NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

MULTIPLE TECHNOLOGY APPRAISAL

Adalimumab and dexamethasone for treating non-infectious uveitis [ID763]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - AbbVie
   - Allergan Ltd UK
   - Birdshot Uveitis Society
   - Olivia's Vision
   - Royal College of Ophthalmologists
   - Royal National Institute of Blind People
   - NHS England
   - Healthcare Improvement Scotland

   'No comment' response received from Department of Health

3. **Comments on the Appraisal Consultation Document from experts:**
   - Dr Srilakshmi Sharma – Clinical Expert, nominated by AbbVie

4. **Comments on the Appraisal Consultation Document received through the NICE website**

5. **Assessment Group response to company Appraisal Consultation comments** – prepared by ScHARR

6. **Comments from AbbVie following the committee meeting**

7. **Assessment Group addendum provided following the committee meeting** – prepared by ScHARR

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal

Adalimumab and dexamethasone for treating non-infectious uveitis

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation.

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

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.

Comments received from consultees

Consultee	Comment [sic]	Response
AbbVie	1. Do you consider that all of the relevant evidence has been taken into account? Yes.	Thank you for your comment.
AbbVie	2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Yes	Thank you for your comment.

AbbVie	3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS? The ACD indicates that adalimumab is recommended as a treatment option in the posterior segment of the eye in adults with inadequate response to corticosteroids, only if there is: • Active disease, that is, current inflammation in the eye, and • Macular oedema, and • Inadequate response to immunosuppressants, and • Systemic disease or both eyes are affected, and • Worsening vision with a risk of blindness. During the committee meeting, the clinical experts mentioned that "patients with macular oedema have a high risk of blindness" (ACD section 4.6, page 10) and that "people with bilateral disease or systemic disease are likely to have a higher risk of blindness compared with people with unilateral or localised disease" (ACD section 4.6, page 11). Given that there is uncertainty around the risk of blindness in patients with severe disease, AbbVie understand why NICE have chosen to use macular oedema as a proxy for patients at high risk of blindness (ACD section 4.20, page 17). Indeed, UK data from Durrani suggests that over one-half of vision loss in patients with uveitis is due to macular oedema. Cystoid macular oedema (CMO) was the main cause of vision loss in 26.8% of patients; other causes include a combination of CMO and cataract in 20% and macular pathology [scaring, atrophy and hole] in 8%1. However, AbbVie wish to highlight their concerns about the criteria for recommending adalimumab. AbbVie agree with the Committee that macular oedema and worsening vision with a risk of blindness are closely linked, in that a decrease in visual acuity is commonly associated with macular oedema. However, other eye conditions can also be associated with a decrease in visual acuity with the potential to lead to low vision or blindness, such as cataract, glaucoma and vitreous debris. Data from Durrani suggests that other causes of vision loss in people with uveitis include cataract (18%), vitreous debris (11%), glaucoma (5%) and non-glaucomatous optic neuropathy (5%)[1]. As such, it may be more clinically plausible to rephrase the recommendation to the suggestion below which would also allow treatment access to patients with	Thank you for your comment. At the second appraisal committee meeting, the committee discussed whether macular oedema should be included as an essential criterion in recommendation 1.1 for adalimumab. The committee agreed that macular oedema was an example of a condition that is associated with a high risk of blindness. The committee removed macular oedema as an essential criterion in recommendation 1.1 but included it as an example of 'worsening vision with a high risk of blindness'. See sections 4.10 to 4.12 of the final appraisal determination (FAD).

	worsening vision with a risk of blindness but not necessarily with concurrent macular oedema. • Active disease, that is, current inflammation to the eye, and • Inadequate response to immunosuppresants, and • Systemic disease or both eyes are affected, and • Worsening vision with a risk of blindness, or • Macular oedema The literature suggests that around one-third to 40% of patients with active uveitis in the posterior segment of the eye have macular oedema[2-4]. This is likely to be higher in the patient population at highest risk of vision loss. Indeed, macular oedema, as measured by optical coherence tomography (OCT) was observed in 50% of patients in VISUAL I (tables 10.1.1.3.33.M and 14.2__10.1.1.3.34.M from VISUAL I Clinical study report)[5]. **References** 1. Durrani OM, Tehrani NN, Marr JE, Moradi P, Stavrou P, Murray PI. Degree, duration, and causes of visual loss in uveitis. British Journal of Ophthalmology 2004; 88(9): 1159-62. 2. Karim R, Sykakis E, Lightman S, Fraser-Bell S. Interventions for the treatment of uveitic macular edema: a systematic review and meta-analysis. Clinical ophthalmology (Auckland, NZ) 2013; 7: 1109-44. 3. Kempen JH, Altaweel MM, Holbrook JT, Jabs DA, Sugar EA. The multicenter uveitis steroid treatment trial: rationale, design, and baseline characteristics. American journal of ophthalmology 2010; 149(4): 550-61.e10. 4. Rothova A, Suttorp-van Schulten MS, Frits Treffers W, Kijlstra A. Causes and frequency of blindness in patients with intraocular inflammatory disease. The British journal of ophthalmology 1996; 80(4): 332-6. 5. AbbVie Limited. A Multicenter Study of the Efficacy and Safety of the Human Anti-TNF Monoclonal Antibody Adalimumab as Maintenance Therapy in Subjects Requiring High Dose Corticosteroids for Active Non-infectious Intermediate Uveitis, Posterior Uveitis, or Panuveitis – Including a Sub-study in Japanese Patients AbbVie Inc. (AbbVie) Clinical Study Report R&D/14/0730 Adalimumab/Protocol M10-877, 2015.	

Consultee	Comment [sic]	Response
	6. Merrill PT, Lim L, Song AP, et al. Predictors for Recurrent or Persistent Inflammation in Patients with Active and Inactive Non-Infectious Uveitis (presentation PO434). American Academy of Opthalmology; 2016; Chicago, IL 7. Nguyen QD, Merrill PT, Jaffe GJ, et al. Adalimumab for the prevention of uveitic flare in patients with inactive non-infectious uveitis requiring corticosteroids: a multicenter, double-masked, placebo-controlled phase 3, randomised controlled trial Lancet 2016; Online first.	
AbbVie	**Minor corrections** 1.1, 1.2 and 4.20 Adalimumab is recommended as an option for treating non-infectious uveitis in the posterior segment of the eye in adults with **inadequate** response to corticosteroids **inadequate** response to immunosuppressants We believe that for clarity inadequacy should be qualified as 'lack of efficacy or inability to tolerate adverse events' Suggested change and justification of amendment: Adalimumab is recommended as an option for treating non-infectious uveitis in the posterior segment of the eye in adults with inadequate response to corticosteroids ***defined as lack of efficacy or inability to tolerate associated adverse events*** inadequate response, ***defined as lack of efficacy or inability to tolerate adverse events,*** to immunosuppressants	Thank you for your comment. The committee discussed the clarity of the recommendations and added 'and' to each criterion listed in recommendation 1.1 to clarify that patients would need to meet all criteria listed to start treatment with adalimumab. The committee also added 'intolerance to immunosuppressants' in recommendation 1.1.

Consultee	Comment [sic]	Response
AbbVie	4.3 The clinical and patient experts stated that treatment options are currently restricted and there was a significant unmet need for both adalimumab and dexamethasone intravitreal implant. The committee heard from the clinical and patient experts that adalimumab and dexamethasone allow corticosteroid sparing, which is important not just for their short-term quality of life but also to avoid glaucoma, diabetes, stroke, and heart attack. The committee recognised that patients and their carers would greatly value a new treatment which prevented or delayed sight loss, particularly if it reduced the significant adverse events associated with current treatments. At the Committee Meeting, the patient experts specifically mentioned changes in mood and behaviour associated with steroid treatment; we suggest this and other adverse events are specifically included. We have used http://www.nhs.uk/Conditions/Corticosteroid-(drugs)/Pages/Introduction.aspx to inform our suggested copy Suggested change and justification of amendment: The clinical and patient experts stated that treatment options are currently restricted and there was a significant unmet need for both adalimumab and dexamethasone intravitreal implant. The committee heard from the clinical and patient experts that adalimumab and dexamethasone allow corticosteroid sparing, which is important not just for their short-term quality of life but also to avoid glaucoma, diabetes, stroke, and heart attack. The committee recognised that patients and their caregivers would greatly value a new treatment which prevented or delayed sight loss, particularly if it reduced the significant adverse events, ***which include changes in mood, mood swings, depression, weight gain, adrenal suppression and infection*** associated with current treatments.	Thank you for your comment. Section 4.3 of the final appraisal determination (FAD) provides a summary and is not intended to include a comprehensive list of adverse events, specific events will be captured under the general term 'adverse events'.

