National Institute for Health and Care Excellence

Multiple Technology Appraisal (MTA)

Adalimumab, dexamethasone and sirolimus for treating non-infectious uveitis

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

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Abbvie	A commissioning policy has been produced in July 2015 for the use of adalimumab as an anti-TNF Treatment option for adults with Severe Refractory Uveitis by the Specialised Commissioning Team, NHS England. This policy is due to be updated in 2016. AbbVie is of the opinion that the use of adalimumab as an anti TNF treatment option for adults with severe refractory uveitis should be covered by NHS England policies, given the small patient numbers and the very specialist nature of this condition. This would be more appropriate than a NICE appraisal.	Comment noted. NICE are aware of the commissioning policy and have referred to it in the scope. No changes to the scope are needed.
	Allergan	No new comment	Noted.
	Birdshot Uveitis Society	Yes, particularly adalimumab	Comment noted. No changes to the scope are needed.

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	Healthcare Improvement Scotland (1)	I believe an appraisal of immunosuppressive treatments for sight-threatening uveitis is appropriate but I am not sure as to why these three have been specifically mentioned. The target patient groups are not necessarily comparable and to do a direct comparison I believe you are not comparing like with like.	Comments noted. The Appraisal Committee will consider each technology within its marketing authorisation only. The technologies under appraisal will be compared with interventions that are relevant based on each technology's place in the treatment pathway. The Appraisal Committee will compare these 3 interventions with each other only if it is considered appropriate. The "comparator" section of the scope has been amended accordingly to make this clear.
	Healthcare Improvement Scotland (2)	Yes. As clinical director, I am regularly having to sign off requests at the moment.	Comment noted. No changes to the scope are needed.
	Olivia's Vision	Yes	Noted.

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	Royal College of Ophthalmologists (RCO)	It is timely and very appropriate	Noted.
	Royal National Institute of Blind People (RNIB)	Yes	Noted.
	Santen	Santen agrees that this is an appropriate topic for review as non-infectious uveitis of the posterior segment of the eye (NIU-PS) is a high burden disease with an early onset, i.e. primarily affecting the working-age population (20-60 years). This inflammatory ocular disease leads to severe vision function impairment or vision loss and poor/reduced vision related quality of life (QoL). As a consequence, NIU-PS causes a significant socioeconomic health impact. As a consequence, NIU-PS causes a significant socioeconomic health impact by, among others, leading to a relevant burden of legal blindness. Uveitis is a leading cause of blindness in England. NIU-PS is estimated to have a prevalence of 18 per 100.000.people (http://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf). Between 1,500 and 5,000 people are diagnosed with non-infectious uveitis intermediate or posterior uveitis in England each year.	Comments noted. No changes to the scope are needed.
Wording	Abbvie	Yes	Noted.
	Allergan	Yes	Noted.

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	Birdshot Uveitis Society	Yes	Noted.
	Healthcare Improvement Scotland (1)	Adalimumab cannot be considered within its marketing authorisation in this context, as it is not licensed for the treatment of sight threatening uveitis and is used 'off label'	EU regulatory submissions for treating uveitis are expected for adalimumab this year. NICE appraises technologies within their marketing authorisations in the UK.
	Healthcare Improvement Scotland (2)	Yes	Noted.
	Olivia's Vision	The wording of the draft remit/appraisal objective should be extended to include non-infectious chronic anterior uveitis. The Sycamore trial demonstrated the efficacy of adalimumab for children with JIA chronic anterior uveitis. There are adults and children with sight threatening complicated idiopathic anterior uveitis for whom adalimumab would be life changing.	The remit formally referred by the Department of Health does not include anterior uveitis. Furthermore, NICE appraises technologies only within their marketing authorisations in the UK.

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	Royal College of Ophthalmologists (RCO)	The wording is clear and reflects the issue.	Noted.
	Royal National Institute of Blind People (RNIB)	Yes	Noted.
	Santen	Santen agrees that it is appropriate to appraise sirolimus intravitreal injection within its proposed licensed indication for chronic NIU-PS. It is not entirely clear where dexamethasone intravitreal implant and adalimumab would fit into current treatment pathways for (chronic) NIU-PS.	Comments noted. The background section of the scope summarises the treatment pathway and suggests the place of dexamethasone intravitreal implant and adalimumab. No changes to the scope are needed.
Timing Issues	Abbvie	The proposed timing of the MTA submission (May 2016) coincides with the ongoing update of the aforementioned commissioning policy and may cause a delay for people needing to access adalimumab treatment. [redacted] The inclusion of adalimumab in this MTA could introduce significant delays to the appraisal. Given the importance of this appraisal to the NHS, the potential for delay would not be in the best interests of patients with non-infectious uveitis	Comment noted. No changes to the scope are needed.

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	Allergan	No comment	Noted.
	Birdshot Uveitis Society	Urgent	Noted.
	Healthcare Improvement Scotland (1)	Thankfully at present in NHS Scotland we already have access to use ozurdex and adalimumab when clinical appropriate on an individual patient basis. If this were not the case then I would feel there is a significant urgency for their consideration. Although the drug company has never submitted an application to the SMC for ozurdex, as it is licensed we use it on an individual patient basis, when felt clinically appropriate. Adalimumab is not licensed for the treatment of sight-threatening uveitis and is therefore not within the remit of SMC.	Comments noted. NICE appraises technologies within their marketing authorisations in the UK. No changes to the scope are needed.
	Healthcare Improvement Scotland (2)	Treatments already being used, but having to be individually signed off, and danger of postcode selectivity	Comments noted.
	Olivia's Vision	It is urgent, especially so for adalimumab which is required by patients who have failed combined immunosuppressant therapy and already have the complications of cataract, raised ocular pressure, or secondary glaucoma, and cystoid macular oedema. Idiopathic uveitis patients, following the decision not to fund the routine use of adalimumab by NHSE in July 2015, currently have no pathway to routinely access this therapy. This issue was the subject of a recent Parliamentary debate, initiated by the MP of an Olivia's Vision's member who needs the therapy and has already had one eye enucleated as a result of chronic anterior uveitis. A second Olivia's Vision member who had an eye enucleated in the summer told us her consultant must wait for the inflammation in her remaining eye to become seriously sight threatening before the consultant could apply for the funding	Comments noted. No changes to the scope are needed.

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		of a dexamethasone implant to preserve sight in her remaining eye. It is not only vision impairment that sight threatened uveitis patients fear, but the loss of their eyes as well.	
	Royal College of Ophthalmologists (RCO)	There is an urgent need to assess the place of novel treatments in any rare condition when trial data is rarely available and effectiveness in clinically similar conditions has already been demonstrated.	Comments noted. No changes to the scope are needed.
	Royal National Institute of Blind People (RNIB)	Urgent	Noted.
	Santen	Given the high unmet need the appraisal is very urgent as there is no alternative treatment for first line maintenance therapy. This appraisal should be given a high priority as eventually the majority of the patient population with chronic NIU-PS will relapse from current therapies and could obtain substantial benefit from sirolimus intravitreal injection. Expected approval date for sirolimus from European commission is June 2016. Sirolimus is expected to launch in the United Kingdom very shortly after this date (Q2/2016).	Comments noted. No changes to the scope are needed.
Additional comments on the draft remit	Royal National Institute of Blind People (RNIB)	Adalimumab, provides a treatment option for those patients who are unresponsive/intolerant to standard treatments i.e. steroids and/ or immunosuppressant or whose sight is threatened by their condition. It is important to note, in November 2015, NHS England made a decision to fund and commission adalimumab as an effective and safe treatment for children with severe refractory (unmanageable) uveitis	Comments noted. The appraisal will consider these technologies for treating uveitis in adults only, as noted in the scope. No changes to the scope are needed.

