National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Anakinra for treating Still's disease [ID1463]

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Swedish Orphan Biovitrum	A clinical commissioning policy for use of anakinra and tocilizumab (NHSE Ref 1609) in Adult Onset Still's Disease (AOSD) has recently been approved by NHS England and adopted into clinical practice. The policy concluded that anakinra should be made available for treatment of AOSD for patients who failed DMARD's. This did not include systemic juvenile idiopathic arthritis (SJIA) which is included in the JIA policy (NHSE ref E03X04). SJIA and AOSD are rare systemic inflammatory disorders that share common clinical manifestations, Although treated as separate diagnostic entities, there is a growing understanding that SJIA and AOSD are one single disease, here referred to as Still´s disease, representing a continuum of a disease entity with onset at different ages: childhood in SJIA and adulthood in AOSD.	Comments noted. No changes to the scope are needed.
	Royal College of Pathologists	A clinical commissioning policy for use of anakinra and tocilizumab (NHSE Ref 1609) in Adult Onset Still's Disease (AOSD) has recently been approved by NHSE and adopted into clinical practice. This policy has already evaluated the clinical evidence and cost effectiveness of anakinra for AOSD. The process which included contribution from clinical experts, extensive literature review and detailed health economic assessment, concluded that anakinra	Comments noted. An appraisal of anakinra has been scheduled into NICE's technology appraisal work programme (see

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		should be made available for treatment of AOSD for patients who failed DMARD's. Therefore in my opinion, the proposed health technology proposal would constitute unnecessary duplication of the work that was already completed. Although, the policy did not include systemic juvenile idiopathic arthritis (sJIA), there is scope to extend the indication based on the evidence the was already gathered for AOSD policy.	https://www.nice.org.uk/guidance/proposed/gid-ta10392). No changes to the scope are needed.
	British Society for Rheumatology (endorsed by Royal College of Physicians)	The remit mentions systemic features of Stills but not the common hyperinflammatory syndrome of macrophage activation syndrome which affects 10% of these patients and for which anakinra is indicated. This is an important point which the remit should make explicit The applicable age range should be explicitly clarified	Comments noted. The background section has been amended to include reference to macrophage activation syndrome (MAS) and the NHS England clinical commissioning policy which recommends anakinra for people with MAS in systemic-onset Juvenile Idiopathic Arthritis (sJIA). People with MAS has also been included as a subgroup to be considered if the evidence allows. The scope is kept broad and inclusive to enable all relevant evidence to be considered; the age range specified in the marketing authorisation and the clinical trials will

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			be considered by the appraisal committee when making its recommendations.
Wording	Swedish Orphan Biovitrum	Yes, although the NHSE policies do not directly reflect the licence indications for the use of Anakinra. Sobi would like Anakinra to be appraised in a similar way to the NHSE policy – as treatment for patients with inadequate response to DMARDS rather than as potential first line therapy (as indication).	Comments noted. The technology will be appraised in line with its marketing authorisation but the company may wish to provide evidence for an 'optimised' position in the treatment pathway in its submission, which reflects its anticipated use in clinical practice.
	Royal College of Pathologists	Yes, but see above.	Comment noted. No changes to the scope are needed.
Timing Issues	Swedish Orphan Biovitrum	Not urgent, NHSE policies in place.	Comment noted. An appraisal of anakinra has been scheduled into NICE's technology appraisal work programme (see https://www.nice.org.uk/guidance/proposed/gid-ta10392). No changes

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			to the scope are needed.
	Royal College of Pathologists	This appraisal is not a priority for AOSD since there is an existing treatment policy in place. The situation is less evident for sJIA as currently the only treatment option is tocilizumab.	Comments noted. An appraisal of anakinra has been scheduled into NICE's technology appraisal work programme (see https://www.nice.org.uk/guidance/proposed/gid-ta10392). No changes to the scope are needed.
	British Society for Rheumatology (endorsed by Royal College of Physicians)	This should be a priority because: 1. Anakinra has been used for many years in children with systemic onset JIA and many will be transferring care to adult settings. These young adults should not have their treatment interrupted due to lack of the technology appraisal. 2. Children and adults can present with or develop macrophage activation syndrome (MAS) in up to 10% of cases. Some will also develop some features of MAS and be identified before a full blown picture develops. This is a life threatening condition with multisystemic organ involvement. Current treatments are not always successful and some patients require prolonged intensive care admission. The use of Anakinra as first line treatment in these situations can be lifesaving, reduces mortality, need for other treatments and reduces the intensive care stay. These patients may sustain avoidable morbidity and are draining NHS resources today and therefore the technology appraisal should include this particular indication as	Comments noted. An appraisal of anakinra has been scheduled into NICE's technology appraisal work programme (see https://www.nice.org.uk/guidance/proposed/gid-ta10392). The background section has been amended to include reference to MAS and the NHS England clinical commissioning policy which recommends anakinra for people with