Consultee	Comment [sic]	Response
AbbVie	4.4 The VISUAL trials compared adalimumab plus background therapy (that is, immunosuppressants with or without steroids) with placebo plus background therapy In VISUAL I patients had a high dose steroid burst (60 mg/day) which was then tapered to 0 at week 15. In VISUAL II patients took 10-35 g/day of steroid at baseline, which was tapered to 0 by week 19 The VISUAL studies allowed patients to take one immunosuppressant and about one-third of patients in VISUAL I took concomitant immunosuppressants (mostly methotrexate, cyclosporine and mycophenolate mofetil). In VISUAL II, about one-half of patients took concomitant immunosuppressants (mostly methotrexate, cyclosporine and mycophenolate mofetil) Suggested change and justification of amendment: The VISUAL trials compared adalimumab plus background therapy (***a steroid burst [60 mg/day in VISUAL I and 10-35 mg/day in VISUAL II] tapered to zero with or without one immunosuppressant***) with placebo plus background therapy	Thank you for your comment. Section 4.4 of the FAD has been amended to clarify the treatments used in the VISUAL trials.
AbbVie	4.4 The AG advised that an indirect comparison was not appropriate because patient characteristics in VISUAL I, VISUAL II and HURON differed and there was a lack of common comparators and outcomes. AbbVie believe that adalimumab and dexamethasone intravitreal implant should not be compared since they are not generally used in the same patient population. As stated in section 4.2 Adalimumab would generally be used in people with bilateral or systemic disease or both, whereas dexamethasone is used in people with unilateral disease. Suggested change and justification of amendment: The AG advised that an indirect comparison was not appropriate because patient characteristics in VISUAL I, VISUAL II and HURON differed and there was a lack of common comparators and outcomes. **Furthermore, comparison of adalimumab and dexamethasone intravitreal implant is not clinically relevant since the agents are not generally used in the same patient population**	Thank you for your comment. Section 4.4 of the FAD has been amended to include reference to the use of dexamethasone and adalimumab at different stages in the treatment pathway.

Consultee	Comment [sic]	Response
AbbVie	4.5 It heard that because maintenance treatment with immunosuppressants and corticosteroids may control inactive disease, the next line of therapy, such as adalimumab or dexamethasone intravitreal implant may not be needed. AbbVie believes that this sentence may be imprecise since a proportion of patients with inactive disease are unable to continue on maintenance treatment with high dose corticosteroids and immunosuppressants due to the burden of adverse events. In the Committee meeting and in their written responses, the patient experts raised the issue of intolerable adverse events with both high dose corticosteroids and immunosuppressants. Patients with inactive disease who experience a flare on treatment without adalimumab are at increased risk of vision loss. In such cases adalimumab may be required to control inflammation and disease flare and reduce the risk of vision loss. A post-hoc analysis of the VISUAL studies revealed that VISUAL II patients receiving placebo who experienced 2 or more flares in the previous 12 months had a significantly higher risk of recurrent and persistent inflammation than those with ≤1 flare (HR of 1.95 for 2 flares versus ≤1 flare and HR of 4.23 for ≥3 flares versus ≤1 flare, $p<0.001$)[6]. Recurrent and persistent inflammation is correlated with loss of vision and the ultimate aim of controlling a uveitis flare is to preserve visual acuity and visual function. Suggested change and justification of amendment: AbbVie require more clarification around the optimal treatment option for patients who are not able to tolerate the adverse events associated with maintenance treatment or they do experience disease flare. **References** 6. Merrill PT, Lim L, Song AP, et al. Predictors for Recurrent or Persistent Inflammation in Patients with Active and Inactive Non-Infectious Uveitis (presentation PO434). American Academy of Opthalmology; 2016; Chicago, IL	Thank you for your comment. At the second appraisal committee meeting, the committee added 'intolerance to immunosuppressants' in recommendation 1.1.

Consultee	Comment [sic]	Response
AbbVie	4.6 The committee noted that most patients in the VISUAL trials had bilateral or systemic non-infectious uveitis. 90% of patients in VISUAL I had bilateral disease and 95% in VISUAL II, therefore we suggest most is edited to the majority (over 90%), as per 4.8 Suggested change and justification of amendment: The committee noted that **the majority (over 90%)** of patients in the VISUAL trials had bilateral or systemic non-infectious uveitis.	Thank you for your comment. Section 4.6 of the FAD has been amended to include the proportion of patients (over 90%) in the VISUAL trials that had bilateral or systemic non-infectious uveitis.
AbbVie	4.19 The committee also noted that people with inactive disease would be unlikely to have treatment with adalimumab in clinical practice, because its mechanism of action suggests limited benefit. AbbVie believes that this sentence is inaccurate since adalimumab has been shown to demonstrate clinical benefit in the VISUAL II study[7]. Suggested change and justification of amendment: The committee also noted that people with inactive disease would be unlikely to have treatment with adalimumab in clinical practice, ***since adalimumab is not cost effective in such patients.*** **References** 7. Nguyen QD, Merrill PT, Jaffe GJ, et al. Adalimumab for the prevention of uveitic flare in patients with inactive non-infectious uveitis requiring corticosteroids: a multicenter, double-masked, placebo-controlled phase 3, randomised controlled trial Lancet 2016; Online first.	Thank you for your comment. The text in section 4.20 of the FAD has been amended.
AbbVie	4.20 Taking all of this into account, itrecommended Insert space Suggested change and justification of amendment: Taking all of this into account, it recommended	Thank you for your comment. Section 4.21 of the FAD has been edited to correct this.

Consultee	Comment [sic]	Response
AbbVie	4.20 The committee also agreed that a stopping rule should be included, which reflected the strict criteria for defining treatment failure in the VISUAL I trial. Based on these criteria, it concluded that treatment should be stopped if there is evidence of 1 of the following: Stop adalimumab for non-infectious uveitis in the posterior segment of the eye in adults with inadequate response to corticosteroids if there is 1 of the following: • new active inflammatory chorioretinal or inflammatory retinal vascular lesions or both • anterior chamber cell grade of 0.5+ or less • vitreous haze grade of 0.5+ or less • worsening of best corrected visual acuity by 3 or more lines or 15 letters. Suggested change and justification of amendment: AbbVie require more clarification around the stopping criteria in order to reflect clinical practice.	Thank you for your comment. At the second appraisal committee meeting, the committee discussed the stopping rule for adalimumab. The committee were aware that VISUAL I used 2 definitions for treatment failure, one that was used before 6 weeks and one that was used after 6 weeks. The committee agreed to use the post 6 week definition of treatment failure as part of the stopping rule for adalimumab (see recommendation 1.2). The committee's recommendation are therefore in line with the clinical trial evidence that has underpinned the marketing authorisation granted by the regulator.
AbbVie	4.22 1.1 Error! Reference source not found. to 1.3 Suggested change and justification of amendment: To be corrected	Thank you for your comment. This section has now been edited to correct this.
AbbVie	"Assessment Group response to consultation [AIC] and [redacted]" documents, page 2, Issue 7: Age at start, 4th line It is stated that "*base case was reduced from £99,506 to £94,126*" The correct base case ICER for the active population and 42.7 average age at start is £95,506 Suggested change and justification of amendment: Base case ICER for the active population to be corrected	Thank you for your comment. A corrected version of the assessment group response to consultation has been issued.
AbbVie	"Assessment Group response to consultation [AIC] and [redacted]" documents, page 2, Issue 7: Age at start, 6th line It is stated that "*the base case was reduced from £321,405 to £314,726*" when the average age of VISUAL II trial (i.e. 42.5) is used. However, when using the age of 42.5, the ICER for the inactive population reduces to £314,134. Suggested change and justification of amendment: Reduced base case ICER for the inactive population to be corrected	Thank you for your comment. A corrected version of the assessment group response to consultation has been issued.

Consultee	Comment [sic]	Response
Allergan	Allergan welcomes the recommendation of the dexamethasone intravitreal implant for use in patients with non-infectious posterior segment uveitis. Allergan's comments on the ACD are set out under the headings outlined in NICE's appraisal consultation document.	Thank you for your comments.