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	Royal College of Ophthalmologists (RCO)	There is no evidence that adalimumab is to be preferred over several other biologics used in ocular inflammatory disease. Infliximab is also used with identical indications as adalimumab in ocular inflammatory disease and treatment switching between the two is frequently required. It is not clear how it will help by excluding infliximab from the scope of the remit.	Comments noted. NICE appraises technologies within their marketing authorisations in the UK only; EU regulatory submissions for treating uveitis are expected for adalimumab this year and have already been accepted for sirolimus. The remit formally referred by the Department of Health does not include infliximab. No changes to the scope are needed.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Abbvie	The basis for the number of patients diagnosed with non-infectious posterior segment uveitis stated in the draft scope is not clear and the range appears to be wide.	References for population size estimates are provided in the scope. The data were sourced from the North East Treatment Advisory Group

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			publication Ozurdex dexamethasone ocular implant for uveitis (January 2012), published as part of their treatment appraisal of dexamethasone intravitreal implant. The data originates from Eurostat 2010 data used in the European Medicines Agency public summary of opinion on orphan designation for dexamethasone intravitreal implant (document reference: EMA/COMP/319872/2010 Rev.1). No changes to the scope are needed.
	Allergan	No comment	Noted.
	Birdshot Uveitis Society	Satisfactory. Final sentence of the remit background should read: If the disease does not respond to these treatments or if they are not tolerated, biological tumour	Comments noted. The background section of the scope has been updated accordingly.

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		necrosis factor (TNF) – alpha inhibitors may be used.	
	Healthcare Improvement Scotland (1)	It is reasonably accurate although I would suggest that in the majority of people the cause in unknown. Uveitis is defined by the predominant sight of the inflammation and therefore the definition of intermediate or posterior uveitis do not exclude the presence of anterior uveitis and it is for this reason I would recommend that the statement 'people with panuveitis' should be changed to people with signs of anterior uveitis. I would also change the statement about using immunosuppressive drugs to 'those whose disease is requiring continued significant oral corticosteroids or are intolerant of corticosteroids,' as most patients, given enough corticosteroids will achieve disease control. The main indication of second line immunosuppression is to act as a steroid sparing agent, to allow reduction in the steroid dosage and reduce the risk of longterm side effects of systemic steroids, while maintaining disease control.	Comments noted. The scope has been updated accordingly to clarify some of these issues. The background section of the scope is intended to provide a brief summary of the disease and how it is managed, it is not designed to be exhaustive and therefore no further changes to the scope are needed.
	Healthcare Improvement Scotland (2)	Good. Most ophthalmologists treat cases of uveitis, but the difficult ones where these treatments are more likely to be employed are usually passed to a sub-specialist in the field.	Comments noted. No changes to the scope are needed.
	Olivia's Vision	Chronic, complicated anterior uveitis should be added.	Comments noted. The remit formally referred by the Department of Health does not include anterior uveitis. Furthermore, NICE appraises technologies only within their

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			marketing authorisations in the UK. No changes to the scope are needed.
	Royal College of Ophthalmologists (RCO)	The combined incidence of intermediate, post and panuveitis is 4-5/100,000.	Thank you for providing this estimate. It is not clear whether this estimate is specific to England, where it was sourced from and in what year. The scope has not been updated.
	Royal National Institute of Blind People (RNIB)	Yes	Noted.
	Santen	Santen considers the Background section to be accurate and appropriate, but to be complete it should contain information about: • NIU-PS is a long-term debilitating disease because it may lead to partial or complete loss of vision/blindness. • NIU-PS is a chronic disease that needs to be assessed from a long-term perspective as patients cycle from one treatment to the next depending on their flares and that even when asymptomatic the inflammation remains. As with all inflammatory diseases there are damages linked to ongoing inflammation. This is why there is a need for an efficacious treatment that can be used on the long-term to control the underlying inflammation. • Intermediate, posterior, and pan-uveitis are the most severe and	Comments noted. The background section of the scope is intended to provide a brief summary of the disease and how it is managed. It is not designed to be exhaustive, therefore no changes to the scope are needed.

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		highly recurrent forms of uveitis. They often cause blindness if left untreated. • NIU-PS affects mainly people between 20 and 60 years, i.e. young people in their most productive years (“early onset”). • Treatment of NIU-PS has a high burden as current medications are poorly tolerated and not indicated for the long-term treatment of the disease. • Key symptoms are decreased vision, vision loss, blurred vision, floaters, light sensitivity and eye pain. These symptoms impact the patient’s vision, appearance and comfort as well as QoL. • Vitreous haze is the clinical endpoint accepted by regulatory authorities and health care professionals. • NIU-PS needs early and sustained treatment to prevent disease progression and hence maintain patient’s vision and QoL. • 4 out of 5 patients will experience moderate to severe vision impairment during their lives, and ultimately up to 35% of them will become legally blind. • Treatment of patients with NIU-PS with intravitreal corticosteroid injections or implants is associated with adverse events including cataract, retinal detachment and an increase in IOP leading to glaucoma. Regular monitoring of IOP is required. • Because adalimumab suppresses TNF, which is part of the immune system, latent infections, such as tuberculosis, can be reactivated, and the immune system may be unable to fight new infections. This has led to fatal infections. Up-to-date the safety profile of adalimumab used in patients with NIU-PS is unclear; however in the pivotal trials for its other licensed indications the most common adverse events associated of systemic adalimumab include	

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		infections, injection site reactions, headache and musculoskeletal pain. As mentioned above, more serious adverse reactions associated with the use of systemic adalimumab include life-threatening infections such as sepsis, opportunistic infections and TB, hepatitis B reactivation and malignancies including lymphoma and leukaemia.	
The technology/ intervention	Abbvie	Yes	Noted.
	Allergan	No comment	Noted.
	Birdshot Uveitis Society	Yes	Noted.
	Healthcare Improvement Scotland (1)	Yes	Noted.
	Healthcare Improvement Scotland (2)	Yes. Ozurdex is familiar to many ophthalmologists as it is also used for treratment of cystoids macular oedema in retinal vein occlusion and diabetic macular oedema.	Comment noted. No changes to the scope are needed.
	Olivia's Vision	Yes	Noted.
	Royal College of Ophthalmologists (RCO)	Yes	Noted.
	Royal National Institute of Blind	Yes	Noted.

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	People (RNIB)		
	Santen	• Compared to the currently available pharmacological treatments for NIU-PS, sirolimus has a first-in-class mechanism of action. • In particular, sirolimus inhibits and regulates a critical inflammation pathway (i.e. the mammalian Target of Rapamycin (mTOR) pathway) which plays a fundamental role in stimulating T-cell proliferation leading to the release of proinflammatory cytokines. • Thereby, mTOR regulates path-physiological changes (e.g. macular oedema and vitreous haze) and prevents the accumulation of ocular damage. • If the inflammation is not treated/ undertreated, pathophysiological reversible changes in the eye such as vitreous haze lead to vision impairment. These reversible changes cumulate into an irreversible structural damage due to recurrent episodes of inflammation (flare-ups) which consequently leads to vision loss. • Sirolimus intravitreal injection has been studied in the SAKURA (**S**tudy **A**ssessing double-mas**K**ed **u**veitis T**R**e**A**tment) study, a pivotal Phase III study comparing three different doses of sirolimus intravitreal injection (44µg, 440µg, 880µg) for 6 months, and in the long-term-extension (12 resp. 24 months (only 880µg)). • Sirolimus intravitreal injection is well tolerated locally with a negligible systemic adverse effects profile. • As shown in the SAKURA study, sirolimus intravitreal injection has the potential to control the progressive nature of NIU-PS • Sirolimus is injected locally, therefore does not have the type of systemic adverse effects profile associated with corticosteroid oral therapy or with biologics.	Comment noted. The scope is not designed to be exhaustive, and therefore no changes are needed.

