the SF-36, indicating improvement (P=0.009). **(VERY LOW)**
	The RCT provided low certainty evidence of a small improvement in HRQL compared to baseline at six weeks for people treated with IFX for refractory pulmonary sarcoidosis, but statistical significance was not reported. No between group comparison was reported. Two case series provided very low certainty evidence of statistically significant improvements compared to baseline in fatigue severity and physical functioning at 18 weeks to six months for people treated with IFX for refractory mixed sarcoidosis.

Certainty of evidence: Not applicable	**Progressive** No evidence was identified for this outcome.
Steroid use reduction	Steroid use reduction is important to those patients receiving steroids because steroid treatment is linked with iatrogenic health problems including osteoporosis, diabetes, hypertension, obesity, scarring and electrolyte disorders.
Certainty of evidence: Very low	**Refractory** Six case series reported steroid use at baseline and follow-up. Follow-up ranged from 18 weeks to 12 months. Steroid use reduction at 18 weeks • One case series of 45 people with refractory mixed sarcoidosis (van Rijswijk et al 2013) reported that there was no dose reduction. **(VERY LOW)** Steroid use at six months • Three case series (Gilotra et al 2021, Harper et al 2019, Vorselaars et al 2015) reported steroid use at six months. • Gilotra et al 2021 reported lower use of steroids at six-months (10.4±6.1 mg) compared with baseline in 38 people with refractory cardiac sarcoidosis (21.7±17.5 mg) (P=0.001). Harper et al 2019 reported a median (25^{th}-75^{th} percentile) dose of 20 mg (10-30 mg) at baseline in 35 people with refractory cardiac sarcoidosis, which reduced to 7.5 mg (2.5-15 mg) (P<0.01). Vorselaars et al 2015

	reported a mean dose reduction of 8.8 mg among the 19 people with refractory mixed sarcoidosis taking prednisone at baseline (P=0.001)**. (VERY LOW)** Steroid use at 12 months • Four case series reported steroid use at 12 months (Gilotra et al 2021, Harper et al 2019, Heidelberger et al 2017, Sakkat et al 2022). • Gilotra et al 2021 reported lower use of steroids at six-months (7.3±7.3 mg) compared with baseline (21.7±17.5 mg) (P=0.002) in 38 people with refractory cardiac sarcoidosis**.** Harper et al 2019 reported a median (25th-75th percentile) dose of 20 mg (10-30 mg) at baseline, which reduced to 5 mg (0-10 mg) in the 29 people with refractory cardiac sarcoidosis available at 12-month follow-up (P<0.01**).** Heidelberger et al 2017 reported a reduction from 17.5 mg at baseline to 8.4 mg at last follow-up (up to 12 months) (P<0.001) in 46 people with refractory cutaneous sarcoidosis. Sakkat et al 2022 reported a reduction in mean daily dose from 21.7mg±12.7 at baseline to 10.5 mg±8.3 at 12 months (n=22 with mixed sarcoidosis). **(VERY LOW)** **Although one case series provided very low certainty evidence of no reduction in steroid use at 18 weeks, statistically significant reductions in steroid dose compared to baseline after six months (3 case series) and 12 months (4 case series) of treatment with IFX were reported for people with refractory sarcoidosis, with dose reductions in the region of 9 to 15mg per day.**
Certainty of evidence: Not applicable	**Progressive** No evidence was identified for this outcome
Important outcomes	
Sarcoid disease activity **Certainty of evidence:** **Very low**	Sarcoid disease activity is important to patients because it provides a method of measuring treatment response. **Refractory** Four case-series reported sarcoid disease activity as the number of responders following treatment with IFX, with follow-up at six to 12 months. Sarcoid disease activity at six months One case series of 56 people with refractory mixed sarcoidosis (Vorselaars et al 2015) calculated a composite overall response rate based on organ function, inflammatory activity and quality of life response. 40% had an excellent response, 39% a good response, 17% a partial response and 4% no response. **(VERY LOW)** Sarcoid disease activity at 12 months Three case series reported sarcoid disease activity at 12 months following treatment for refractory disease with IFX (Harper et al 2019, Heidelberger et al 2017, Sakkat et al 2022).