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		it will cost the NHS less today and prevent morbidity related problems tomorrow.	MAS in sJIA. People with MAS has also been included as a subgroup to be considered if the evidence allows.
Additional comments on the draft remit	Swedish Orphan Biovitrum	No	Noted.
	British Society for Rheumatology (endorsed by Royal College of Physicians)	Limiting to the marketing authorisation will negatively impact on the need to recognise the role of Anakinra in managing a life threatening presentation/complication that is macrophage activation syndrome (MAS) despite the good available evidence.	Comments noted. The technology can only be appraised within its marketing authorisation. The background section has been amended to include reference to MAS and the NHS England clinical commissioning policy which recommends anakinra for people with MAS in sJIA. People with MAS has also been included as a subgroup to be considered if the evidence allows.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Swedish Orphan Biovitrum	Background information does not include reference to the use of Anakinra as current best clinical practice for treatment of AOSD and SJIA in European Reference Network (ERN) specialist centres.	Comment noted. The background section is intended to provide a brief overview of the disease and its associated management in the NHS. No changes to the scope are needed.
	Royal College of Pathologists	The background information does not include the fact that anakinra was previously used in routine clinical practice for both AOSD and sJIA. It also does not state that anakinra is approved for treatment of macrophage activation syndrome (MAS), a recognised complication of both AOSD and sJIA.	Comments noted. The background section has been amended to include reference to the NHS England clinical commissioning policy which recommends anakinra for people with MAS in sJIA.
	British Society for Rheumatology (endorsed by Royal College of Physicians)	The information is accurate. The information is not complete as it does not refer to macrophage activation syndrome (MAS)	Comments noted. The background section has been amended to include reference to MAS.
The technology/ intervention	Swedish Orphan Biovitrum	Yes, although the appraisal should be in line with NHSE policy rather than licence indication – not first line treatment but when inadequate response to DMARDs.	Comments noted. The technology will be appraised in line with its marketing authorisation but the company may

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			wish to provide evidence for an 'optimised' position in the treatment pathway in its submission, which reflects its anticipated use in clinical practice.
	Royal College of Pathologists	Yes	Comment noted. No changes to the scope are needed.
	British Society for Rheumatology (endorsed by Royal College of Physicians)	Yes	Comment noted. No changes to the scope are needed.
Population	Swedish Orphan Biovitrum	Yes.	Comment noted. No changes to the scope are needed.
	Royal College of Pathologists	Yes. Additional groups to consider are patients who go on to develop MAS.	Comment noted. People with MAS has been included as a subgroup to be considered if the evidence allows.
	British Society for	Macrophage activation syndrome is not defined as a group.	Comment noted. People with MAS has

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	Rheumatology (endorsed by Royal College of Physicians)		been included as a subgroup to be considered if the evidence allows.
Comparators	Swedish Orphan Biovitrum	The current NHSE policy for AOSD positions anakinra and tocilizumab as third line therapies, for patients with inadequate response to DMARD's. Therefore tocilizumab should be the primary comparator. Anti-TNF inhibitors are rarely used in Stills disease due to lack of efficacy and these should not be used as a comparator. Canakinumab is licensed for both AOSD and SJIA and although not included in the NHSE policy or used in routine clinical practice, it could be used as a comparator of efficacy.	Comments noted. The technology will be appraised in line with its marketing authorisation but the company may wish to provide evidence for an 'optimised' position in the treatment pathway in its submission, which reflects its anticipated use in clinical practice. The comparators section has been amended to remove reference to TNF-alpha inhibitors. The comparators section has been amended to include canakinumab.
	Royal College of Pathologists	The current commissioning policy places anakinra and tocilizumab (interchangeable) as a third line therapies, for patients with inadequate response to DMARD's. The best alternative care is DMARD's alone. Both anakinra and tocilizumab are superior to anti-TNF inhibitors, and these should	Comments noted. The comparators section has been amended to

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		not be used as a comparator. On the other hand, there is no mention of canakinumab, which is licensed for both AOSD and sJIA, but currently not used in routine clinical practice.	remove reference to TNF-alpha inhibitors. The comparators section has been amended to include canakinumab.
	British Society for Rheumatology (endorsed by Royal College of Physicians)	Where the patient has MAS as part of their AOSD analkinra is the preferred option for immediate treatment rather than tocilizumab – this needs to be specified Canakinumab is missing as a comparator	Comments noted. The background section has been amended to include reference to the NHS England clinical commissioning policy which recommends anakinra for people with MAS in sJIA, and people with MAS has been included as a subgroup to be considered if the evidence allows. The comparators section has been amended to include canakinumab.
Outcomes	Swedish Orphan Biovitrum	Yes.	Comment noted. No changes to the scope are needed.