Allergan	**<u>Has all of the relevant evidence been taken into account?</u>** **1. Restriction to patients with macular oedema and duration of treatment effect** Allergan welcomes the recommendation of the dexamethasone intravitreal implant as a treatment option for patients with non-infectious posterior segment uveitis who have macular oedema but considers that the clinical and cost effectiveness evidence also support its use in patients without macular oedema. **1.1 Duration of treatment effect for patients with macular oedema** In the post-authorisation long-term safety study (CONSTANCE), 22.3% of the eyes treated with dexamethasone intravitreal implants for non-infectious posterior segment uveitis did not have macular oedema (1). Within this study, eyes without macular oedema had a mean time to retreatment of 44 weeks compared with 35 weeks in eyes with macular oedema. The longer time to retreatment will decrease the ICER to a level that may be considered cost-effective even when a lower risk of blindness is included in the model. Using the committee's preferred utility for blindness (0.57) and increasing the duration of dexamethasone treatment effect from 30 weeks to 44 weeks decreases the deterministic ICER from £25,257 to £14,016 per QALY gained vs limited current practice (LCP). Following the committee's reasoning that the risk of blindness is lower in patients without macular oedema, changing the annual rate of blindness to 0 (i.e. no risk of blindness), results in an ICER of £30,898 per QALY gained vs LCP. In a scenario analysis using the 44 weeks treatment duration, the committee's preferred utility of 0.57 for blindness and the low background rate of blindness from Tomkins Netzer et al. results in an ICER of £19,658 per QALY gained. Allergan considers that there is likely to be a risk of blindness for patients without macular oedema, albeit smaller than for patients with macular oedema, and that the ICER is therefore likely to be within the range normally considered a cost-effective use of NHS resources. Allergan considers that the prolonged time to retreatment in patients without macular oedema compared to those with, and the improvement in ICER that results from extended duration of treatment effect in the model, means that both the clinical and cost-effectiveness evidence supports use in all patients with active posterior segment uveitis, not just those patients with macular oedema. The clinical effectiveness of dexamethasone in patients without macular oedema is supported by the HURON study. Patients in the HURON study did not have	Thank you for your comment. At the second appraisal committee meeting, the committee discussed the use of macular oedema as an essential criterion in recommendation 1.3 for dexamethasone. The committee agreed that the background rate of blindness would be low for most people who will be treated with dexamethasone because they are likely to have unilateral disease (see sections 4.10 to 4.12 of the FAD). Therefore the committee removed reference to macular oedema in recommendation 1.3. Section 4.18 of the FAD has been amended to highlight that there may be variation in the number of implants used in clinical practice.

	macular oedema as entry criteria and the Central Macular Thickness in the DEX 700 group was modestly raised at 344 µm at entry. **1.2 Duration of treatment effect for all patients** Section 4.17 of the ACD includes description of the assessment group opinion "that dexamethasone would only provide a treatment benefit for around 6 months". Allergan considers that the 30-week treatment effect assumption gives a higher ICER for the dexamethasone intravitreal implant than would be the case if a longer treatment effect were to be modelled. In the CONSTANCE study, the mean time between injections for all patients with non-infectious posterior segment uveitis who received at least two injections, excluding patients with remission after a single implant, was 36.77 weeks (SD 18.218 weeks; median [range] 31.14 weeks [15.14-106.29 weeks]). Analysis of the distribution of average time between subsequent injections demonstrated that approximately 55% of eyes had a longer average time between subsequent injections than the modelled 30-week duration of effect, as shown in Figure 1. The modelled 30-week duration of effect is therefore likely to overestimate the ICER since increasing the duration of treatment in the assessment group model leads to improved ICERs for dexamethasone intravitreal implants vs LCP. Allergan therefore considers that clarification should be made of the potential for substantially longer duration of treatment effect with dexamethasone intravitreal implants. These data on time to retreatment do not take account of patients who achieve long term control with a single implant. The assessment group model does not account for the benefits of any patients achieving long term control ("remission") on the dexamethasone intravitreal implant. Figure provided by Allergan but not replicated in this table. **2. Number of injections per eye** Section 4.17 of the ACD refers to the opinion of clinical experts that "a maximum of 3 implants would be used consecutively in clinical practice". Allergan acknowledges that the consideration for retreatment should be based on the ophthalmologist's opinion regarding whether the patient may benefit from retreatment without being exposed to significant risk. There are observational data to indicate that patients with non-infectious posterior segment uveitis receive more than 3 consecutive implants in the same eye. Among all patients receiving dexamethasone intravitreal implants for non-infectious posterior segment uveitis in the long-term safety study (CONSTANCE), the mean number of injections per study eye was 2.2 (standard deviation (SD) 1.26), with a median number of injections of 2.0 (range 1-6) (1). Analysing the distribution of number of injections	

Consultee	Comment [sic]	Response
	per study eye in this cohort demonstrates that 16.48% of eyes received more than 3 implants (Figure 2). Allergan considers that it is probable that a non-negligible proportion of patients may continue to benefit from treatment with dexamethasone intravitreal implants beyond a potential imposed limit of 3 implants. This analysis also demonstrates that 35.11% of eyes received one implant, which will include a proportion of patients who enter remission, with appropriate and lasting control of their condition, after a single implant. Allergan concludes that some patients may require more than 3 implants in the same eye and that it would be inappropriate to restrict access in clinical practice to a maximum number of implants per eye on cost grounds as the budget impact will be low. Figure provided by Allergan but not replicated in this table. **References** 1. Allergan. Post-authorisation Safety Study (PASS) Observational Clinical Study Report CONSTANCE 206207-025 2016.	

Consultee	Comment [sic]	Response
Allergan	**<u>Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?</u>** **1. Cost of blindness** Section 4.22 of the ACD states "the reduction (that is, improvement) in ICERs resulting from overestimated costs of blindness were likely to be at least partly offset by the low rate of background blindness in this high-risk group." Allergan considers that the term "partly offset" implies a comparable impact on the modelled ICER when in fact, changing the source for the background rate of blindness has a far greater impact than changing the cost of blindness. Allergan therefore considers that this should be rephrased to "the reduction (that is, improvement) in ICERs resulting from overestimated costs of blindness were likely to be offset by the low rate of background blindness in this high-risk group". **2. Wording regarding general usage of dexamethasone** Section 4.2 notes that the committee "heard from clinical experts that adalimumab would generally be used in people with bilateral or systemic disease or both, whereas dexamethasone is used in people with unilateral disease." Allergan considers that reference to dexamethasone should include the wording "generally be used" in the same way that this wording is applied to adalimumab. Therefore, Allergan proposes that this sentence should be revised to indicate that the committee "heard from clinical experts that adalimumab would generally be used in people with bilateral or systemic disease or both, whereas dexamethasone would generally be used in people with unilateral disease." **3. Spelling mistake** In section 4.21 of the ACD "macula oedema" should be amended to "macular oedema".	Thank you for your comment. Section 4.19 of the FAD has been amended. The recommendation for dexamethasone does not currently specify unilateral or bilateral disease. Section 4.2 of the FAD has been amended to highlight that there may be variation in the use of dexamethasone in practice. The spelling error in section 4.21 has now been corrected.

Consultee	Comment [sic]	Response
Allergan	**<u>Are the provisional recommendations sound and a suitable basis for guidance to the NHS?</u>** As described above, Allergan considers that there is reasonable justification for extension of the recommendation for the dexamethasone intravitreal implant to include patients without macular oedema. Allergan also considers that the current wording of Section 4.17 of the ACD may limit use of dexamethasone intravitreal implant to three consecutive implants at a retreatment interval of 6 months, despite evidence of clinical effectiveness and cost-effectiveness beyond this number of implants. There is evidence that a substantial proportion of patients experience a much longer duration of effect, and there is likely to be a proportion of patients for whom adequate control of their condition is achieved with a single injection.	Thank you for your comment. At the second appraisal committee meeting, the committee discussed the use of macular oedema as an essential criterion in recommendation 1.3 for dexamethasone. The committee agreed that the background rate of blindness would be low for most people who will be treated with dexamethasone because they are likely to have unilateral disease (See sections 4.10 to 4.12 of the FAD). Therefore the committee removed reference to macular oedema in recommendation 1.3. Section 4.18 of the FAD has been amended to highlight that there may be variation in the number of implants used in clinical practice. Healthcare professionals starting treatment with dexamethasone should refer to the summary of product characteristics for more details on the recommended dosing intervals for dexamethasone intravitreal implant.

Birdshot Uveitis Society	Comment 1: start criteria should not be 'all of the following' but should be 'one of the following' because: • macular oedema is only one of the causes of loss of vision due to inflammation in uveitis. Given that the rationale for these recommendations is visual impact, then worsening vision, from whatever cause, in uveitis which is active despite treatment with corticosteroids and immunosuppressants, should be sufficient indication to start treatment with adalimumab. Thus • the recommendations relating to 'macular oedema' and 'worsening vision with a risk of blindness' should be combined to read: 'worsening vision relating to the uveitis (eg, from macular oedema) with a risk of blindness.' Comment 2: the appraisal is based on the ICER of who has the most to gain from treatment due to visual impact, and not on considering those in whom treatment will be the most effective. This raises two inequality issues: • there may be some patients with unilateral non-infectious uveitis who need to have access to systemic therapies, especially those in whom local therapies, such as dexamethasone implants, are contraindicated (eg, those who have had previous steroid-induced raised intraocular pressure); • there will also be some patients with unilateral non-infectious uveitis who already have reduced vision in their other eye for whatever reason (eg, amblyopia, previous injury or unrelated eye disease) and who require systemic treatment to preserve vision in their uveitic eye. **Current wording** Adalimumab is recommended as an option for treating non-infectious uveitis in the posterior segment of the eye in adults with inadequate response to corticosteroids, only if there is: • macular oedema active disease, that is, current inflammation in the eye • inadequate response to immunosuppressants • systemic disease or both eyes are affected and • worsening vision with a risk of blindness. **Suggested amended wording**	Thank you for your comment. At the second appraisal committee meeting, the committee discussed whether macular oedema should be included as an essential criterion in recommendation 1.1 for adalimumab. The committee agreed that macular oedema was an example of a condition that is associated with a high risk of blindness. The committee removed macular oedema as an essential criterion in recommendation 1.1 but included it as an example of 'worsening vision with a high risk of blindness'. See sections 4.10 to 4.12 of the FAD. The committee were aware that the majority (>90%) of patients in the VISUAL trials had bilateral disease. The committee considered the cost effectiveness results for the use of adalimumab when the risk of permanent blindness was low and agreed that this was not in the range normally considered a cost-effective use of NHS resources. The committee discussed the use of adalimumab when one eye is affected. The committee recognised that people with unilateral disease in the better seeing eye where the other eye has poor visual acuity were at a high risk of permanent blindness. The committee included reference to treating one eye where is it the better seeing eye in recommendation 1.1

Consultee	Comment [sic]	Response
	Adalimumab is recommended as an option for treating non-infectious uveitis in the posterior segment of the eye in adults with inadequate response to corticosteroids if there is one of the following: • active disease, that is, current inflammation in the eye • inadequate response to immunosuppressants • systemic disease or both eyes are affected* • worsening vision relating to the uveitis (eg, from macular oedema) with a risk of blindness * active disease involving only one eye may be treated where this eye is the better seeing eye and local therapies are contraindicated or ineffective.	