	• Harper et al 2019 described 24 of 36 (66.7%) people with refractory cardiac sarcoidosis as responders (20 of whom had steroid dose reduction, 12 improved dysrhythmia control and eight improved EF); nine people were described as non-responders (five of whom improved in at least one domain), and 3 remained stable. • Heidelberger et al 2017 described 31 of 46 (67.4%) people with refractory cutaneous sarcoidosis as responders (13 complete response, 18 partial response); 11 of 31 responders (35%) relapsed during treatment (8 during dose spacing or reduction of anti-TNF (n=3) or tapering of SS (n=3) or IS (n=2). • Sakkat et al 2022 stated that, of 11 people with refractory mixed sarcoidosis who discontinued treatment with IFX due to improvement or resolution of disease activity, seven relapsed. Median time to relapse: 8±2.04 months. **(VERY LOW)** **These studies provide very low certainty evidence that the majority of people (67% to 96%) treated with IFX for refractory were classified as having at least a partial response at six to 12 months, although definitions of response varied between studies and reduction in sarcoid disease activity was not maintained in 35% to 64% of responders.**
Certainty of evidence: Not applicable	**Progressive** No evidence was identified for this outcome.

Organ-specific disease activity	Measures of organ-specific disease activity are important to patients as objective measures of functioning of affected organs. Given the progressive nature of sarcoidosis, disease activity results might not be expected to return to normal following treatment, however, stabilisation may indicate treatment has successfully limited disease progression.
Certainty of evidence: **Very low to low**	**Refractory** In total, one RCT and six case-series provided data on organ-specific disease activity following treatment with IFX for refractory sarcoidosis. Follow-up ranged from six weeks to 12 months. Organ-specific activity included pulmonary function, upper airway function, cardiac function, cutaneous response, a general ePOST score for non-pulmonary sarcoidosis, peripheral lymph nodes, gastrointestinal function, uveitis and arthritis. Pulmonary function at six weeks • One RCT (n=19) (Rossman et al 2006) of 19 people with refractory pulmonary sarcoidosis reported VC as a measure of pulmonary function at six weeks: o a larger increase in % change from baseline expected VC in the IFX group (15.22±9.91%) vs the PB group (8.39±3.33%), although statistical significance was not reported for the change from baseline, and no between group comparison was reported. **(LOW)** o 2/13 IFX and 0/6 PB patients had a 15% improvement from baseline VC (no statistical significance reported for change from baseline, and no between group comparison reported). **(LOW)** o similar observed mean VC at baseline (2.47±0.2) and six weeks (2.65±0.19) in the IFX group, and in the PB group (2.37±0.31 at baseline; 2.40±0.28 at six weeks) (no between group statistical significance reported). **(LOW)** o an increase in % expected VC, from 59.63±3.69 at baseline to 64.68±3.60 in the IFX group, compared to an increase from 65.5±2.99 to 67.67±3.31 in the PB group (no between group statistical significance reported). **(LOW)** Pulmonary function at 18 weeks • One case series of 45 people with refractory mixed sarcoidosis (van Rijswijk et al 2013) reported statistically significant improvements compared to baseline for various measures: o % predicted FVC: +5.4±7.6 (P<0.0001) **(VERY LOW)** o % predicted FEV1: +5.3±8.3 (P<0.0001) **(VERY LOW)** o % predicted DLCO: +3.1±7.3 (P=0.012) **(VERY LOW)** Pulmonary function at six months • One case series of 56 people with refractory mixed sarcoidosis (Vorselaars et al 2015) reported improvements in various measures for a subgroup (n=28) with pulmonary treatment indication. o % predicted FVC: baseline: 73.6; change at 6 months: +6.6 (P=0.0007) **(VERY LOW)**