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	Royal College of Pathologists	Yes	Comment noted. No changes to the scope are needed.
	British Society for Rheumatology (endorsed by Royal College of Physicians)	The outcome measure of inflammatory markers in bloods is mentioned but specific markers of macrophage activation syndrome and especially serum ferritin should be specified. The blood monitoring in MAS should include more than just inflammatory markers. Ferritin is the most important to be monitored but a composite picture should be formed using FBC, UE, LFT, LDH, CK, Clotting, Fibrinogen, D-Dimers as well as ESR/CRP. NK cell activity, perforin activity, sCD25 are all additional markers that may assist diagnosis or point towards other disease process.	Comments noted. The outcomes section has been amended to broaden the reference to blood markers.
Economic analysis	Swedish Orphan Biovitrum	None.	Noted.
	Royal College of Pathologists	OK	Noted.
	British Society for Rheumatology (endorsed by Royal College of Physicians)	In cases where patients develop MAS the time horizon should be shorter.	Comment noted. No changes to the scope are needed.
Equality and Diversity	Swedish Orphan Biovitrum	None.	Noted.
	Royal College of Pathologists	OK	Noted.

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	British Society for Rheumatology (endorsed by Royal College of Physicians)	In systemic onset juvenile arthritis anakinra is licensed and NICE approved for treatment where MAS is present. If similar provision is not made in adult onset stills there is clear inequality between the treatment of children and adults with the same condition given that SJIA and AOSD are considered to be the same disease.	Comments noted. Equalities issues raised will be acknowledged in the equality impact assessment published with the final scope. No changes to the scope are needed.
Other considerations	Swedish Orphan Biovitrum	None.	Noted.
	Royal College of Pathologists	Please see earlier comments about the existing policy and suggestion to expand this to include sJIA.	Comments noted. Please see earlier responses.
	British Society for Rheumatology (endorsed by Royal College of Physicians)	1. Limiting to market authorisation risks excluding patients with MAS from this appraisal when they are the most severely affected. MAS can be the presenting feature of Still's when the patient does not yet have the diagnosis and it is essential that Anakinra can be offered as a first line treatment. 2. Anakinra is already part of the treatment pathway for children with SoJIA. Still's is a continuum of the spectrum of presentation and therefore should have equal access.	Comments noted. Please see earlier responses.
Innovation	Swedish Orphan Biovitrum	Yes, Anakinra has been described as a huge step forward in the treatment of Stills disease, is currently best clinical practice used by ERN specialist centres for autoinflammatory diseases and could improve the lives of many patients with Stills disease, as well as reduce serious associated complications. Kineret is the only IL-1 inhibitor to be licensed for treatment for children under the age of two.	Comments noted. The potential innovative nature of the technology will be considered by the appraisal committee. No changes

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		Kineret may alter Still's disease pathophysiology and enable the withdrawal or tapering of glucocorticoids, therefore preventing patients from developing side effects associated with long term use of glucocorticoids. The 2011 American College of Rheumatology Recommendations for the Treatment of JIA, and the treatment recommendations issued by CARRA, where anakinra is recommended as one of the initial therapeutic options for patients with SJIA with active systemic features and varying degrees of synovitis although not indicated for the treatment of Still's disease at the time of recommendation.	to the scope are needed.
	Royal College of Pathologists	Yes. Anakinra is a step change in treatment of AOSD and sJIA. We have previously demonstrated that significant reduction in health-related costs (hospital admissions, A&E attendance, OP follow appointments) can be achieved with timely introduction of anakinra into treatment pathway. Furthermore, prevention of serious complications such as MAS and death, must be considered.	Comments noted. The potential innovative nature of the technology will be considered by the appraisal committee. No changes to the scope are needed.
	British Society for Rheumatology (endorsed by Royal College of Physicians)	Because the remit does not mention MAS (also called HLH) which is the most severe complication of AOSD an opportunity to consider the use of IL-1 blockade to reduce intensive care needed for patients will be missed. I am not a health economist but as a clinician regularly treating young people with MAS secondary to SJIA I know that anakinra reduces the chances they will need to go to ITU and this is identical issue in AOSD but not specified in the remit or scope	Comments noted. The background section has been amended to include reference to MAS, and people with MAS has also been included as a subgroup to be considered if the evidence allows.
Questions for consultation	Swedish Orphan Biovitrum	**At which stage in therapy do you anticipate anakinra would be used?**	Thank you for your comments.