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		• Sirolimus is indicated for the treatment of chronic NIU-PS, i.e. early control of inflammation flare-ups and act as a first line maintenance therapy	
Population	Abbvie	The population is defined appropriately. AbbVie does not consider that there are groups that should be considered separately	Comment noted. No changes to the scope are needed.
	Allergan	The remit's wording of the proposed population is wider than the indication of Ozurdex for uveitis. Ozurdex is licensed for posterior uveitis only (so is Sirolimus). Humira's study could result in an extended indication to pan-uveitis compared to Ozurdex and Sirolimus. We thus understand the rationale of the proposed remit but how will the indirect comparisons be conducted remains unclear at this stage. So are the potential recommendations of this appraisal. Many sub-group analysis are likely to be used and the resulting effects on the statistical significance of these comparisons might prevent any robust conclusion.	Comments noted. The Appraisal Committee will consider each technology within its marketing authorisation only. The technologies under appraisal will be compared with interventions that are relevant based on each technology's place in the treatment pathway. The Appraisal Committee will compare these 3 interventions with each other only if it is considered appropriate. The "comparator" section of the scope has been amended accordingly to make this clear. The

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			Appraisal Committee will consider potential uncertainties in the evidence base when making its recommendations.
	Birdshot Uveitis Society	1) Yes 2) Yes, those for whom oral systemic treatment is not clinically advisable or who cannot tolerate it	Comment noted. No changes to the scope are needed.
	Healthcare Improvement Scotland (1)	I would also suggest the inclusion of patients with anterior uveitis complicated by cystoid macular oedema, as they often required systemic or intravitreal therapy.	Comments noted. The remit formally referred by the Department of Health does not include anterior uveitis. Furthermore, NICE appraises technologies only within their marketing authorisations in the UK. No changes to the scope are needed.
	Healthcare Improvement Scotland (2)	Yes. Patients with only anterior uveitis do also get cystoids macular oedema and sometimes need these treatments too, so anterior uveitis should at least be mentioned as a consideration.	Comments noted. The remit formally referred by the Department of Health does not include anterior uveitis. Furthermore, NICE

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			appraises technologies only within their marketing authorisations in the UK. No changes to the scope are needed.
	Olivia's Vision	Chronic, complicated anterior uveitis should be added.	Comments noted. The remit formally referred by the Department of Health does not include anterior uveitis. Furthermore, NICE appraises technologies only within their marketing authorisations in the UK. No changes to the scope are needed.
	Royal College of Ophthalmologists (RCO)	The appropriate population should be those patients with uveitis, other than anterior uveitis, requiring long term local or systemic immunosuppression.	Comments noted. The Appraisal Committee appraises technologies within their marketing authorisations. The population suggested by the Royal College of Ophthalmologists is narrower than the populations in existing

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			marketing authorisation or clinical trials and therefore no changes to the scope are needed. In addition, attendees at the scoping workshop in June 2015 agreed that dexamethasone intravitreal implant and sirolimus intravitreal injection could be used at multiple points in the treatment pathway (that is, they would not be restricted to use in people who are intolerant to, or whose disease has not responded to, immunosuppressive therapies).
		Within this population patients should be stratified by their risk of long-term visual loss, and their risk of intolerance to existing treatments – for both ocular and systemic reasons.	Comments noted. Attendees at the scoping workshop in 2015 noted that non-infectious uveitis contains a variety of subgroups. However, attendees did not

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			identify subgroups for whom the technologies were more likely to be effective or cost-effective. They also considered that stratifying the population into subgroups would result in smaller sample sizes which would increase the uncertainty in the evidence base. The workshop attendees agreed that it is feasible to compare the effects of different treatments across different subgroups because of the common outcomes (related to inflammation), and that recommendations could be tailored to different subgroups. This does not preclude the Appraisal Committee from considering evidence in subgroups during the course of the

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			appraisal. No changes to the scope are needed.
	Royal National Institute of Blind People (RNIB)	Yes – the population is defined appropriately	Comment noted. No changes to the scope are needed.
	Santen	Treatment of chronic non-infectious uveitis of the posterior segment. Patients with pan-uveitis should be considered separately.	Comments noted. The Appraisal Committee will consider each technology within its marketing authorisation only. If appropriate, the Committee will make separate recommendations for the different types of uveitis. No changes to the scope are needed.
Comparators	Abbvie	AbbVie does not consider that adalimumab should be compared to the treatments as outlined in the scope. As adalimumab would be used after all other treatments options have been explored, best supportive care should be listed as a comparator	Comments noted. Best supportive care has been included as a comparator. Best supportive care is considered relevant only when all other treatment options have been tried. The

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			Appraisal Committee will agree the most appropriate comparators for each technology, based on the marketing authorisation and advice from experts, during the course of the appraisal.
	Allergan	Allergan welcomes the addition of Humira to the list of comparators as it reflects feedback collected about clinical practice and could potentially expand the options available to patients suffering from uveitis.	Comments noted. No changes to the scope are needed.
	Birdshot Uveitis Society	1) Yes 2) All have disadvantages. All are used for treating different types of non-infectious uveitis	Comments noted. No changes to the scope are needed.
	Healthcare Improvement Scotland (1)	I believe you have covered the most commonly used treatments. Personally I have found methotrexate relatively ineffective, have never used intravitreal methotrexate and I don't think chlorambucil is available in UK. In Scotland we also use infliximab, golimumab, tocilizumab and interferon alpha. Rituximab has also been used for individuals with associated scleritis.	Comments noted. No changes to the scope are needed.
	Healthcare Improvement Scotland (2)	Yes. It should be noted that the current systemic treatments are not without their dangers, and intravitreal treatments proposed are much better targeted with lower overall risk.	Comments noted. No changes to the scope are needed.

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	Olivia's Vision	These are standard treatments. Corticosteroids are nearly always considered as the first treatment option. The side effects, ocular and systemic, contraindicate their use long term. The dexamethasone implant is useful in sparing patients the systemic side effects of high dose oral corticosteroid but when repeated implants are employed, the ocular side effects, cataract and secondary glaucoma, need to be considered. The implant may be useful in providing cover when patients begin immunosuppressant therapy which requires time to build up a therapeutic effect. Historically, oral corticosteroid accompanies the early stages of immunosuppressant therapy and is expected to be lowered to a dose of 10mgs as the immunosuppressant(s) becomes effective. The side effects of the initial high dose oral corticosteroid are difficult for patients to manage. The dexamethasone implant provides an alternative therapy for those patients who cannot tolerate the side effects of immunosuppressant therapy and could be considered rescue therapy in the early stages of disease for complications such as cystoid macular oedema. It would also allow younger adult patients the opportunity to come off immunosuppressant therapy to allow safe child bearing. . Iluvian, which is longer lasting implant, should be considered as a comparator. The therapeutic action of infliximab is similar to that of adalimumab. However, infliximab often exerts its therapeutic effect rapidly and could be considered more efficacious than adalimumab for patients most at risk of permanent damage to structures within their eyes without timely intervention. As such, it could be considered 'best alternative care' to adalimumab. Infliximab is only routinely used to treat Behcets uveitis. Like adalimumab, it is not routinely used to treat other forms of non-infectious intermediate,	Comments noted. Iluvian (fluocinolone intravitreal implant) will be considered as part of the "intravitreal corticosteroid implants". No changes to the scope are needed.