	○ % predicted FEV1: baseline: 55.8; change at 6 months: +5.8 (P<0.0001) **(VERY LOW)** ○ % predicted DLCO: baseline: 56.6%; change at 6 months: +4.1 (P=0.001) **(VERY LOW)** ○ % predicted 6MWD: baseline: 61.0; change at 6 months: +4.2 (P value not reported) **(VERY LOW)** Pulmonary function at 12 months • One case series of 14 people with refractory mixed sarcoidosis (Sakkat et al 2022) reported change from baseline as: ○ FEV1: +90ml (55% increase) (95% CI -0.31 to 0.39)[b] **(VERY LOW)** ○ FVC: -20ml (0.77% decrease) (95% CI − 0.18 to 0.24) **(VERY LOW)** ○ % with treatment success (defined as an increase in absolute FVC or FEV1 by >10% or no change in FVC or FEV1 (± 10% from baseline): 78.6% (95% CI 49.2–95.3) **(VERY LOW)** Cardiac function at six months • Two case series reported cardiac function at six months compared to baseline (Gilotra et al 2021, Harper et al 2019). • Gilotra et al 2021 reported that mean (SD) LVEF% changed from 52.6±15.9 (n=37) at baseline to 53.8±17.1 (n=26) at six months, based on FDG-PET findings (statistical significance not reported). They also reported no significant change in LVEF on ECG before and after treatment (from 45±16.5% to 47±15.0%; P=0.10; n=29). **(VERY LOW)** • Harper et al 2019 reported EF% as median (25th-**75th** percentile), with no change **(**P=0.43) from baseline 41 (32-55) (n=31) to six months 41 (35-54) (n=28). **(VERY LOW)** • Harper et al 2019 also reported ICD therapy use, reducing slightly from 4/25 (16%) at baseline to 2/23 (8.7%) at 6 months (statistical significance not reported) **(VERY LOW)** Cardiac function at 12 months • Two case series reported change in cardiac function from baseline to 12 months (Gilotra et al 2021, Harper et al 2019). • Gilotra et al 2021 reported that LVEF changed from 52.6±15.9 (n=37) at baseline to 49.3±16.1 (n=15) at 12 months (statistical significance not reported). **(VERY LOW)** • Harper et al 2019 reported ICD therapy use, reducing slightly from 4/25 (16%) at baseline to 2/16 (12.5%) at 12 months (P=0.45). This study did not report EF% at 12 months. **(VERY LOW)** Cutaneous sarcoidosis activity • One case series (n=46) (Heidelberger et al 2017) described the OCRR at 3, 12 and 6 months. The baseline value was not reported. **(VERY LOW)** ○ 3 months: 24% (95% CI 14% to 40%) ○ 6 months: 46% (95% CI 32% to 62%) ○ 12 months: 79% (95% CI 64% to 98%)

	Cutaneous sarcoidosis activity at 12 months
	• Two case series described changes in cutaneous sarcoidosis at 12 months (Heidelberger et al 2017, Sakkat et al 2022).
	• Heidelberger et al 2017 reported that the median ePOST severity score (ranging from 0 to 6 for increasing severity) was 5 at baseline and 3 at last follow-up.
	• Sakkat et al 2022 defined treatment success as a 50% improvement in skin lesions in comparison to baseline images, with treatment success seen in 91.7% (61.5% to 99.8%) of the 12 people with cutaneous sarcoidosis in this study. **(VERY LOW)**
	Other organ-specific disease activity
	• One case series (Sakkat et al 2022) also reported treatment success rates following treatment with IFX, for other organs not already covered.
	  ○ upper airway (n=7): 71.5% (29.0% to 96.3%) had improvement in structural change on serial exam and imaging. **(VERY LOW)**
	  ○ peripheral lymph nodes (n=1): 100% (2.5% to 100%) had resolution of lymphadenopathy, based on clinical assessment. **(VERY LOW)**
	  ○ gastrointestinal sarcoidosis (n=1): 100 (2.5% to 100%) had resolution of symptoms and normalization of laboratory testing. **(VERY LOW)**
	  ○ uveitis (n=1): 100% (2.5% to 100%) had resolution of symptoms and improvement of abnormalities on serial eye exam. **(VERY LOW)**
	  ○ arthritis (n=1): 100% (2.5% to 100%) had resolution of symptoms and normalization of laboratory testing. **(VERY LOW)**
	For the population of people with refractory sarcoidosis, one RCT study presents low certainty evidence of improvements in pulmonary function in terms of % expected VC at six weeks following treatment with IFX. One case series and the subgroup of people with pulmonary indication in another case series provide very low certainty evidence of statistically significant improvements compared to baseline in % predicted FVC, FEV1 and DLCO at 18 weeks and 6 months, respectively, and the subgroup from one case series presents low certainty evidence of improvement from baseline 6MWD at six months (statistical significance not reported). Changes in pulmonary function did not appear to be significant at 12 months, although 78.6% were considered to have had treatment success at that time, (defined as an increase in absolute FVC or FEV1 by >10% or no change in FVC or FEV1 (± 10% from baseline).
	In terms of cardiac function, very low certainty evidence suggests that compared to baseline, there were no statistically significant changes in LVEF, EF or ICD therapy use at six or 12 months.
	Very low certainty evidence from one case series reported that 24% of people treated with IFX for refractory cutaneous sarcoidosis responded at three months, rising to 46% at six months. At 12 months, results from two case series reported that the proportion of responders to IFX was between 79% and 92%.