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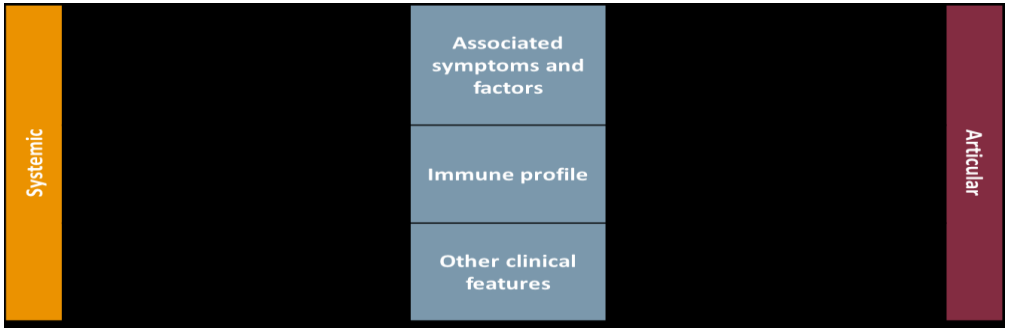
		As described above, as third line treatment, when corticosteroids and DMARDS are inadequate. **Are people with systemic juvenile idiopathic arthritis that has continued into adulthood likely to be covered by this appraisal?** Yes, absolutely, that should be part of this appraisal **How is active disease defined? How might features of moderate to high disease activity be defined and differentiated?** Active disease is defined as follows :  The two subtypes, 'Systemic' and 'Articular' are terms used in the NHSE policy for AOSD and this probably applies to SJIA as well. This then defines the cytokine to be inhibited IL-1 or IL-6 as a first step, but allows for a switch over if not adequately controlled. **Which treatments are considered to be established clinical practice in the NHS for systemic juvenile idiopathic arthritis and adult-onset Still's disease?** First line treatment : Corticosteroids and NSAID's Second line Treatment: DMARDS e.g. Methotrexate. Third line: IL-1 or IL-6 blockade dependant on Systemic v Articular, followed by switch from IL-1/IL-6 to alternative if inadequate response.	The comparators section has been amended to remove reference to TNF-alpha inhibitors. The comparators section has been amended to include canakinumab. People with MAS has been included as a subgroup to be considered if the evidence allows. The potential innovative nature of the technology will be considered by the appraisal committee.

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		Have all relevant comparators for anakinra been included in the scope? No, Canakinumab is an IL-1 inhibitor which is licenced for Stills disease (along with other autoinflammatory diseases) so should be considered a comparator. TNF inhibitors are rarely used for Stills disease. **Are the outcomes listed appropriate?** Yes. **Are the subgroups suggested in 'other considerations' appropriate?** Yes. **Are there any other subgroups of people in whom anakinra is expected to be more clinically effective and cost effective or other groups that should be examined separately?** Although the 'Systemic' v 'Articular' subgroups provide a starting point in differentiation of Stills disease patients it is not definitive so some scope is required to use an 'Either/Or' strategy when treating Stills disease. Also, patients who are more likely to develop a life threatening condition such as MAS should be considered and experts in these conditions consulted as to the evidence and best current clinical practice. **Where do you consider anakinra will fit into the existing NICE pathway for musculoskeletal conditions?** Probably best fits into 'Musculoskeletal conditions: general and other', although could potentially also fit the 'Blood and immune system conditions: general and other' as it is not necessary for joint involvement prior to diagnosis of Stills disease, especially if it is the more 'Systemic' form. **Do you consider anakinra to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?** Yes, it is a "Step change" treatment and is used via the NHSE policy for AOSD and SJIA as current best practice for the more 'Systemic' form of Stills disease.	

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		Consensus amongst ERN specialist centres is that Anakinra has changed the outlook and outcomes for many patients with Stills disease. **Do you consider that the use of anakinra can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** Yes, because Stills disease is relatively rare the RCT evidence is limited. The EMA issued the licence for Stills disease based on some clinical trial evidence, some real world based evidence and an acceptance of current best clinical practice. This may not be reflected fully in any QALY calculation due to the relative lack of RCT data and benefits not covered within the licence such as potential to prevent MAS/HLH type complications – again, this is current best practice but evidence is limited due to Stills disease being relatively rare. **Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.** Members of the 'Clinical Network for Autoinflammatory Diseases' are currently doing research and working on a pathway for MAS in Sheffield (Rachel Tattersall), Bristol (Professor Ramanan) and the National Amyloidosis Centre, Royal Free Hospital (Helen Lachmann) which needs to be taken into account. Also, the full clinical submission to EMA would be more useful than focusing on RCT's during this process as it is more comprehensive, informative and accurate. **To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.** No, it is current best practice in ERN specialist centres **Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?** Yes, potentially similar efficacy (although there are no head-to-head studies to prove this) to Tocilizumab & Canakinumab, albeit in slightly different groups of	