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		posterior or pan uveitis. Both therapies should be in routine use as they are in rheumatology as 'life changers.' The use of adalimumab for adult patients should follow the use recently approved by NHSE for paediatric patients. Should a single immunosuppressant fail to control inflammation within 3 to 6 months, then therapy with adalimumab should begin. In rheumatoid arthritis, early control of inflammation is believed to alter the progression of the disease. Without the routine funding of anti TNF therapy in uveitis when immunosuppressants fail, it is difficult to know whether the same principle would apply to uveitis. However, earlier use of anti TNF would certainly avoid the complications of cataract, glaucoma, cystoid macular oedema and vitritis requiring surgery and the higher risk associated with such surgery in uveitic eyes. Patients would also be able to continue working and making contribution to the economy.	
	Royal College of Ophthalmologists (RCO)	The comparators only include one biologic. Several different biologics are in use to treat ocular inflammatory disease associated with a wide variety of systemic inflammatory diseases, as well as isolated uveitis syndromes.	Comments noted. The comparators have been updated accordingly.
	Royal National Institute of Blind People (RNIB)	Yes these are the standard treatments currently used within the NHS. Topical and systemic corticosteroids are used within the NHS as first line treatments. Immunosupressive treatments are used where patients are unresponsive to other treatments or where the dose of steroids needs to be reduced if they are causing significant side affects.	Comments noted. No changes to the scope are needed.
	Santen	To date there are no licensed and proven treatments for treatment of chronic NIU-PS available. Current standard of care options treat the disease only symptomatically in the acute phase and are not indicated for chronic	Comments noted. The NICE methods guide (section 6.2.1–4) states

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		treatment of NIU-PS. Their use on the long-term is not warranted due to their adverse event profile.
		Therefore, Santen would question the proposed comparators:
		• **Periocular/intravitreal corticosteroid injection**: comparison with sirolimus intravitreal injection is limited as no long term data are available.
		• **Intravitreal corticosteroid implants**: i.e. dexamethasone intravitreal implant has not been studied for chronic treatment and is associated with severe adverse effects (e.g. IOP increase, cataract, retinal tear/retinal detachment,). Even if there is an indication for use of dexamethasone intravitreal implant in NIU-PS, it is not often used in the UK. Santen would question whether comparing with dexamethasone intravitreal implant is the most appropriate approach if comparing the Phase III Study HURON (c**H**ronic **U**veitis evaluation of the int**R**avitreal dexamethas**ON**e implant) with the SAKURA study.
		  • In the HURON study, dexamethasone intravitreal implant has been administered only once. Therefore, it is difficult to compare chronic treatment with sirolimus intravitreal injection against a single dexamethasone intravitreal implant in an MTA.
		  • In the HURON study, patients with a history of glaucoma, clinically significant IOP in response to steroid treatment, or with recent use of hypotensive medication were excluded. Therefore, it remains unclear, how safety data can be applied to the targeted patient population.
		  • In the HURON study, dexamethasone intravitreal implant used a sham injection, while in the SAKURA Study an active control arm was used.
		  • In addition, corticosteroid non-responders were excluded in the
			that the Appraisal Committee can consider as comparators technologies that do not have a marketing authorisation for the indication defined in the scope when they are considered to be part of established clinical practice for the indication in the NHS. When considering an 'unlicensed' medicine, the Appraisal Committee will have due regard for the extent and quality of evidence, particularly for safety and efficacy, for the unlicensed use. Note that the Appraisal Committee can only make recommendations about an intervention within its marketing authorisation in the UK.
			The attendees at the scoping workshop in

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		HURON study • In the HURON study, patients with pan-uveitis were excluded (in SAKURA these patients were included indicating a more severe patient population) • In the HURON study the incidence of cataracts as adverse effects in the dexamethasone intravitreal arm is double the number of adverse effects in the sham arm. Cataract is a crucial adverse effect especially for the targeted patient population (young, working adults). • Additionally, no long-term safety data of NIU-PS are available from the HURON study, making it further difficult to compare the two studies. Furthermore, from comparing the two study designs Santen would like to add: • Dexamethasone intravitreal implant is injected once. There is currently no experience of repeat administrations in NIU-PS. • Dexamethasone intravitreal implant has no orphan drug designation. Dexamethasone intravitreal implant is indicated for single administration treatment of active NIU-PS, and not as a first line maintenance therapy • **Systemic corticosteroids**: are associated with severe adverse effects in the chronic use (e.g. Cushing Syndrome, adrenal suppression) and are not suitable for long-term therapy. Additional monitoring is required (e.g. bone marrow, liver function test, IOP increase). • **Immunosuppressive therapies/biologicals**, e.g. adalimumab (unlicensed in the UK for this indication) in combination with corticosteroids: not being licensed limits their use in clinical practice for special patient populations only, e.g. patients with a chronic rheumatoid arthritis or with bilateral eye involvement that may be	June 2015 did not agree that no treatment or 'watchful waiting' would be appropriate comparators for this population. The workshop attendees recognised that treatment choice depends on patient characteristics, but agreed that the comparators listed in the draft scope are used in clinical practice to treat non-infectious uveitis and therefore should be included in the scope. Attendees at the scoping workshop considered that a NICE multiple technology appraisal would be appropriate. No changes to the scope are needed.

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		linked to a systemic autoimmune disease. **In conclusion, it could be considered that "No treatment" is currently the standard of care for the maintenance treatment of (chronic) NIU-PS.**	
Outcomes	Abbvie	It may be useful to be more clear on which complications are meant with "complications associated with uveitis"	Comment noted. "Complications associated with uveitis" is not an outcome in the scope. Potential consequences of uveitis are described in the background section of the scope. No changes to the scope are needed.
		Additionally, the following outcomes are of importance: • Ocular inflammation • Ocular pain • Work productivity and activity impairment	Comments noted. Ocular inflammation is captured within the outcomes in the draft scope. It is understood that ocular pain will be captured in health-related quality of life measures. In line with NICE's processes and the documented reference case, costs will be considered from

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			an NHS and Personal Social Services perspective. Consultees will have an opportunity to submit evidence on the benefits not captured in the QALY calculation. Where evidence allows the Committee will consider this information during the course of the appraisal. No changes to the scope are needed.
	Allergan	Allergan strongly believes that the following outcomes should be added to the list: - Optical Coherence Tomography (OCT) - vitreous haze - impact of treatment on burden of systemic corticosteroids and immunosuppressive agents	Comments noted. Vitreous haze is captured within the outcomes in the draft scope. Specific measurement scales and methods are not included in scopes, so as not to appear to view any one assessment tool as superior to another. Consultees will have an opportunity to submit evidence on the

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			benefits not captured in the QALY calculation. Where evidence allows the Committee will consider this information during the course of the appraisal. All outcomes data in the submissions will be considered. No changes to the scope are needed.
	Birdshot Uveitis Society	Include: Electro-diagnostic testing (ERG testing) and Visual Function Response (a combination of best corrected visual acuity and the National Eye Institute Visual Function Questionnaire-25 [NEI VFQ-25])	Comments noted. Specific measurement scales are not included in scopes, so as not to appear to view any one assessment tool as superior to another; the Committee would normally consider the appropriateness of specific outcome measures during the course of the appraisal. All outcomes data in the submissions will be considered. No changes to the scope

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			are needed.
	Healthcare Improvement Scotland (1)	One of the difficulties in studies designed for treatment of patients with uveitis is that, as is mentioned, there are many know different causes and even more unknown. This makes treatment comparisons difficult. Most researchers involved in the assessment of uveitis would use SUN descriptions to quantify disease activity. I feel that using only visual acuity as the only visual outcome measure is greatly over simplifying things.	Comments noted. No changes to the scope are needed.
	Healthcare Improvement Scotland (2)	Yes . It should be noted that these patients are usually having to attend hospital appointments very frequently with associated difficulty, cost and disruption to normal (ofter working) life. These treatments would reduce that burden.	Comments noted. Hospital visits and associated resource use and costs will be captured in the economic analyses. No changes to the scope are needed.
	Olivia's Vision	Yes	Noted.
	Royal College of Ophthalmologists (RCO)	These are immunosuppressive treatments – there is no outcome measure of anti-inflammatory effect such as cell counts, macular oedema, vitreous flare. Some are used specifically as steroid sparing agents to improve the management of glaucoma or reduce the risk of cataract formation. All these are markers of the risk of visual loss. Adverse treatment effects are of considerable importance as all treatments under consideration may have significant rates of complete patient intolerance.	Comments noted. These outcomes are captured within the outcomes in the draft scope. No changes to the scope are needed.
	Royal National Institute of Blind	Visual acuity is routinely used to measure visual function and on its own is not a reasonable and efficient way to measure an individual's visual	Comment noted. In line with NICE's processes