Certainty of evidence: Not applicable	**Progressive** No evidence was identified for this outcome.
Radiographic changes **Certainty of evidence:** Very low to low	Changes to the appearance of X-rays and scans of affected organs or systems are important to patients as they are used to help determine treatment success and requirement for further treatment. Given the progressive nature of sarcoidosis, imaging results might not be expected to return to normal, however, stabilisation may indicate treatment has successfully limited disease progression and may be associated with improvement in clinical features. **Refractory** One RCT and six case series reported radiographic changes at follow-up ranging from six weeks to 12 months. Radiographic change at six weeks • One RCT (Rossman et al 2006) of 19 people with refractory pulmonary sarcoidosis reported radiologic improvement in 23% of 13 IFX patients compared with 0% of six PB patients. No statistical analysis was reported. **(LOW)** Radiographic change at 18 weeks • One case series (van Rijswijk et al 2013) reported ^{18}F-FDG PET (SUVmax) for 45 people with refractory mixed sarcoidosis. Mean±SD change from baseline was -2.7±3.4 (P< 0.00005) for pulmonary parenchyma and -2.3±3.4 (P<0.0005) for the mediastinum. **(VERY LOW)** Radiographic change at six months • One case series of 56 people with refractory mixed sarcoidosis (Vorselaars et al 2015) and one case series of 38 people with refractory cardiac sarcoidosis (Gilotra et al 2021) reported radiographic change at six months. • Vorselaars et al 2015 reported decreases in SUVmax of 2.97 (P<0.0001) for the mediastinum, 3.93 (P<0.0001) for the lung parenchyma **and** 5.76 (P<0.0001) for the lungs and index localisation (e.g. heart) in 49 patients with mixed refractory sarcoidosis. **(VERY LOW)** • Vorselaars et al 2015 reported mean change±SD from baseline 18F-FDG PET (SUVmax) to be -5.3±5.6 for lung parenchyma, -2.7±3.8 for the mediastinum and -5.5±5.6 for the index localisation in a subgroup of 28 patients with refractory pulmonary sarcoidosis. Statistical significance was not reported. **(VERY LOW)** • Gilotra et al 2021 reported that SUVmax values were 0.54±1.6 for 23 people with refractory cardiac sarcoidosis at six months, compared with 4.1±4.5 at baseline (n=34). **(VERY LOW)** Radiographic change at 12 months • One case series (Gilotra et al 2021) reported that SUVmax values were 0.65±1.5 for 11 people with refractory cardiac sarcoidosis at six months, compared with 4.1±4.5 at baseline (n=34). **(VERY LOW)**