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		patients – Systemic v Articular phenotypes may respond differently to IL-1 & IL-6 but both can be equally effective in the appropriate patients. It is not necessarily easy to identify prior to treatment which of these would be most effective, it is usually a case of trial and error, at least until predictive biomarkers can be identified. With Tocilizumab, it would be important to take into account, when comparing with Anakinra, the infusion costs for administration in a hospital setting. **Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?** Yes, although, as discussed above, other factors should be accounted for. **Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year?** No.	
	Royal College of Pathologists	None	Noted.
	British Society for Rheumatology (endorsed by Royal College of Physicians)	Q. At which stage in therapy do you anticipate anakinra would be used? A. This treatment should be first line in: 1. The presence of MAS even if a diagnosis of Still's was not previously made. 2. After failing NSAID/Steroids if the features are predominantly systemic with no or minimal arthritis. Q. Are people with systemic juvenile idiopathic arthritis that has continued into adulthood likely to be covered by this appraisal? A. People with systemic juvenile idiopathic arthritis that has continued into adulthood should continue to access Anakinra either by virtue of continuation	Thank you for your comments. People with MAS has been included as a subgroup to be considered if the evidence allows. The potential innovative nature of the technology will be considered by

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		of a childhood treatment or the new policy, which ever has the lower threshold. Q. How is active disease defined? How might features of moderate to high disease activity be defined and differentiated? A. This is a physician decision using clinical judgment and lab results. Disease activity scores are more suited to patients with arthritis and less reflective of systemic features. They only enables distinction of patients with inactive disease or mild disease activity from those with moderate or high disease activity, but is not suitable to quantify the absolute level of disease activity. Q. Which treatments are considered to be established clinical practice in the NHS for systemic juvenile idiopathic arthritis and adult-onset Still's disease? A. Methotrextae, Anakinra, Tocilizumab, IVIG (short term) Q. Have all relevant comparators for anakinra been included in the scope? A. All that are available in the NHS but Canakinumab should also be considered. Q. Are the outcomes listed appropriate? A. Yes. Need to have more detailed outcomes for patients who develop MAS. Q. Are the subgroups suggested in 'other considerations' appropriate? Are there any other subgroups of people in whom anakinra is expected to be more clinically effective and cost effective or other groups that should be examined separately?	the appraisal committee.

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		A. Patients with Macrophage Activation Syndrome (MAS) should be included. Both as a presenting features without prior diagnosis of Still's and as a complication of patients with Still's. Q. Do you consider anakinra to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? A. Yes. It is definitely a step change in treatment and outcomes for adults with Still's disease and all ages with MAS. Q. Do you consider that the use of anakinra can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? A. The range of immediate, short term and long term outcomes are, in my opinion, worth the investment. It will result in better health and social outcomes both short and long term. Long term morbidity from steroid treatment is inadequately captured and use of anakinra is likely to avoid many of these Q. To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly. A. There will be no barriers to adoption. Clinicians are eagerly awaiting its introduction. Q. Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.	

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		Rheumatology (Oxford). 2018 Feb 21. doi: 10.1093/rheumatology/key006. [Epub ahead of print] **Macrophage activation syndrome in adults: recent advances in pathophysiology, diagnosis and treatment.** **Carter SJ[1], Tattersall RS[1,2], Ramanan AV[3,4].**	
Additional comments on the draft scope	Swedish Orphan Biovitrum	No.	Noted.
	Royal College of Pathologists	None	Noted.
	British Society for Rheumatology (endorsed by Royal College of Physicians)	The scope states 'In the systemic form, the predominant symptoms are acute onset characterised by fever, weight loss and other systemic manifestations'. The most feared systemic manifestation is MAS and this is from a clinician's point of view a key indicator for anakinra and this should be considered. We have recently published a review to support this view Rheumatology (Oxford). 2018 Feb 21. doi: 10.1093/rheumatology/key006. [Epub ahead of print] **Macrophage activation syndrome in adults: recent advances in pathophysiology, diagnosis and treatment.** Carter SJ[1], Tattersall RS[1,2], Ramanan AV[3,4].	Comments noted. The background section has been amended to include reference to MAS.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Merck Sharp & Dohme