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	People (RNIB)	disability. Patients are interested in what they can continue to do such as read, write, drive, undertake day-to- day activities, remain in employment and look after family members i.e. a child or parent.	and the documented reference case, costs will be considered from an NHS and Personal Social Services perspective. The impact on the patient will be captured in health-related quality of life measures. Consultees will have an opportunity to submit evidence on the benefits not captured in the QALY calculation. Where evidence allows the Committee will consider this information during the course of the appraisal. No changes to the scope are needed.
	Santen	The proposed outcomes described in the scope are appropriate. Santen suggests the addition of the following patient relevant outcomes: • Grading intraocular inflammation by: Vitreous haze: VH 0; VH 0 or 0.5+ • Percentage of patients with disease remission • Change from baseline in best corrected visual acuity (BCVA)	Comments noted. The majority of these outcomes are captured in the outcomes in the draft scope. Furthermore, specific measurement scales

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		• Improvement of BCVA (response; having improvement ≥2 lines and /or > 3 lines) • Corticosteroids tapering success • Use of and time to rescue therapy • Safety of long-term use and maintenance of effect on VH and BCVA (12 months, 24 months) and QoL (12 months) • Time to retreatment Additionally, Santen would like to propose a combined endpoint: Visual Function Response (VFR) as a patient relevant endpoint (s. below)	are not included in scopes, so as not to appear to view any one assessment tool as superior to another. The Committee would normally consider the appropriateness of specific outcome measures during the course of the appraisal. All outcomes data in the submissions will be considered. No changes to the scope are needed.
Economic analysis	Abbvie	No comments to add	Noted.
	Allergan	The costs of monitoring and of adverse events will be important elements of the assessment. Data and evidence about certain costs such as the consequences of high dose corticosteroid will have to be carefully considered and if not available, scenario analysis could be the only base to inform the committee decision on.	Comments noted. No changes to the scope are needed.
	Birdshot Uveitis Society	None	Noted.
	Healthcare Improvement	Uveitis ranks fifth in the causes of legal blindness in the developed world, and is believed to be responsible for 10% of cases of visual loss in the age	Comments noted. No changes to the scope

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	Scotland (1)	group of 20–60 years. As it is a chronic disease for many, it should be assessed as such and the long term morbibity from the disease and complications of the treatment assessed.	are needed.
	Healthcare Improvement Scotland (2)	Appropriate – but see above.	Noted.
	Olivia's Vision	Insufficient knowledge to comment productively here.	Noted.
	Royal College of Ophthalmologists (RCO)	The prime aim of treatment is to reduce the lifetime risk of irreversible visual loss. Short-term treatment effects on quality of life and visual function have to be linked to an assessment of the much longer term impact on lifetime visual function and health costs.	Comments noted. No changes to the scope are needed.
	Royal National Institute of Blind People (RNIB)	The scope notes that 'Costs will be considered from an NHS and Personal Social Services perspective' By limiting considerations to NHS and Personal Social Services costs, NICE fails to recognise the full impact of sight loss on society and the Exchequer. By failing to focus on the whole picture i.e. psychological, physical and social problems associated with blindness there is a real danger of sub-optimal investment in new treatments.	Comments noted. The impact, in terms of mental, physical and social functioning, of the technologies (and their comparators) on uveitis will be captured in health-related quality of life measures. The consultees will have an opportunity to provide evidence on the benefits not captured in health-related quality of life measures in their

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			submissions. Where evidence allows the Committee will consider this information during the course of the appraisal. No changes to the scope are needed.
	Santen	The economic analysis will be conducted in line with the NICE reference case. A life time horizon will be used to reflect all the key differences between the relevant treatment options in terms of costs and effects and in order to adequately addressing the chronic (and progressive) nature of NIU-PS.	Comments noted. No changes to the scope are needed.
Equality and Diversity	Abbvie	No comments to add	Noted.
	Allergan	No comment	Noted.
	Birdshot Uveitis Society	1) No 2) Inequality already exists in UK because uveitis patients in Scotland and Wales have NHS access to adalimumab and infliximab if either is considered to be clinically necessary. Inequality would also result if newer technologies are not funded, because only those patients able to afford private treatment would be able to access them. 3) No	Comment noted. No changes to the scope are needed. The Appraisal Committee will take into account potential equality issues relevant to its recommendations.

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	Healthcare Improvement Scotland (1)	I am unable to comment on the situation in England. Within NHS Scotland I am not aware of any restriction or discrimination against any individual when it is felt a specific treatment is appropriate on clinical grounds, as defined the Scottish Uveitis Network Clinical Guidelines. www.sun.scot.nhs.uk	Comments noted.
	Healthcare Improvement Scotland (2)	I do not foresee any equality issues. On the contrary, patients with other disabilities are more likely to be adversely affected by side effects of systemic treatments which the proposed intravitreal treatments would reduce.	Comment noted. No changes to the scope are needed. The Appraisal Committee will take into account potential equality issues relevant to its recommendations.
	Royal College of Ophthalmologists (RCO)	There are wide ethnic variations in the incidence and severity of several of the uveitis types which may impact on the relative impact of disease in different groups. The treatments vary in the need for, and frequency of, hospital administration, and therefore accessibility and compliance with treatment may be an issue for some groups.	Comment noted. No changes to the scope are needed. The Appraisal Committee will take into account potential equality issues relevant to its recommendations.
	Royal National Institute of Blind People (RNIB)	If these technologies are not made available to patients, it would lead to inequity in access to sight-saving treatments, as only patients able to afford private treatment would benefit.	Comment noted. No changes to the scope are needed. The Appraisal Committee will take into account

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			potential equality issues relevant to its recommendations.
	Santen	Notably, when considering the proposed methodologies to calculate burden of illness and wider societal benefit aimed at informing Value-based-assessment of new interventions later this year. • Young patients requiring maintenance treatment who should not be exposed to a possible early replacement of the lens. • Patients at risk of systemic side-effects from long-term corticosteroid use OR patients in need to limit the dose/length of use of corticosteroids	Comment noted. No changes to the scope are needed. The Appraisal Committee will take into account potential equality issues relevant to its recommendations.
Innovation	Abbvie	AbbVie considers that adalimumab will be a step-change as it will be the first anti-TNF licensed for this indication and population.	Comments noted. Innovation will be considered by the Appraisal Committee when formulating its recommendations. The companies will have an opportunity to provide evidence on the innovative nature of their products in their submissions. No changes to the scope are needed.
	Birdshot Uveitis Society	1) Yes, by increasing the currently small range of treatments available for what are difficult to treat, chronic, sight-threatening conditions	Comments noted. See response to AbbVie's

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		2) See the patient testimonials included in NHS England Clinical Commissioning policy (July 2015) Infliximab (Remicade) and adalimumab (Humira) as anti-TNF treatment options for adult patients with severe refractory uveitis, cited on page 3 of Appendix B (draft scope) of this appraisal	comments on innovation above.
	Healthcare Improvement Scotland (1)	I cannot comment on the current situation in NHS England. However as mentioned in NHS Scotland we already have access to the use of ozurdex and adalimumab in the treatment of sight threatening uveitis and therefore do not see them as innovative but rather essential. With regard sirolimus I look forward to it as a potentially useful addition in the treatment of sight threatening uveitis. I would assume the role in the first instance would be for unilateral idiopathic intermediate or posterior uveitis or anterior uveitis with cystoid macular oedema. From published studies it appears to be effective in about 40% denovo uveitis patients. When compared with systemic mycophenolate with an 82% success rate and tacrolimus with a 68% success rate then it is significantly less efficacious. Obviously there is the benefit of few systemic side effects. Many patients require long term treatment and at present we don't have any data longer than 12 months in relation to retinal toxicity and efficacy.	Comments noted. See response to AbbVie's comments on innovation above.
	Healthcare Improvement Scotland (2)	Yes, which is why I have already been signing off individual named-patient requests for these treatments. However, that is a slow route which adds to the difficulties (and appointments) for the patient and doctor.	Comments noted. See response to AbbVie's comments on innovation above.
	Olivia's Vision	Adalimumab is a step change in the management of uveitis. The dexamethasone implant is a step change in that it provides clinicians	Comments noted. See response to AbbVie's comments on