	These studies provide low certainty evidence of radiologic improvement at six weeks in people treated with IFX for refractory pulmonary sarcoidosis. There was very low certainty evidence from one case series for statistically significant improvements at 18 weeks for patients treated with IFX for refractory mixed sarcoidosis. Very low certainty evidence was reported for statistically significant improvement in radiological changes from baseline to six months in people with refractory mixed sarcoidosis. One study presented improvement from baseline to six and 12 months in people with refractory cardiac sarcoidosis, but statistical significance was not reported.
Certainty of evidence: Not applicable	**Progressive** No evidence was identified for this outcome.
Normalisation of calcium, lymphocytes, angiotensin-converting enzyme (ACE) and cytokine blood tests **Certainty of evidence:** Very low	Assessment of inflammatory biomarkers is important to patients because these blood tests are a quantifiable measure of disease activity and treatment response. Return to normal levels can indicate biochemical remission and may be associated with improvement in clinical features.
	Refractory Two case series reported change in ACE and serum sIL-2R, at 18 weeks and six months. ACE and serum sIL-2R at 18 weeks • One case series (van Rijswijk et 2013) reported a statistically significant reduction compared to baseline in serum ACE Z-score in 45 people with refractory mixed sarcoidosis: -2.01±3.31; P<0.0005. **(VERY LOW)** • van Rijswijk et al 2013 also reported a significant reduction compared to baseline in serum sIL-2R in 45 people with refractory mixed sarcoidosis: 2879±3755 pg/ml; P<0.00001. **(VERY LOW)** ACE and serum sIL-2R at 12 months • One case series (Vorselaars et al 2015) reported a significant decrease of serum ACE of 28.2 U/L (P=0.0003) from baseline in 49 patients with refractory mixed sarcoidosis. **(VERY LOW)** o In a subgroup with pulmonary sarcoidosis (n=28), a reduction in serum ACE of 21.8±43.3 U/L compared to baseline was reported (statistical significance not reported). **(VERY LOW)** o Vorselaars et al 2015 also reported a reduction in ACE Z-score of 1.78±3.33 compared to baseline in a subgroup with pulmonary sarcoidosis (n=28) (statistical significance not reported). **(VERY LOW)** • Vorselaars et al 2015 reported a significant decrease in serum sIL-2R (n=47) from baseline of 4269.4 pg/ml (P<0.0001). **(VERY LOW)** o In a subgroup with pulmonary sarcoidosis (n=28), Vorselaars et al 2015 reported a reduction in serum sIL-2R from baseline of 3955±3883 pg/ml. **(VERY LOW)** **Two case series provided very low certainty evidence of statistically significant reductions in ACE (either serum ACE or Z-value) and serum IL-2R compared to baseline. One of the case series also**

Certainty of evidence: Not applicable	**reported reductions in these markers for a subgroup of patients with pulmonary indication, but did not report statistical significance for these. None of the studies provided evidence for calcium, lymphocytes and cytokine blood tests.**
	Progressive No evidence was identified for this outcome.
Safety	
Presence of serious treatment-emergent adverse events (grade 3, 4 or 5) **Certainty of evidence:** Very low to low	**Refractory** One RCT and six case series reported data on adverse events, although serious treatment-emergent adverse events were not always distinguished from other adverse events. Adverse events at six weeks • One RCT (Rossman et al 2006) reported that 2/13 (30.8%) of the IFX group and 1/6 (16.7%) of the PB group had at least one AE at six weeks (1 IFX patient had right leg cellulitis; acute renal failure, pulmonary emboli, reoccurrence of cellulitis; 1 IFX patient had decreased white blood cell count and elevated creatine phosphokinase; 1 PB patient had shortness of breath). **(LOW)** Serious adverse events at 18 weeks • One case series (van Rijswijk et al 2013) reported that 1/45 (2.2%) people were hospitalised due to pneumonia, and 0/45 had tuberculosis. **(VERY LOW)** Serious adverse events at six months • One case series (Vorselaars et al 2015) reported that 3/56 (5.4%) people were hospitalised due to pneumonia and had to discontinue treatment. **(VERY LOW)** Serious adverse events and adverse events at 12 months • Four case-series reported a mixture of AE and SAE at 12 months. Gilotra et al 2021 reported 3 cases of shingles, 1 case of metapneumovirus pneumonia and one urinary tract infection. Harper et al 2019 reported one case of pneumonia pulmonary embolism, 1 case of c difficile diarrhoea, one case of shingles and one case of sepsis. Sakkat et al 2022 did not report SAE separately from AE.). Heidelberger et al 2017 reported that 7/46 (15.2%) people were hospitalised for a grade 3 or 4 infection **(VERY LOW)** **Data on SAE were not generally presented clearly and separately from other AE. For people with refractory sarcoidosis, there was low certainty evidence of an SAE rate of approximately 31% at six weeks, and very low certainty evidence that approximately 2% to 5% of people may experience an AE at 18 weeks to six months. Very low certainty evidence suggests that around 15% of people on IFX may experience a grade 3 or 4 infection requiring hospitalisation at 12 months.**
Certainty of evidence:	**Progressive** No evidence was identified for this outcome.