Birdshot Uveitis Society	Comment 1: the stop criteria in the appraisal consultation document are ambiguous and do not harmonise either with the VISUAL studies or the criteria set out in the Interim Clinical Commissioning Policy Statement: Adalimumab for Severe Refractory Uveitis https://www.england.nhs.uk/wp-content/uploads/2017/03/clin-com-pol-statment-170010ps.pdf. The stop criteria should read: • Failure to reduce to 0.5+ or less for anterior chamber cells • Failure to reduce to 0.5+ or less for vitreous haze. Comment 2: anterior chamber activity alone should not be used as a reason for switching systemic medication for posterior uveitis. A flare which shows anterior chamber activity has little implication for vision. It can be safely treated with drops. **Current wording** Stop adalimumab for non-infectious uveitis in the posterior segment of the eye in adults with inadequate response to corticosteroids if there is 1 of the following: • new active inflammatory chorioretinal or inflammatory retinal vascular lesions or both • anterior chamber cell grade of 0.5+ or less • vitreous haze grade of 0.5+ or less • worsening of best corrected visual acuity by 3 or more lines or 15 letters **Suggested amended wording** Stop adalimumab for non-infectious uveitis in the posterior segment of the eye in adults with inadequate response to corticosteroids if there is one of the following: • new active inflammatory chorioretinal or inflammatory retinal vascular lesions or both • failure to reduce to (or maintain) vitreous haze grade of 0.5+ or less • worsening of best corrected visual acuity by 3 or more lines or 15 letters. Alternatively, see the NHS England interim policy https://www.england.nhs.uk/wp-content/uploads/2017/03/clin-com-pol-statment-170010ps.pdf :	Thank you for your comment. At the second appraisal committee meeting, the committee discussed the stopping rule for adalimumab. The committee were aware that VISUAL I used 2 definitions for treatment failure, one that was used before 6 weeks and one that was used after 6 weeks. The committee agreed to use the post 6 week definition of treatment failure as part of the stopping rule for adalimumab (see recommendation 1.2). The committee's recommendation are therefore in line with the clinical trial evidence that has underpinned the marketing authorisation granted by the regulator.

Consultee	Comment [sic]	Response
	'Adults who respond to treatment with adalimumab will continue treatment for 18 months at which time a trial of treatment withdrawal will be undertaken. If relapse occurs, restarting adalimumab will be considered using the start criteria stated in this policy. Response to treatment with adalimumab is defined as achieving one or more of the following criteria: • Reduction in daily oral prednisolone dose by 5mg, or to ≤10mg • Reduction in conventional second-line immunosuppressive treatment • For eyes with impaired visual acuity, an improvement in visual acuity by ≥5 LogMAR letters (0.1 log units) • For eyes with reduced visual field, an improvement in visual field based on an assessment using Humphrey, Goldmann or Octopus perimetry • For eyes with increased central macular thickness, a ≥10% reduction in central macular thickness.' **Stop criteria would then be:** 'Adalimumab for the treatment of uveitis is stopped using following criteria: 1. Failure to achieve the response criteria defined above after 3 months of treatment 2. Adverse reaction to adalimumab.'	
Birdshot Uveitis Society	**Dexamethasone** We believe that the recommendations unfairly discriminate against patients with uveitis refractory to other treatments (or for whom other treatments are contraindicated) and who do not have macular oedema, but whose vision is worsening due to active inflammation. **Suggested amended wording** Dexamethasone intravitreal implant is recommended as an option for treating non-infectious uveitis in the posterior segment of the eye in adults, only if there is: • active disease, that is, current inflammation in the eye and • worsening vision relating to the uveitis (eg, from macular oedema) with a risk of blindness.	Thank you for your comment. At the second appraisal committee meeting, the committee discussed the use of macular oedema as an essential criterion in recommendation 1.3 for dexamethasone. The committee agreed that the background rate of blindness would be low for most people who will be treated with dexamethasone because they are likely to have unilateral disease (see sections 4.10 to 4.12 of the FAD). Therefore the committee removed reference to macular oedema in recommendation 1.3.

Consultee	Comment [sic]	Response
Birdshot Uveitis Society	4.2 '…whereas dexamethasone is used in people with unilateral disease.' 4.6 '…current clinical practice preferred dexamethasone for unilateral disease.' 4.21 '…people who have dexamethasone in current clinical practice are likely to have disease affecting only one eye…' The statement at 4.2 is an incorrect extrapolation of those at 4.6 and 4.21. For patients with uveitis affecting only one eye, a clinical choice, ie, a treatment option, would be to treat only the affected eye with a dexamethasone intravitreal implant rather than treating the whole person with systemic steroids. Both eyes may be affected by the disease, but one eye may be more badly affected than the other and require an implant.	Thank you for your comment. The recommendation for dexamethasone does not currently specify unilateral or bilateral disease. Section 4.2 of the FAD has been amended to highlight that there may be variation in the use of dexamethasone in practice.
Birdshot Uveitis Society	4.3 '…adalimumab and dexamethasone allow corticosteroid sparing… This should read …'adalimumab and dexamethasone allow systemic corticosteroid sparing…'	Thank you for your comment. Systemic corticosteroid sparing should be captured as part of the broader term 'corticosteroid sparing'.
Birdshot Uveitis Society	4.17 '…a maximum of 3 implants would be used consecutively in clinical practice. We disagree that a maximum of 3 implants would be used consecutively in clinical practice. This was a clinician's personal view given at the first appraisal committee meeting. Clinical experience on repeat administration of dexamethasone implants in uveitis will accrue over time. See Statement of Product Characteristics for Ozurdex https://www.medicines.org.uk/emc/print-document?documentid=23422	Thank you for your comment. The recommendation for dexamethasone does not currently specify the number of implants that should be used. Section 4.18 of the FAD has been amended to highlight that there may be variation in the number of implants used in practice. Healthcare professionals starting treatment with dexamethasone should refer to the summary of product characteristics for more details on the recommended dosing intervals for dexamethasone intravitreal implant.

Consultee	Comment [sic]	Response
Birdshot Uveitis Society	**Implementation** Treatment recommendations for the use of adalimumab and dexamethasone intravitreal implant in non-infectious uveitis for patients in Scotland and Northern Ireland should be noted here.	Thank you for your comment. Section 5 of the FAD explains how NICE recommendations will be implemented if a treatment receives a positive appraisal. The way NICE was established in legislation means that our guidance is officially England-only. However, we have agreements to provide certain NICE products and services to Wales, Scotland and Northern Ireland. Therefore section 5 of the final appraisal determination (FAD) refers to England and Wales only. For more details see https://www.nice.org.uk/about/who-we-are
Birdshot Uveitis Society	Page 33 The AG assumed that the treatments were only effective whilst they were being given. Therefore, patients who are no longer being treated with adalimumab, and patients who received the dexamethasone implant more than 6 months ago, will accrue no additional health gains'. We disagree with this statement. The goal of treatment for non-infectious uveitis is attaining a state of clinical remission and maintaining it after stopping treatment. For patients achieving this goal, the continuing 'additional health gains' are considerable.	Thank you for your comment. The Assessment Group carried out exploratory analyses that included some remission in patients treated with adalimumab (see sections 4.9 and 4.13 of the FAD).
NHS England	Yes – the key RCTs in this area have been identified (the two VISUAL studies and the HURON study); there is much more limited evidence to support the cost effectiveness assessments, but the best available evidence has been considered.	Thank you for your comment
NHS England	Yes. The clinical evidence is reasonably well defined now post the VISUAL and HURON studies. The cost effectiveness evidence is limited and therefore the estimates are necessarily imprecise, however we would agree with the baseline estimates used.	Thank you for your comment