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		with a swift rescue therapy. The diagnosis of serious, underlying disease is not always straightforward. For example, Behcet's patients may lose sight before a diagnosis is made and treatment begins in a specialist Behcet's centre. The dexamethasone implant buys time and preserves vision while diagnosis is being made. Sirolimus, delivered in the eye, is useful for intermediate uveitis or birdshot uveitis when disease is mild to moderate and there is no underlying systemic disease, or when immune suppressants are not tolerated. It may not be a step change in other instances and lacks extensive clinical studies to support its efficacy when compared with other agents used to manage posterior uveitis	innovation above.
	Royal College of Ophthalmologists (RCO)	There is a great need to introduce a wider choice of both local and systemic treatments in those patients unresponsive to contemporary treatments who remain at high risk of permanent visual loss. Poorly controlled disease not only has a direct impact on HRQoL, but a significant disruption to employment from the increased need for hospital visits and surgical interventions. The economic impact on a population of working age largely otherwise well with a normal expected lifespan will be very different to the assessment of treatment benefit in diseases such as macular degeneration and diabetic retinopathy.	Comments noted. See response to AbbVie's comments on innovation above.
	Santen	Santen considers the sirolimus intravitreal injection technology to be innovative. Sirolimus intravitreal injection can be considered as step change in treatment of NIU-PS, which may result in: • First mTOR inhibitor that can be used for first line maintenance therapy	Comments noted. See response to AbbVie's comments on innovation above.

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		• First-in-class local immunoregulatory therapy, i.e. non-steroidal agent • local (i.e. Non-systemic therapy) • Strong efficacy profile with Long-term control of ocular inflammation(up to 24 months) • Ability to sustain in remission • Tolerable safety profile with acceptable i.e. adverse effects (glaucoma, IOP increase, cataract) at the same level as normal population • QoL (including Visual Function response)	
Other considerations	Abbvie	No comments to add	Noted.
	Allergan	No comment	Noted.
	Birdshot Uveitis Society	Consideration of hospital costs associated with surgical insertion procedures and any additional procedures which may be required when either dexamethasone or sirolimus intravitreal products are used	Comments noted. Costs and resource will be considered as part of the cost-effectiveness analysis. No changes to the scope are needed.
	Healthcare Improvement Scotland (1)	As mentioned previously	Comments noted.
	Healthcare Improvement Scotland (2)	nil	Noted.

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	Royal College of Ophthalmologists (RCO)	There are likely to be quite different pathways in different types of uveitis leading to consideration of these treatments. For example, those with steroid induced glaucoma would have a relative contraindication to intravitreal steroids; those with high risk of retinal detachment, or who are phakic would have a relative contraindication to intravitreal treatments. There may be other groups in whom all three treatments would have similar local and systemic risks and in whom a more simple comparison of cost-effectiveness could be made. Simplifying the analysis too much may easily lead to clinically illogical conclusions that could not be implemented.	Comments noted. No changes to the scope are needed.
	Santen	As noted above Santen believes evaluating NIU-PS for patients with and without pan-uveitis would be important to assess efficacy and safety adequately.	Comments noted. No changes to the scope are needed.
Questions for consultation	Abbvie	Questions from consultation: • Is infliximab routinely used to treat non-infectious intermediate, posterior or pan uveitis? No • What is the expected place in the treatment pathway for adalimumab? Adalimumab would be expected to be used in people who do not respond to corticosteroids, immunotherapy or sirolimus • Would adalimumab be used for previously untreated people? No • Would adalimumab be used instead of local treatments (such as periocular or intravitreal corticosteroid injections)? Or would it be used instead of systemic treatment?	Comments noted. No changes to the scope are needed.

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		Only in instances where people are unable to take such treatments i.e. due to contra-indications, intolerance or adverse effects experienced with such treatments. • Would adalimumab be used on its own? Or in addition to the existing treatment options? It could be used on its own or in combination with immunomodulators such as mycophenolate mofetil, methotrexate, cyclosporine or azathioprine • NICE intends to appraise this technology through its Multiple Technology Appraisal (MTA) Process. We welcome comments on the appropriateness of appraising this topic through this process. As stated earlier, AbbVie is of the opinion that the use of adalimumab as an anti TNF treatment option for adults with severe refractory uveitis should be covered by NHS England policies, given the small patient numbers and the very specialist nature of this condition. This would be more appropriate than a full NICE appraisal.	
	Allergan	Systemic steroids are frequently used as 1st line. Generally, around 60-75 mgs p.o. tapering down over 4 weeks or so. If the uveitis is not controlled, additional agents can be added, including immunosuppressive agents, which also serve to allow a reduction in the steroid dose.	Comments noted. No changes to the scope are needed.
	Healthcare Improvement Scotland (1)	I don't understand why these three drugs are being compared to one another, as although they may all be used in the treatment of sight threatening uveitis, their indications would likely be very different. Why is the consultation considering adalimumab at this stage and not also considering all the other off-label drugs we use for the treatment of sight threatening uveitis. For example in a patient with bilateral sight threatening uveitis with Crohn's disease having treatment failure on a combination	Comments noted. The Appraisal Committee will consider each technology within its marketing authorisation only. The technologies under appraisal will be

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		treatment with prednisolone, tacrolimus and mycophenolate then the switch to adalimumab may provide a reasonable financially comparable alternative, with improved disease control and improved quality of life. This is not the sort of patient I would generally consider ozurdex for and if the patient has already had treatment failure of systemic tacrolimus it would be unlikely that intravitreal sirolimus would be effective.	compared with interventions that are relevant based on each technology's place in the treatment pathway. The Appraisal Committee will compare these 3 interventions with each other only if it is considered appropriate. The "comparator" section of the scope has been amended accordingly to make this clear. If appropriate, the Committee will make separate recommendations for the different types of uveitis. No further changes to the scope are needed.
	Healthcare Improvement Scotland (2)	Treatments for any one patient would need to be tailored to that patient. This is a slightly heterogeneous group, but the common denominator is the uveitis.	Comments noted. No changes to the scope are needed.
	NHS England	**Q1) Have all relevant comparators for dexamethasone intravitreal implant, sirolimus intravitreal injection and adalimumab been included**	Comments noted. No changes to the scope

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		in the scope? From the consultation document "The interventions listed above compared with each other, and: □ _Periocular or intravitreal corticosteroid injections □ _Intravitreal corticosteroid implants □ _systemic corticsteroids □ _Systemic immunosuppressive therapies including azathioprine, methotrexate, cyclophosphamide, ciclosporin, chlorambucil, tacrolimus, mycophenolate mofetil and infliximab □ _Intravitreal methotrexate" **Answer: Yes** **Q2) Which treatments are considered to be established clinical practice in the NHS for treating non-infectious intermediate, posterior or pan uveitis?** **Answer: The following would be considered standard practice for intermediate/posterior/panuveitis,** although access to some of these drugs is variable across the country (marked with a *) • **First line**/rescue therapy: Corticosteroids – usually systemic, sometimes periocular or intraocular (dexamethasone implant* or triamcinolone preparations) • **Second line**: commonly mycophenolate mofetil, methotrexate, azathioprine, tacrolimus, ciclosporin, dexamethasone implant • **Third line**: Adalimumab*, infliximab*	are needed.