Not applicable	
Treatment-emergent adverse events leading to treatment discontinuation **Certainty of evidence:** Very low to low **Certainty of evidence:** Not applicable	**Refractory** One RCT and six case series reported data on discontinuations due to adverse events following treatment with IFX for refractory sarcoidosis. Discontinuations due to AE at six weeks • One RCT (Rossman et al 2006) reported that 15% of IFX vs 17% of PB patients discontinued treatment with IFX due to AE. **(LOW)** Discontinuations due to AE at 18 weeks • One case series (van Rijswijk et al 2013) reported that 1/45 (2.2%) discontinued due to AE. **(VERY LOW)** Discontinuations due to AE at six months • One case series (Vorselaars et al 2015) reported that 5/56 (8.9%) discontinued due to AE. **(VERY LOW)** Discontinuations due to AE at 12 months • Four case-series reported discontinuation rates due to AE of 2.6%, 2.8%, 24% and 21% (Gilotra et al 2021, Harper et al 2019, Heidelberger et al 2017, Sakkat et al 2022, respectively). **(VERY LOW)** For people with refractory sarcoidosis, one RCT provided low certainty evidence of a 15% discontinuation rate at six weeks in the IFX group, with a similar rate (17%) of discontinuation in the PB group. There was very low certainty evidence from case series of discontinuation rates at 18 weeks to 12 months, ranging from approximately 2% to 24%. **Progressive** No evidence was identified for this outcome.

Abbreviations

ACE: angiotensin-converting enzyme; AE: adverse events; CIS: Checklist Individual Strength; DLCO: diffusing capacity of the lungs for carbon monoxide; ECG: electrocardiography; EF: ejection fraction; ePOST: extrapulmonary Physician Organ Severity Tool; FEV1: forced expiratory volume in 1 second; ^{18}F-FDG PET (SUVmax): maximum standard uptake value on positron emission tomography (PET) using glucose analogue fluorine-18-labeled fluorodeoxyglucose (FDG); FVC: forced vital capacity; HRQL: Health-related quality of life; ICD: implantable cardioverter defibrillator; IFX: infliximab; IS: immunosuppressive agents; LVEF: left ventricular ejection fraction; OCRR: overall cutaneous response rate; PB: placebo; PGA: Patient Global Assessment; RCT: randomised controlled trial; SAE: serious adverse events; SD: standard deviation; SF-36: 36-item Short Form questionnaire; sIL-2R: soluble interleukin-2 receptor; SS: systemic steroids; SUVmax: maximum standard uptake value; VC: vital capacity; 6MWD: six-minute walking distance

a. HRQL tools

- SF-36: physical functioning subscale or total score (physical and mental health subscales combined). 0-100 scale: lower scores indicate lower quality of life.
- Checklist Individual Strength; fatigue severity dimension: higher scores indicate greater fatigue, cut-off score of 35 for severe fatigue.

- Patient Global Assessment score: visual analogue scale 0-100, higher scores indicate lower quality of life.

b. This is the confidence interval given in the paper, but it does not appear to include the difference of 90ml (55% increase).

In people with refractory sarcoidosis, excluding neurosarcoidosis, what is the cost effectiveness of infliximab combined with current standard care (topical or systemic corticosteroids and /or at least one DMARD) compared with current standard care alone?
In people with progressive sarcoidosis, excluding neurosarcoidosis, what is the cost effectiveness of infliximab with or without steroids compared with steroids alone or no treatment?