NHS England	The recommendations are largely sound but there is one significant error (which may be typographical – see 1.2B below) and there are a number of places where the recommendations (1.1-3) would benefit from clarification. Specifically: 1.1 START/INCLUSION CRITERIA It is not clear whether inclusion requires all the listed criteria to be met, but our assumption is that this is what is expected (given the discussion of cost effectiveness and the aim to direct to those patients where there is most to gain). This should be clarified, but also we disagree with two points: 1.1A) Macular oedema should not be an essential criterion. We support the NICE MTA in its aim to direct and limit Adalimumab to those at most risk of visual loss, however this is already captured in the criterion 'worsening vision relating to uveitis with a risk of blindness'. The presence of macular oedema is indeed one of the causes of loss of vision due to inflammation in uveitis, but it is not the only cause of reversible inflammation-induced sight-loss and there is no data from any of the trials to suggest that patients who are losing vision due to active inflammation without macular oedema would be any less likely to benefit. We would suggest that the line relating to macular oedema is removed. 1.1B) There may be rare cases where adalimumab would be considered in unilateral disease (assuming all other criteria have been met). This would occur in the unusual situation where a patient is contraindicated from local therapy (e.g. due to known steroid-induced ocular hypertension/glaucoma), had failed local therapy or had already lost the other eye to other disease. The cost effectiveness argument would be equally valid in a patient with unilateral disease in their better seeing/only eye as in the patient with bilateral disease. NICE may wish to provide some provision for this within their recommendations such as a footnote to the effect that "*active disease involving only one eye may be treated where this is the better seeing eye and/or local therapies are contraindicated or ineffective" 1.2 STOPPING CRITERIA 1.2A) The stopping criteria state that they are based on the VISUAL trials. This was based on detecting 'Treatment Failure' as a trial endpoint and is not the same as 'Treatment Failure' in clinical practice. We would almost never stop treatment with a systemic agent at the first sign of breakthrough inflammation as is suggested by the application of the VISUAL criteria. For example if a patient had	Thank you for your comment. At the second appraisal committee meeting, the committee discussed whether macular oedema should be included as an essential criterion in recommendation 1.1 for adalimumab. The committee agreed that macular oedema was an example of a condition that is associated with a high risk of blindness. The committee removed macular oedema as an essential criterion in recommendation 1.1 but included it as an example of 'worsening vision with a high risk of blindness'. See sections 4.10 to 4.12 of the FAD. The committee discussed the use of adalimumab when one eye is affected. The committee recognised that people with unilateral disease in the better seeing eye where the other eye has poor visual acuity were at a high risk of permanent blindness. The committee included reference to treating one eye where is it the better seeing eye in recommendation 1.1 The committee discussed the clarity of the recommendations and added 'and' to each criterion listed in recommendation 1.1 to clarify that patients would need to meet all criteria listed to start treatment with adalimumab. The committee also added 'intolerance to immunosuppressants' in recommendation 1.1. The committee discussed the stopping rule for adalimumab. The committee were aware that VISUAL I used 2 definitions for treatment failure, one that was used before 6 weeks and one that was used after 6 weeks. The committee agreed to use the post 6 week definition of treatment failure as part of the stopping rule for adalimumab (see recommendation 1.2). The committee's

Consultee	Comment [sic]	Response
	been having flares of inflammation every month on their previous treatment regimen, and then had complete remission for six months after stopping adalimumab, it would seem wrong to withdraw adalimumab due to a minor flare of disease affecting one domain (eg 1+ Anterior Chamber cells) which could be adequately controlled with either topical or local therapy PROVIDED that the adalimumab was continued. It is however appropriate that adalimumab should indeed be stopped where it is clear that it is not being effective, Considering all available evidence reviewed by NICE, and current delivery of care we would recommend that the NICE recommendations should align with those of the continuation and stopping criteria of the NHS England Interim policy, namely: *"Adults who respond to treatment with adalimumab will continue treatment for 18 months at which time a trial of treatment withdrawal will be undertaken. If relapse occurs, restarting adalimumab will be considered using the start criteria stated in this policy. Response to treatment with adalimumab is defined as achieving one or more of the following criteria:* • *Reduction in daily oral prednisolone dose by 5mg, or to ≤10mg* • *Reduction in conventional second-line immunosuppressive treatment* • *For eyes with impaired visual acuity, an improvement in visual acuity by ≥5 LogMAR letters (0.1 log units)* • *For eyes with reduced visual field, an improvement in visual field based on an assessment using Humphrey, Goldmann or Octopus perimetry* • *For eyes with increased central macular thickness, a ≥10% reduction in central macular thickness* *Stop Criteria* *Adalimumab for the treatment of uveitis is stopped using following criteria:* *1. Failure to achieve the response criteria defined above after 3 months of treatment* *2. Adverse reaction to adalimumab "* 1.2B) Furthermore the stopping criteria provided by NICE are mis-quoted (or mis-adapted) from the VISUAL trials. Where it states 'AC cells of 0.5+ or less' and 'vitreous haze grade of 0.5+ or less' it should read 'failure to reduce to AC cells/vitreous haze grade of 0.5+ or less' . This issue would be superseded if our recommendation in point 1.2A is followed	recommendation are therefore in line with the clinical trial evidence that has underpinned the marketing authorisation granted by the regulator. The committee was aware that the majority (>90%) of patients in the VISUAL trials had bilateral disease. The committee considered the cost effectiveness results for the use of adalimumab when the risk of permanent blindness was low and agreed that this was not in the range normally considered a cost-effective use of NHS resources.

Consultee	Comment [sic]	Response
NHS England	Whilst NHS England is not the responsible commissioner for ozurdex (which falls to CCGs), we have included comments based on how the use of ozurdex aligns with the indications in the NHS England interim policy. As per previous discussion around adalimumab you might suggest that this is an unfair discrimination against patients with uveitis refractory to other treatments who do not happen to have macular oedema but are getting worsening vision due to active inflammation which would respond to ozurdex therefore you recommend that the crtiera are as follows (which also harmonises with those for adalimumab) 1.3 In line with our discussion in 1.1, it is not clear whether all criteria on the inclusion criteria for dexamethasone implant are meant to be essential. If they are, then we disagree with the inclusion of macular oedema as an essential criterion. In line with our comments above we would recommend that this is amended to: Dexamethasone intravitreal implant is recommended as an option for treating non-infectious uveitis in the posterior segment of the eye in adults, only if there is: • active disease, that is, current inflammation in the eye and • worsening vision with a risk of blindness (e.g. from macular oedema) Given the lack of current evidence NICE may wish to consider a requirement to collect such data as part of its recommendations. This is a requirement of the NHS England interim commissioning policy	Thank you for your comment. At the second appraisal committee meeting, the committee discussed the use of macular oedema as an essential criterion in recommendation 1.3 for dexamethasone. The committee agreed that the background rate of blindness would be low for most people who will be treated with dexamethasone because they are likely to have unilateral disease (See sections 4.10 to 4.12 of the FAD). Therefore the committee removed reference to macular oedema in recommendation 1.3. The committee discussed the clarity of the recommendations and added 'and' to each criterion listed in recommendation 1.1 to clarify that patients would need to meet all criteria listed to start treatment with adalimumab. The committee also added 'intolerance to immunosuppressants' in recommendation 1.1. The committee discussed the available clinical evidence and considered it was adequate for decision making (see section 4.4 of the FAD).
Olivia's Vision	We thank the committee for its decision to recommend both technologies and we look forward to the publication of clinical guidelines which will allow uveitis specialists to increase the number of therapies available to their sight threatened patients. We thank you for the opportunity to comment on your draft recommendations.	Thank you for your comment.

Consultee	Comment [sic]	Response
Olivia's Vision	**Recommendations.** **1.1 Adalimumab** Bullets 1 and 3 are problematic for us. We are concerned that the recommendation does not adequately reflect the clinical need for adalimumab as a treatment option. This seems to arise from comments found in 4.5 and 4.19: 'The committee also noted that people with inactive disease would be unlikely to have treatment with adalimumab in clinical practice, because its mechanism of action suggests limited benefit. Therefore, it concluded that adalimumab could not be recommended for treating inactive non-infectious uveitis.' This does not recognise that the disease may be inactive because it is controlled by an immunosuppressant, the side effects of which are not tolerated by the patient. We would like bullet 3 altered to read: **'inadequate response to, or intolerance of, an immunosuppressant(s).'** Bullet 4 also concerns us. In the Summary of Appraisal Committee's Key Conclusions, page 22, the following comment appears: 'The committee heard from clinical experts that adalimumab would generally be used in people with bilateral or systemic disease, whereas dexamethasone is used in people with unilateral disease.' The word, 'generally' is important here and we would like bullet 4 to include unilateral uveitis without systemic disease. A severity of disease and threat to vision, in such cases, will have been established through the initiation of second line therapy with immunosuppressants. When this fails to control inflammation, or is not tolerated, therapy with dexamethasone may be contraindicated through the associated risk of additional ocular morbidity. It is not clear whether all these criteria should be met for adalimumab to be prescribed. We feel meeting two of the criteria is sufficiently indicative of a need for biologic therapy.	Thank you for your comment. The committee discussed the clarity of the recommendations and added 'and' to each criterion listed in recommendation 1.1 to clarify that patients would need to meet all criteria listed to start treatment with adalimumab. The committee also added 'intolerance to immunosuppressants' in recommendation 1.1. The committee discussed the use of adalimumab when one eye is affected. The committee recognised that people with unilateral disease in the better seeing eye where the other eye has poor visual acuity were at a high risk of permanent blindness. The committee included reference to treating one eye where is it the better seeing eye in recommendation 1.1