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		• **Fourth line**: Cyclophosphamide, chlorambucil **Q3) Are corticosteroids always considered as the first treatment option?** **Answer:** Yes, except where specifically contraindicated (see below) **Q4) Are there people for whom corticosteroids would not be a treatment option?** **Answer:** Systemic corticosteroids may be avoided in patients with uncontrolled diabetes, psychosis, severe osteoporosis, uncontrolled steroid-induced ocular hypertension/glaucoma or other co morbidities which might be critically worsened by the administration of systemic corticosteroids. [Intraocular corticosteroids may be avoided in patients with known steroid-induced ocular hypertension/glaucoma.]	
		Q5) Is infliximab routinely used to treat non-infectious intermediate, posterior or pan uveitis? **Answer:** Infliximab or adalimumab have been routinely used as a third line therapy through exceptional funding routes in many units across England for the past decade. However, access has not been universal and has been limited since the introduction of specialised commissioning.	Comments noted. No changes to the scope are needed.
		Q6) Is triamcinolone acetonide routinely used to treat non-infectious intermediate, posterior or pan uveitis? If so, which formulation is used? **Answer:** The use of standard 'intra-articular' triamcinolone acetonide is widespread either as an intravitreal bolus (2-4mg in 0.05-0.1ml) or periocular (40mg). This preparation is unlicensed for this use and the	Comments noted. No changes to the scope are needed.

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		manufacturer has issued a specific warning that it should not be used for this indication. One unit in England uses Triessence, a preparation which is sourced from the USA, and which is a preservative free preparation which is licensed for intraocular use for diagnostic use only; it is not licensed for the treatment of uveitis.	
		Q7) What is the expected place in the treatment pathway for adalimumab? **Answer:** It is anticipated that adalimumab would be used as third line treatment i.e. failure of one or more second line therapies or where all such therapies are contraindicated. **Q8) Would adalimumab be used for previously untreated people?** **Answer:** Only in very rare circumstances where coticosteroids are absolutely contraindicated or in extremely severe sight immediately sight threatening disease. **Q9) Would adalimumab be used instead of local treatments (such as periocular or intravitreal corticosteroid injections)? Or would it be used instead of systemic treatment?** **Answer:** It would be used instead of systemic therapies **Q10) Would adalimumab be used on its own? Or in addition to the existing treatment options?** **Answer:** Typically adalimumab would be used in addition to existing treatment options to enable disease control. However, in rare circumstances (e.g. where all other therapies are contraindicated) or where other immunosuppressant have been successfully withdrawn it may be used as	Comments noted. No changes to the scope are needed.

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		monotherapy.	
		Q11) Are the outcomes listed appropriate? From the consultation document: “The outcome measures to be considered include: □ _visual acuity (the affected eye) □ _visual acuity (both eyes) □ _adverse effects of treatment □ _health-related quality of life. “ **Answer:** These are important measures of outcome but there are some caveats. **1) Limitations of the use of visual acuity as an outcome measure for uveitis** In most patients with uveitis the activity of the disease (ie level of inflammation) does not correlate directly with visual function nor is the effect immediate. The downstream effect of the disease on visual function (most commonly measured as visual acuity) is multifactorial and may only be manifest several years later as a consequence of the cumulative effect of damage accrued (1). With regard to the use of ‘visual acuity (both eyes)’, we propose that this would only be appropriate for patients with bilateral disease. **2) Importance of direct measures of inflammation** All the interventions being considered in this HTA act directly on inflammation, and therefore would be appropriately assessed by endpoints which measure the level of inflammation. The measures of inflammation	Comments noted. Vitreous haze and other measures of inflammation are captured within the outcomes in the draft scope. Specific measurement scales and methods are not included in scopes, so as not to appear to view any one assessment tool as superior to another. No changes to the scope are needed.

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		highlighted by the Standardization of Uveitis Nomenclature working group (2)for this use are vitreous haze and anterior chamber cells. The measurement of cystoid macular oedema by optical coherence tomography is another common outcome measure of inflammation in uveitis, although this particular manifestation of inflammation does not occur in all patients (3). **3) Composite/multifactorial outcome measures** A challenge in the design of studies to measure treatment effect in uveitis, has been that the manifestations of disease activity (inflammation) are variable both across the cohort and even in an individual patient. To deal with this, many studies (including the recent VISUAL studies [NCT01138657, NCT01124838]) have used an endpoint that allows for measurement of multiple different aspects of the disease (reflecting what is done in clinical practice). This is commonly summarised as either 'time to treatment failure' or 'time to control of disease'. **In summary we would suggest that the following outcome measures be considered:** • **visual acuity** (the affected eye) • **visual acuity** (both eyes, if both eyes affected) • **adverse effects of treatment** • **health-related quality of life** • **Specific measures of inflammation:** o **vitreous haze,** (affected eye) o **anterior chamber cells (affected eye)** o **cystoid macular oedema** as measured by either optical	

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		coherence tomography or angiography (affected eye) • **broader outcome measures** which reflect clinical practice such as: ○ **time to flare of disease** (sometimes described as 'time to treatment failure') which may be defined by worsening of one or more clinically significant parameters ○ **time to control of disease** (treatment success) which may be defined by improvement or complete resolution of one or more clinically significant parameters	
		Q12) Are there any subgroups of people in whom dexamethasone intravitreal implant, sirolimus intravitreal injection or adalimumab are expected to be more clinically effective and cost effective or other groups that should be examined separately? **Answer:** It is possible that these treatments will prove to be particularly effective in some subgroups of people, but this is not currently known. Specific points: 1) Studies in which a high proportion of patients had uveitic macular oedema are more likely to achieve improvement in visual acuity, whatever the intervention used. 2) There is a particularly strong argument to treat patients who have isolated ocular disease (particularly unilateral or asymmetric disease) with local therapies where these are shown to be safe and effective so as to avoid the systemic side-effects associated with systemic therapies. Dexamethasone intravitreal implant is particularly useful as a perioperative adjunct to cataract surgery to improve the likelihood of a successful outcome and optimise visual acuity improvement.	Comments noted. Attendees at the scoping workshop in 2015 noted that non-infectious uveitis contains a variety of subgroups. However, attendees did not identify subgroups for whom the technologies were more likely to be effective or cost-effective. They also considered that stratifying the population into subgroups would result in smaller sample sizes which would increase the uncertainty in the

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			evidence base. The workshop attendees agreed that it is feasible to compare the effects of different treatments across different subgroups because of the common outcomes (related to inflammation), and that recommendations could be tailored to different subgroups. This does not preclude the Appraisal Committee from considering evidence in subgroups during the course of the appraisal. No changes to the scope are needed.
		Q13) NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. **Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims.** In particular, please tell us if the proposed remit and scope: □ _could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which	Comments noted. No changes to the scope are needed.

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		dexamethasone intravitreal implant, sirolimus intravitreal injection and adalimumab will be licensed; □ _could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology; □ _could have any adverse impact on people with a particular disability or disabilities. Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts. **Answer: No, the remit and scope is very unlikely to lead to unlawful discrimination, and no specific measures other than voluntary reporting of any potential discrimination is required.**	
		Q14) Do you consider dexamethasone intravitreal implant, sirolimus intravitreal injection and adalimumab 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)? **Answer: Yes, each of these drugs have the potential to make a substantial impact but each has a distinct role:** 1. **Dexamethasone intravitreal implant – key role as a local corticosteroid therapy which is formulated for intraocular use** and is long-acting. Role to rapidly control uveitis in the posterior segment of the eye whilst avoiding the side-effects of systemic therapies. Access to effective local therapies is likely to have a major	Comments noted. Innovation will be considered by the Appraisal Committee when formulating its recommendations. The companies will have an opportunity to provide evidence on the innovative nature of their products in their submissions. No changes to the scope