Outcome	Evidence statement
Cost effectiveness	**Refractory** **No evidence was identified for cost effectiveness.**
	Progressive **No evidence was identified for cost effectiveness.**

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

Outcome	Evidence statement

Subgroups
Certainty of evidence:
Very low
	Refractory
	Two case series (Heidelberger et al 2017; Vorselaars et al 2015) reported subgroup analyses.
	• Heidelberger et al 2017compared people with a skin-only indication for IFX (n=21) against those with visceral involvement (n=25).
	  ○ Baseline ePOST score was 5 in the skin-only indication group compared with 3 in the visceral involvement group (P<0.001), indicating more serious disease in the skin-only group. The study did not report the ePOST score for the subgroups at follow-up.
	  ○ There was a higher use of concomitant systemic steroids among people with a skin-only indication (18; 76%) compared with 7 (33%) of people with visceral involvement (P=0.003).
	  ○ There was little difference in the OCRR between subgroups (13 (62%) for skin-only vs 19 (72%) for visceral involvement; P=0.67).
	  ○ The number of infections was significantly lower among people with a skin-only indication compared with those with visceral involvement (2/21 (9.5%) vs 12/25 (48%), respectively; (P=0.02).
	• Vorselaars et al 2015 presented results for a subgroup of people with pulmonary indication for treatment. ACE was higher in people with extrapulmonary treatment indication (97.8 U/L) than for people with pulmonary indication (86.2 U/L).

	There was very limited information available on subgroups. Very low certainty evidence from one case series suggests that people with skin-only indications for IFX use may have fewer infections than those with visceral involvement, but they may be more likely to require concomitant systemic corticosteroids. There did not appear to be any difference in OCRR. However, baseline differences in ePOST score suggest that people with a skin-only indication may have had more severe disease before IFX initiation. Very low certainty evidence from one case series found that ACE was higher in people with extrapulmonary indication than for people with pulmonary indication.
Certainty of evidence: Not applicable	**Progressive** No evidence was identified.
Abbreviations ACE: angiotensin-converting enzyme; ePOST: extrapulmonary Physician Organ Severity Tool; IFX: infliximab; OCRR: overall cutaneous response rate	

From the evidence selected,

- **what are the criteria used by the research studies to define refractory and progressive sarcoidosis?**
- **what were the loading dose, loading regime and ongoing schedule/dose used for infliximab?**

Outcome	Evidence statement
Criteria used to define refractory and progressive sarcoidosis	**Refractory** The studies generally defined people with refractory sarcoidosis as those in whom previous treatment had failed, or who had serious adverse effects from corticosteroids/previous treatment (Rossman et al 2006; Heidelberger et al 2017). Van Rijswijk et al 2013 used a broader definition of previous medication that included corticosteroids, antimalarial drugs and methotrexate, and also commented that infliximab was given to people with unremitting disease activity (shown by elevated serum markers or increased uptake on PET scan). Vorselaars et al 2015 required people to be unresponsive to first- and second-line treatment, or to have experienced severe side-effects from these. Studies in cardiac sarcoidosis were more detailed, with Gilotra et al 2021 describing three scenarios under which TNF-α inhibitors would be offered: persistent cardiac inflammation despite immunosuppressive treatment; clinically active cardiac sarcoidosis defined by cardiac clinical events; intolerable side effects from immunosuppression regimens. Similarly, Harper et al 2019 defined refractory cardiac sarcoidosis as “progression of cardiac symptoms or cardiac involvement and failure of management with steroids and steroid sparing agents”. Sakkat et al 2022 did not present exact criteria, simply referring to people with ‘biopsy-proven refractory sarcoidosis’.