Consultee	Comment [sic]	Response
Olivia's Vision	1.2 We appreciate that strict criteria to determine treatment failure are required in clinical trials and the ideal outcome is drug induced remission. However, clinical practice is different with a long-term goal of preserving as much vision as possible for as long as possible. While bullets 1 and 4 strongly suggest treatment failure, bullets 2 and 3 may not be so indicative of this, especially at the lower end of the grades specified. Low grade anterior cells are managed, often easily and successfully, with topical steroid and vitreous haze, at lower grades, depending on location, may have minimal impact on vision. Furthermore, the vitreous contains no structure critical to vision which may be damaged by inflammation. We note that on page 12 of the Pre-meeting briefing, Adalimumab and dexamethasone for treating non-infectious uveitis, clinical experts stated: (The) Most important outcome measure and the most important sight threatening complication of non-infectious posterior uveitis is cystoid macular oedema, but the 'main outcome in clinical trials is vitreous haze and a 2-step improvement may be considered clinically significant.' We further note that neither of these measurements are included in the criteria which describe treatment failure in the NHS Interim Policy, 2017. We would prefer that they are removed from the 'Stop' criteria.	Thank you for your comment. At the second appraisal committee meeting, the committee discussed the stopping rule for adalimumab. The committee were aware that VISUAL I used 2 definitions for treatment failure, one that was used before 6 weeks and one that was used after 6 weeks. The committee agreed to use the post 6 week definition of treatment failure as part of the stopping rule for adalimumab (see recommendation 1.2). The committee's recommendation are therefore in line with the clinical trial evidence that has underpinned the marketing authorisation granted by the regulator.

Consultee	Comment [sic]	Response
Olivia's Vision	**1.3 Dexamethasone** We are not clear whether the wording of this recommendation means people must have both active disease and macular oedema. If this isn't the case, the use of 'and/or' would provide clarity. If both active disease and macular oedema must be present, there are some groups of patients who would benefit from the therapy but be denied it. These include patients for whom systemic therapy is contraindicated such as pregnant women or those who have received, or are being treated for cancer. Some of these patients may have bi-lateral disease and also require more than the three consecutive implants the clinical experts stated were likely to be employed in clinical practice. (4.17, page 16).	Thank you for your comment. At the second appraisal committee meeting, the committee discussed the use of macular oedema as an essential criterion in recommendation 1.3 for dexamethasone. The committee agreed that the background rate of blindness would be low for most people who will be treated with dexamethasone because they are likely to have unilateral disease (See sections 4.10 to 4.12 of the FAD). Therefore the committee removed reference to macular oedema in recommendation 1.3. The recommendation for dexamethasone does not currently specify unilateral or bilateral disease. Sections 4.2 and 4.18 have been amended to highlight that there may be variation in the use of dexamethasone and in the number of implants used in practice. Healthcare professionals starting treatment with dexamethasone should refer to the summary of product characteristics for more details on the recommended dosing intervals for dexamethasone intravitreal implant.

Royal National Institute of Blind People	RNIB welcomes the committee's recommendation that adalimumab and dexamethasone become treatment options for non-infectious uveitis. However we believe that the eligibility criteria outlined in the recommendations are restrictive, denying patients at risk of sight loss effective and appropriate treatment options. **Adalimumab** Recommendations: 1.1 outlines five start criteria for treatment with adalimumab. i) We do not agree that macular oedema should be listed as stand-alone start criteria. Macular oedema is not present in all patients who have worsening vision with the risk of blindness. Patients without macular oedema but with worsening vision and at risk of blindness should be able to access the treatment option of adalimumab. RNIB recommends that macular oedema is removed from the start criteria or alternatively be listed as an 'or' alongside worsening vision with risk of blindness. ii) We do not agree that start criteria should be limited to a bilateral indication. This restriction rules out any patient with non-infectious uveitis in one eye who has already lost vision to a greater extent in the other eye as a result of any sight loss condition or event. Excluding patients with a unilateral indication in these circumstances could result in the loss of remaining useful vision. This would have a huge impact on quality of life for the individual as highlighted in our original submission. While this would only represent a small number of patients it is a significant exclusion. This limitation would also rule out anyone with unilateral disease for whom local therapies are not appropriate due to increased IOP. Additionally, the current criteria means that a patient with a severe unilateral indication and no access to adalimumab could be at risk of losing sight in one eye. This would likely have a significant impact on the patient's life, for example the ability to drive or carry out certain types of employment. While this would only represent a small number of patients it is a significant exclusion. RNIB recommends that patients with unilateral disease who have poorer vision in their other eye be considered in the start criteria to preserve remaining sight. RNIB recommends that patients with unilateral disease and a contraindication such as IOP be considered in the start criteria to preserve bilateral vision.	Thank you for your comment. At the second appraisal committee meeting, the committee discussed whether macular oedema should be included as an essential criterion in recommendation 1.1 for adalimumab. The committee agreed that macular oedema was an example of a condition that is associated with a high risk of blindness. The committee removed macular oedema as an essential criterion in recommendation 1.1 but included it as an example of 'worsening vision with a high risk of blindness'. See sections 4.10 to 4.12 of the FAD. The committee discussed the use of adalimumab when one eye is affected. The committee recognised that people with unilateral disease in the better seeing eye where the other eye has poor visual acuity were at a high risk of permanent blindness. The committee included reference to treating one eye where is it the better seeing eye in recommendation 1.1 The committee discussed the stopping rule for adalimumab. The committee were aware that VISUAL I used 2 definitions for treatment failure, one that was used before 6 weeks and one that was used after 6 weeks. The committee agreed to use the post 6 week definition of treatment failure as part of the stopping rule for adalimumab (see recommendation 1.2). The committee's recommendation are therefore in line with the clinical trial evidence that has underpinned the marketing authorisation granted by the regulator.

Consultee	Comment [sic]	Response
	RNIB recommends that patients with unilateral disease who have worsening vision with the risk of blindness in that eye be considered in the start criteria to preserve bilateral vision. iii) Recommendation 1.2 outlines the stop criteria for treatment with adalimumab. We do not agree that a single flare of inflammation is justification for withdrawing treatment of adalimumab. This would deny a viable treatment option to patients who had achieved greater stability in terms of their condition through treatment with adalimumab. RNIB recommends consideration of the stopping criteria outlined in the NHS England interim policy: https://www.england.nhs.uk/wp-content/uploads/2017/03/clin-com-pol-statment-170010ps.pdf	
Royal National Institute of Blind People	**Dexamethasone** We note that in section 4.2, dexamethasone is recommended for unilateral use only. However it would be possible to treat bilateral non-infectious uveitis with dexamethasone. As a localised therapy this would circumvent the impact of systemic steroids on the patient's quality of life. The ACD recognises the impact of systemic steroids and the benefits of sparing for the patient in section 4.3. RNIB requests that bilateral use of dexamethasone is considered to lessen the impact of treatment on the patient's quality of life.	Thank you for your comment. The recommendation for dexamethasone does not currently specify unilateral or bilateral disease. Sections 4.2 and 4.18 have been amended to highlight that there may be variation in the use of dexamethasone and in the number of implants used in practice. Healthcare professionals starting treatment with dexamethasone should refer to the summary of product characteristics for more details on the recommended dosing intervals for dexamethasone intravitreal implant.
The Royal College of Ophthalmologists	1. Introduction 1.1 The Royal College of Ophthalmologists welcomes the opportunity to respond to this consultation. 1.2 The Royal College of Ophthalmologists is the professional body for ophthalmologists and we champion excellence in the practice of ophthalmology on behalf of our members to optimise care for patients. We set the curriculum and examinations for trainee ophthalmologists, provide training in eye surgery, maintain standards in the practice of ophthalmology, and promote research and advance science in the specialty. 1.3 We work with leaders across the eye health sector to help shape eye services for the benefit of patients.	Thank you.