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		impact for the following situations a) patients in whom local therapy can lead to a reduction, cessation or avoidance of systemic therapy; and b) patients who would otherwise have no effective treatment due to intolerance, lack of effect or contraindication to all available systemic therapies. 2. **Sirolimus intravitreal injection – key role as a local therapy which is not corticosteroid-based.** It therefore has the same potential advantages of the dexamethasone intravitreal implant but avoids the specific side-effects of intraocular corticosteroids (ocular hypertension/glaucoma and cataract). This is likely to have a major impact both as an effective local therapy, with a specific benefit in being suitable for those patients who have proven intolerant to or known to be inappropriate for, intraocular corticosteroids (eg patients with a significant corticosteroid-induced intraocular pressure rises). As discussed for the dexamethosone intravitreal implant above, the availability of effective local therapies would have a major impact in a) patients in whom local therapy can lead to a reduction, cessation or avoidance of systemic therapy; and b) patients who would otherwise have no effective treatment due to intolerance, lack of effect or contraindication to all available systemic therapies. **Adalimumab – key role as a systemic targeted biological therapy.** Adalimumab appears to have a favourable efficacy/safety profile, and is likely to make a major impact in patients who have failed or would not be able to tolerate standard second-line agents.	are needed.
		Q15) Do you consider that the use of dexamethasone intravitreal implant, sirolimus intravitreal injection and adalimumab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? Please identify the nature of the data which you understand to be available	Comments noted. Consultees will have an opportunity to submit evidence on the benefits not captured in

Section	Consultee/ Commentator	Comments [sic]	Action
		to enable the Appraisal Committee to take account of these benefits. **Answer:** All three treatments are likely to lead to significant and substantial health-related benefits. It is very important that it is recognized that currently there may be limited published data for 1these newer agents on which to base the QALY calculation. Evidence may need to be extrapolated from other conditions to identify the QALY benefit arising from 1) avoidance of drug-related harm compared to existing therapies), 2) reduction of monitoring 3) avoidance of sight-loss through greater drug efficacy and through greater adherence to the drug. **References** 1. Denniston AK, Dick AD. Systemic therapies for inflammatory eye disease: past,present and future. BMC Ophthalmol. 2013 Apr 24;13:18. doi:10.1186/1471-2415-13-18. Review. PubMed PMID: 23617902; PubMed Central PMCID:PMC3639939. **2.** Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of Uveitis Nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol. 2005 Sep;140(3):509-16. **3.** Denniston AK, Holland GN, Kidess A, Nussenblatt RB, Okada AA, Rosenbaum JT,Dick AD. Heterogeneity of primary outcome measures used in clinical trials of treatments for intermediate, posterior, and panuveitis. Orphanet J Rare Dis. 2015 Aug 19;10:97. doi: 10.1186/s13023-015-0318-6. PubMed PMID: 26286265; PubMed Central PMCID: PMC4545540	the QALY calculation. Where evidence allows the Committee will consider this information during the course of the appraisal. No changes to the scope are needed.
	Royal College of Ophthalmologists	Steroids are usually the first treatment choice, but in some patients presenting with severe disease, additional immunosuppression is initiated at	Comments noted. No changes to the scope

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	(RCO)	onset. There are groups in whom local and/or systemic steroids are contraindicated completely. Infliximab is routinely used as an initial biologic and frequently as an alternative treatment after adalimumab failure or intolerance. Adalimumab is usually used when one or two conventional immunosuppressants have been inadequate. It is usually used with a conventional immunosuppressant. It can be used when intraocular treatments are contraindicated and as a steroid sparing agent. It is used as monotherapy rarely, usually when there is an intolerance to several conventional immunosuppressants.	are needed.
	Santen	Santen agrees that the outcomes listed above are appropriate, however Santen would like to emphasize , that especially vitreous haze (VH) is a relevant clinical outcome to measure ocular inflammation in this chronic debilitating disease.	Comments noted. Vitreous haze is captured within the outcomes in the draft scope. No changes to the scope are needed.
Additional comments on the draft scope	AbbVie	<u>Budget impact of biologics</u> Between 1500 and 5000 people are diagnosed with non-infectious posterior segment uveitis each year in England (based on data from 2010). Uveitis is more common in people aged 20 to 59, but it can also occur in children, and affects men and women equally. The condition is defined as chronic when the duration is greater than three months, or a relapse occurs less than three months after discontinuing treatment. Both sirolimus and intravitreal dexamethasone will be seen as direct comparators of systemic and intraocular/ intravitreal steroids (injections or	Comments noted. No changes to the scope are needed.

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		implants) +/- immunosuppressant's (un licensed). They will be able to consider this larger population as being potentially their patient pool. In adults uveitis conditions are uncommon and at their most severe only affect about 1 in 10,000 of the population. Of all patients with uveitis in England AbbVie estimate 20% will have sight threatening disease requiring systemic therapy with calcineurin inhibitors and anti-proliferative agents in combination with low-dose corticosteroids. These are effective in over 60% of patients. Of the 40% that do not respond to the above treatment, further escalation of treatment is available. This includes combining conventional second line agents and using sub optimally high doses of corticosteroids. The remaining 10% remain unresponsive and may be considered for biologic therapy, a number estimated by NHS England at around 220 new patients per annum in England. So these patients have exhausted all of their options and thus are left with no other therapeutic alternatives (the most appropriate comparator being no other treatment/best supportive care). The only other way in which they would be eligible for a biologic medicine would be if they had significant systemic disease (e.g. rheumatoid arthritis). <u>Comments on the provisional matrix of consultees and commentators</u> AbbVie does not consider that adalimumab should be included in this appraisal so the company should not be a consultee	
	Santen	Santen would like to address the combined endpoint Visual Function Response (VFR) as new patient relevant endpoint which includes BCVA and the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25). In addition to vision loss, significant reductions in vision-related functioning have been reported in patients with uveitis, as assessed by patient reported	Comments noted. The Committee would normally consider the appropriateness of specific outcome measures during the

Section	Consultee/ Commentator	Comments [sic]	Action
		outcomes (PRO) measures. PRO measures of vision-related functioning, [such as the visual function questionnaire (VFQ-25)] complement clinical measures such as vitreous haze, and provide the patient's perspective on disease burden and outcomes of treatment. The rationale for exploring a new VFR measure, which combines BCVA and VFQ-25, is supported in the literature on therapies for inflammatory eye diseases. Several authors emphasize specific issues around the use of (BC)VA as the traditional functional outcome measure in clinical trials, and consider (BC)VA to be a poor marker of efficacy of a drug in inflammatory eye diseases. These authors also recognize that (BC)VA, despite efforts towards standardization, is a subjective parameter, which may be affected by patient-related factors such as general health. Vision-related functioning is recognized as a broader measure than (BC)VA, because it evaluates a patient's ability to conduct activities of daily living (e.g. reading, driving, face recognition) for which e.g. peripheral, contrast and colour vision, as well as (BC)VA are important. New measures for VFR are thought to be potentially more sensitive and meaningful outcomes to the patient than the classical (BC)VA and vision-related functioning measures. The VFR has been presented/published among others at the following congresses: • Lescrauwaet B, Duchateau L, Verstraeten T, Thurau S.: Improved Visual Function Is Associated With Inflammation Reduction In Subjects With Non-Infectious Uveitis (NIU) of The Posterior Segment Treated With Intravitreal Sirolimus: Results From Sakura Study 1. Value Health. 2015 Nov;18(7):A426. doi: 10.1016/j.jval.2015.09.586. Epub 2015 Oct 20. Presented as ISPOR 18th Annual European Congress, Milan, Italy, November 7-11, 2015. • Miserocchi E, Bodaghi B, Lescrauwaet B, Verstraeten T, Duchateau	course of the appraisal. No changes to the scope are needed.

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		L, Visual function evaluation in subjects with non-infectious uveitis of the posterior segment treated with intravitreal sirolimus monotherapy: Results of Sakura Study 1, a phase III multinational study. Presented at European Society of Ophthalmology Congress, Vienna, Austria, June 6-9, 2015.	

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

Department of Health
Roche