	Progressive No evidence was identified.
Loading dose, loading regime and ongoing schedule/dose used for infliximab	**Refractory** Studies generally reported use of IV IFX at a dose of 5mg/kg for the majority of patients. Three studies used a standard dosing schedule of 5mg/kg at weeks 0 and 2 (Rossman et al 2006), or at weeks 0 and 2 then every four weeks up to 18 weeks (van Rijswijk et al 2013) or six months (Vorselaars et al 2015). A slightly lower dose of 3 to 5mg/kg at weeks 0, 2 and 6 was reported by Sakkat et al 2022, followed by IFX every four to eight weeks for a variable duration that was individualised depending on clinical response, adverse events and the availability of funding. Most patients received 12 months of treatment, five completed 36 weeks. Harper et al 2019 used 5mg/kg of infliximab every four to six weeks with titration up to 10mg/kg for lack of response and lengthening of dosing interval to every eight weeks if the patient exhibited stability. 78% of participants had four-weekly dosing. Duration of treatment was unclear, but study stated that most received several years of IFX treatment; 35 of 36 patients completed at least six months and 29 completed at least one year of treatment. Gilotra et al 2021 mentions a “standard dosing frequency” and an average maximum dose of 6.1±2.2 (although 70% had a maximum dose of 5mg/kg). Treatment was for nine months, with a final follow-up 3 months after completion of IFX treatment. Heidelberger et al 2017: simply mentions “various regimen” and duration of treatment is not clear. The median (range) of follow-up was 45 (3 to 109) months.
	Progressive No evidence was identified.
Abbreviations: IV: intravenous; IFX: infliximab; PET: positron emission tomography; TNF-α: tumour necrosis factor-alpha	

Patient Impact Summary
The condition has the following impacts on the patient’s everyday life: • **mobility:** Patients have slight problems in walking about • **ability to provide self-care:** Patients have moderate problems in washing or dressing • **undertaking usual activities:** Patients have moderate problems in doing their usual activities • **experience of pain/discomfort:** Patients have moderate pain or discomfort

- **experience of anxiety/depression:** Patients are moderately anxious or depressed

Further details of impact upon patients:

Sarcoidosis is a disease that is causes by inflammation throughout the body. Fatigue is the one of the most reported symptoms, with the majority of sarcoidosis patients displaying symptoms of fatigue at time of diagnosis. Chronic fatigue after sarcoidosis is often accompanied by pain (throat, head, lymph nodes, joints); concentration and memory problems; sickness after exertion; anxiety and depression; uncomfortable walking; decreased muscle strength; less physical activity. As such, chronic fatigue after sarcoidosis decreases quality of life significantly.

Additionally, those with pulmonary sarcoidosis will struggle on daily basis with seemingly simple tasks, such as walking more than 100 meters a day. For these patients, sarcoidosis can have an extremely debilitating and devastating impact on their lives.

Some patients will suffer with ocular sarcoidosis which can affect their vision, leaving some severely visually impaired. For these patients the disease can remove all sense of independence in their lives and make them entirely dependent on others.

Sufferers in support groups often talk about their struggles with GPs, family, and employers to have their mental and physical symptoms understood.

Patients with more severe sarcoidosis are usually treated with conventional disease modifying anti-rheumatic drugs (cDMARDs) first line. However, for the small proportion of patients who have refractory or progressive sarcoidosis, they will not show any response to cDMARDs. This is a particular concern since they will return to life- or organ-threatening disease activity. To treat this, they will often be given high dose steroids to suppress disease progression. Long term steroid use leads to long term side effects such as weight gain, osteoporosis, depression, infection, and early cardiovascular disease. (SarcoidosisUK.org)

Further details of impact upon carers:

Those living with and caring for people with sarcoidosis may find themselves in this role suddenly and it can require a complete upheaval in the way they are living their life.

Often, they might be providing help with medication, hospital appointments or emergency attendances and hospitalisations and this requires a lot of organisation and time whilst trying to balance other responsibilities such as employment or childcare. Carers of people with sarcoidosis often reduce their working hours or give up work to provide care. These challenges are only more substantial for carers of people with severe disease and limited treatment options, who live with more uncertainty and morbidity.

Considerations from review by Rare Disease Advisory Group
RDAG were supportive of the proposition

Pharmaceutical considerations
This policy proposition recommends the use of intravenous infliximab as a treatment option for refractory sarcoidosis (excluding neurosarcoidosis) in adults. The recommendations are outside of the marketing authorisation of infliximab, so use is off-label and Trust policy regarding unlicensed medicines should apply. Access for children aged six years and older is available in line with the Commissioning Medicines for Children policy; a separate prior approval form is available for children.

Considerations from review by National Programme of Care
The proposal received the full support of the Internal Medicine PoC on the 30th May 2023.