The Royal College of Ophthalmologists	2. START/INCLUSION CRITERIA 2.1 It is not clear whether inclusion requires all the listed criteria to be met. This needs to be elucidated. There are several points where points: a) Macular oedema should not be an essential criterion. We understand and support the NICE MTA in its aim to direct and limit Adalimumab to those at most risk of visual loss, however this is already highlighted in the criterion 'worsening vision relating to uveitis with a risk of blindness'. The presence of macular oedema is only one of reversible inflammation-induced vision loss the causes of loss of vision due to inflammation in uveitis, but it is not the only cause of and there is no data from any of the trials to suggest that patients who are losing vision due to active inflammation without macular oedema would be any less likely to benefit. We would suggest that the sentence pertaining to macular oedema be removed. b) There may be the rare cases where adalimumab would be considered in unilateral disease (assuming all other criteria have been fulfilled). This could occur in the situation where a patient is contraindicated from local therapy (e.g. due to known steroid-induced ocular hypertension/glaucoma), had failed local therapy or had already lost the other eye to other disease. The cost effectiveness argument would be equally valid in a patient with unilateral disease in their better seeing/only eye as in the patient with bilateral disease. NICE may wish to provide some provision for this within their recommendations such as a footnote to the effect that "*active disease involving only one eye may be treated where this is the better seeing eye and/or local therapies and or systemic therapies are contraindicated or have been ineffective"	Thank you for your comment. The committee discussed the clarity of the recommendations and added 'and' to each criterion listed in recommendation 1.1 to clarify that patients would need to meet all criteria listed to start treatment with adalimumab. The committee also added 'intolerance to immunosuppressants' in recommendation 1.1. The committee discussed whether macular oedema should be included as an essential criterion in recommendation 1.1 for adalimumab. The committee agreed that macular oedema was an example of a condition that is associated with a high risk of blindness. The committee removed macular oedema as an essential criterion in recommendation 1.1 but included it as an example of 'worsening vision with a high risk of blindness'. See sections 4.10 to 4.12 of the FAD. The committee discussed the use of macular oedema as an essential criterion in recommendation 1.3 for dexamethasone. The committee agreed that the background rate of blindness would be low for most people who will be treated with dexamethasone because they are likely to have unilateral disease (See sections 4.10 to 4.12 of the FAD). Therefore the committee removed reference to macular oedema in recommendation 1.3. The committee discussed the use of adalimumab when one eye is affected. The committee recognised that people with unilateral disease in the better seeing eye where the other eye has poor visual acuity were at a high risk of permanent blindness. The committee included reference to treating one eye where is it the better seeing eye in recommendation 1.1

The Royal College of Ophthalmologists	**3. STOPPING CRITERIA** 3.1 The stopping criteria state that they are based on the VISUAL trials. This was based on detecting 'Treatment Failure' as a trial endpoint and is not the same as 'Treatment Failure' in clinical practice. A systemic treatment would rarely be discontinued at the first sign of breakthrough inflammation as is suggested by the application of the VISUAL criteria. For example if a patient had been having flares of inflammation every month on their previous treatment regimen, and then had complete remission for six months on adalimumab, it would seem wrong to withdraw adalimumab due to a minor flare of disease affecting one domain (e.g. 1+ Anterior Chamber cells) which could be adequately controlled with either topical or local therapy PROVIDED that the adalimumab was continued. It is however appropriate that adalimumab should indeed be stopped where it is clear that it is not being effective. 3.2 Considering all available evidence reviewed by NICE, and current delivery of care we would recommend that the NICE recommendations should align with those of the continuation and stopping criteria of the NHSE Interim policy, namely: *"Adults who respond to treatment with adalimumab will continue treatment for 18 months at which time a trial of treatment withdrawal will be undertaken. If relapse occurs, restarting adalimumab will be considered using the start criteria stated in this policy. Response to treatment with adalimumab is defined as achieving one or more of the following criteria:* • *Reduction in daily oral prednisolone dose by 5mg, or to ≤10mg* • *Reduction in conventional second-line immunosuppressive treatment* • f*or eyes with impaired visual acuity, an improvement in visual acuity by ≥5 Log MAR letters (0.1 log units)* • *For eyes with reduced visual field, an improvement in visual field based on an assessment using Humphrey, Goldmann or Octopus perimetry* • *For eyes with increased central macular thickness, a ≥10% reduction in central macular thickness* *Stop Criteria* *Adalimumab for the treatment of uveitis is stopped using following criteria:* *1. Failure to achieve the response criteria defined above after 3 months of treatment*	Thank you for your comment. At the second appraisal committee meeting, the committee discussed the stopping rule for adalimumab. The committee were aware that VISUAL I used 2 definitions for treatment failure, one that was used before 6 weeks and one that was used after 6 weeks. The committee agreed to use the post 6 week definition of treatment failure as part of the stopping rule for adalimumab (see recommendation 1.2). The committee's recommendation are therefore in line with the clinical trial evidence that has underpinned the marketing authorisation granted by the regulator.

Consultee	Comment [sic]	Response
	2. Adverse reaction to adalimumab" 3.3 Furthermore the stopping criteria provided by NICE are mis-quoted (or mis-adapted) from the VISUAL trials. Where it states 'AC cells of 0.5+ or less' and 'vitreous haze grade of 3 0.5+ or less' it should read 'failure to reduce to AC cells/vitreous haze grade of 0.5+ or less'. This issue would be superseded if our recommendation in point 2a were followed.	

Consultee	Comment [sic]	Response
The Royal College of Ophthalmologists	3.4 Additional thoughts about the macular oedema for ozurdex - again as per previous discussion around adalimumab you might suggest that this is an unfair discrimination against patients with uveitis refractory to other treatments who do not happen to have macular oedema but are getting worsening vision due to active inflammation which would respond to ozurdex therefore you recommend that the criteria are as follows (which also harmonises with those for adalimumab) 3.5 In line with our discussion in 1a, it is not clear whether all criteria on the inclusion criteria for dexamethasone implant are meant to be essential. If they are, then we disagree with the inclusion of macular oedema as an essential criterion. In line with our comments above we would recommend that this be amended to: *Dexamethasone intravitreal implant is recommended as an option for treating non-infectious uveitis in the posterior segment of the eye in adults, only if there is:* • *active disease, that is, current inflammation in the eye and* • *worsening vision with a risk of blindness (e.g. from macular oedema)* 3.6 Although in many patients the option of Adalimumab as 1st choice may be correct there may be circumstance where bilateral Ozurdex for patients with bilateral uveitis is a preferred treatment particularly where there is no systemic disease or there has been no response or an adverse affect to Adalimumab or other systemic therapies. 3.7 We do not agree that there should be a limit on how long Ozurdex can be used for. The guidance should say not more than 3 injections in 12 months. We believe it should be re-usable for as long as necessary, as long as the patient benefits, and there are no adverse events. There is concern about using Ozurdex for bilateral uveitis however we do not share these concerns. There are valid indications for bilateral treatment. There is concern about using more than three implants in one eye consecutively. However, members have reported experience with patients who have had no cumulative harm from repeated implants, many more than three, for multiple indications including uveitis.	Thank you for your comment. The committee discussed the use of macular oedema as an essential criterion in recommendation 1.3 for dexamethasone. The committee agreed that the background rate of blindness would be low for most people who will be treated with dexamethasone because they are likely to have unilateral disease (See sections 4.10 to 4.12 of the FAD). Therefore the committee removed reference to macular oedema in recommendation 1.3. The recommendation for dexamethasone does not currently specify unilateral or bilateral disease. Sections 4.2 and 4.18 of the FAD have been amended to highlight that there may be variation in the use of dexamethasone and in the number of implants used in practice. Healthcare professionals starting treatment with dexamethasone should refer to the summary of product characteristics for more details on the recommended dosing intervals for dexamethasone intravitreal implant.

Comments received from clinical specialists and patient experts

Nominating organisation	Comment [sic]	Response
AbbVie	**Section 4.4** National Institute for Health and Care Excellence Page 10 of 28 Appraisal consultation document – Adalimumab and dexamethasone for treating non-infectious uveitis Issue date: March 2017 *"evidence for adalimumab came from the VISUAL I and VISUAL II trials and the evidence for dexamethasone intravitreal implant came from the HURON trial. The VISUAL trials compared adalimumab plus background therapy (that is, immunosuppressants with or without steroids) with placebo plus background therapy and HURON compared dexamethasone plus background therapy with a sham procedure plus background therapy. "* **Response**: In the VISUAL trials, approximately 70% of comparator participants were on sham treatment and no corticosteroids; 30% were on sham treatment plus another immunosuppressant. Post hoc analysis to examine the effects of immunosuppressant therapy was either not made available or not calculated in this industry-sponsored trial. The HURON and VISUAL trials had similar inclusion criteria is non infectious uveitis. The HURON trial was not exclusively for cystoid macular oedema.	Thank you for your comment. Section 4.4 of the FAD has been amended to clarify steroid and immunosuppressant use in the VISUAL trials.

Nominating organisation	Comment [sic]	Response
AbbVie	***Section 4.4*** *National Institute for Health and Care Excellence Page 10 of 28 Appraisal consultation document – Adalimumab and dexamethasone for treating non-infectious uveitis Issue date: March 2017* *"The committee agreed that there was a lack of evidence on therapy for non-infectious uveitis, with varied and often limited current treatments available. However, the available clinical evidence was adequate for decision-making.* *the available clinical evidence was adequate for decision-making"* **Response**: There is now adequate evidence for biological effect of adalimumab in uveitis to support decision making but inadequate direct evidence to support commissioning criteria proposed. There is, in fact, randomized controlled trial evidence to support other immunosuppressive therapies (eg mycophenolate, methotrexate and tacrolimus) in uveitis. However, there is no direct comparison between adalimumab and a comparator. See comment 1. (above)	Thank you for your comment section 4.4 of the FAD has been amended to refer to the lack of relevant evidence for this appraisal.

Nominating organisation	Comment [sic]	Response
AbbVie	***Section 4.20*** *National Institute for Health and Care Excellence Page 17 of 28 Appraisal consultation document – Adalimumab and dexamethasone for treating non-infectious uveitis Issue date: March 2017* *"treatment would be more cost effective in those at higher risk of permanent legal blindness, and bilateral disease with macular oedema was a useful proxy for this"* a/ Not all forms of sight threatening inflammation cause cystoid macular oedema although a significant proportion does. For example, vitreous inflammation or an ischaemic retinal vasculitis can cause loss of sight where there is no macular oedema. Therefore, bilateral disease affecting the posterior segment of the eye alone is likely to be a useful proxy and 'bilateral disease with macular oedema', too restrictive. b/ In situations where the eye with unilateral posterior/pan or intermediate uveitis is the only eye eg the other eye is lost due to trauma or another ocular problem eg amblyopia the risk of legal blindness is equally high. I appreciate that worsening vision with a risk of blindness is a useful criterion which could potentially capture this group.	Thank you for your comment. At the second appraisal committee meeting, the committee discussed whether macular oedema should be included as an essential criterion in recommendation 1.1 for adalimumab. The committee agreed that macular oedema was an example of a condition that is associated with a high risk of blindness. The committee removed macular oedema as an essential criterion in recommendation 1.1 but included it as an example of 'worsening vision with a high risk of blindness'. See sections 4.10 to 4.12 of the FAD. The committee discussed the use of adalimumab when one eye is affected. The committee recognised that people with unilateral disease in the better seeing eye where the other eye has poor visual acuity were at a high risk of permanent blindness. The committee included reference to treating one eye where is it the better seeing eye in recommendation 1.1
AbbVie	Could the draft policy exclude from full consideration any people protected by the equality legislation who fall within the patient population for which non- infectious Uveitis will be licensed? No, not that I am aware of	Thank you for your comment
AbbVie	Could the draft policy 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 No such selective restrictions are anticipated.	Thank you for your comment

Nominating organisation	Comment [sic]	Response
AbbVie	Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities. No, I do not think a person with a specific disability will be adversely affected.	Thank you for your comment

Comments received from commentators

Commentator	Comment [sic]	Response
Healthcare Improvement Scotland	Yes. As far as I am aware all RCTs have been included. There are many case series and advisory papers in the literature that have been beneficial in guiding current clinical practice but these are the only RCTs.	Thank you for your comment.
Healthcare Improvement Scotland	Yes and no. I believe the analysis to be appropriate for the information available. However although it may be useful, at a specific time point, to differentiate between unilateral and bilateral disease from an economic point of view, it is often not possible to differentiate who will in future develop second eye involvement. To make a decision not to treat a patient with unilateral disease and potentially result in irreversible vision loss, may make health economic sense at the time. This decision makes assumptions that patients need only one eye to function and if the other eye were involved then it would be possible to get disease control with treatment. This is not always possible and inflammatory eye disease is often asymmetrical in its disease process and the response to treatment. I would have concerns for rationing treatment with adalimumab to those with bilateral disease at this time point, as this could have significant long term implications for individuals and does not reflection current NHS Scotland practice.	Thank you for your comment. The committee were aware that the majority (>90%) of patients in the VISUAL trials had bilateral disease. The committee considered the cost effectiveness results for the use of adalimumab when the risk of permanent blindness was low and agreed that this was not in the range normally considered a cost-effective use of NHS resources. The committee discussed the use of adalimumab when one eye is affected. The committee recognised that people with unilateral disease in the better seeing eye where the other eye has poor visual acuity were at a high risk of permanent blindness. The committee included reference to treating one eye where is it the better seeing eye in recommendation 1.1

Commentator	Comment [sic]	Response
Healthcare Improvement Scotland	I would agree with the committee's conclusion that fewer young blind individuals enter residential care than their older comparators. However blindness is generally for life. It is therefore likely that although the majority blind or visually impaired due to sight threatening uveitis will be younger and not require residential care at point of registration, as they age they are likely to require residential care at an earlier stage than those without visual impairment. I would therefore suggest that the model may be an underestimate. I am not a health economist however and would not begin to suggest I understand the modelling but would be grateful for clarification.	Thank you for your comment. The committee was aware that the Assessment Group based the proportion of people requiring residential care on a Health Technology Assessment for treating age-related macular degeneration. The committee discussed this issue and agreed that given that the starting age of people with uveitis in the model was likely to be lower compared with people with age related macular degeneration, the proportion requiring residential care was likely to be overestimated. See section 4.17 of the FAD for further details.

Healthcare Improvement Scotland	I appreciate from the data presented that in inactive disease there is insufficient QALY to warrant the use of adalimumab. However it is not always as straight forward in clinical practice to define inactive disease. Does this term mean inactive disease off treatment or inactive disease off prednisolone? With sight-threatening uveitis, hopefully once disease control has been achieved, the intention is to taper therapy dependent on disease activity. Often patients are on a combination of systemic steroids and two systemic immunosuppressive agents at the time of commencing adalimumab. The primary aim of biologic therapy in these patients can be to get the prednisolone to as low a level as possible. Patients have often already been on a moderately high dose of prednisolone for a minimum of 6 months by this stage but often longer. They will possibly have osteoporosis, be cushingoid, iatrogenic adrenal suppression, weight gain, hypertension and diabetes. These are just a few of the side effects our patients experience on their journey toward adalimumab. During this time they will have had visual difficulties that create problems undertaking daily activities including driving and working. They also require regular hospital clinic attendance, which, in this often young patient group, require taking more time off work. However as the document reads at present the only patients with sight-threatening uveitis who would qualify for treatment with adalimumab would be those with worsening vision with a risk of blindness due to bilateral active intraocular inflammation in the presence of macular oedema, not responding to immunosuppression, with an underlying systemic disease that is, current inflammation in the eye macular oedema inadequate response to immunosuppressants systemic disease or both eyes are affected and worsening vision with a risk of blindness. 1.2 'Stop adalimumab for non-infectious uveitis in the posterior segment of the eye in adults with inadequate response to corticosteroids if there is 1 of the following': • new active inflammatory chorioretinal or inflammatory retinal vascular lesions or both • anterior chamber cell grade of 0.5+ or less • vitreous haze grade of 0.5+ or less • worsening of best corrected visual acuity by 3 or more lines or 15 letters. By these criteria any patient with active chorioretinal or retinal lesions should have treatment stopped, however these lesions are not mentioned in treatment commencement guidelines. Also when you have control of the anterior chamber or vitreous activity you are obliged to stop the treatment. Although the data does not	Thank you for your comment. The committee were aware that the majority (>90%) of patients in the VISUAL trials had bilateral disease. The committee considered the cost effectiveness results for the use of adalimumab when the risk of permanent blindness was low and agreed that this was not in the range normally considered a cost-effective use of NHS resources. The terms active and inactive disease are defined in the VISUAL trials. At the second appraisal committee meeting, the committee discussed whether macular oedema should be included as an essential criterion in recommendation 1.1 for adalimumab. The committee agreed that macular oedema was an example of a condition that is associated with a high risk of blindness. The committee removed macular oedema as an essential criterion in recommendation 1.1 but included it as an example of 'worsening vision with a high risk of blindness'. See sections 4.10 to 4.12 of the FAD. The committee discussed the use of adalimumab when one eye is affected. The committee recognised that people with unilateral disease in the better seeing eye where the other eye has poor visual acuity were at a high risk of permanent blindness. The committee included reference to treating one eye where is it the better seeing eye in recommendation 1.1 The committee discussed the stopping rule for adalimumab. The committee were aware that VISUAL I used 2 definitions for treatment failure, one that was used before 6 weeks and one that was used after 6 weeks. The committee agreed to use the post 6 week definition of treatment failure as part of the stopping rule for adalimumab (see

	support the commencement of adalimumab in patients with inactive disease, what this recommendation is actually referring to is maintenance therapy once disease control has been achieved. I believe this approach will greatly increase burden for the patient and the service. In other areas where adalimumab is used, for example rheumatoid arthritis, this is not an approach that has been found to provide clinical efficiency and cost effectiveness. Although I am not aware that this data exists at present for the management of patients with uveitis I would suspect a similar outcome would arise for those requiring anti-TNF therapy. Although the letter loss was defined by the trials, I feel that a loss of 3 lines or 15 letters is too long to wait and I would be looking to stop and change therapy before this stage. Patients would struggle to continue normal activities if they had lost this level of vision before a decision to change treatment had been made. I am not sure why worsening macular oedema has not been included in the stopping criteria when it was included as a major commencement criteria. With the recommendations as they are currently any patient without macula oedema despite sight-threatening uveitis (eg occlusive retinal vasculitis, severe vitritis) would not qualify for either adalimumab or dexamethasone. *Recommended dose and schedules* *'Repeat doses should be considered when a patient experiences a response to treatment followed subsequently by a loss in visual acuity and in the physician's opinion may benefit from retreatment without being exposed to significant risk'.* Visual acuity is not one of the indications for commencing treatment and am therefore unsure why is it in the retreatment criteria. *4.2 The committee heard from the clinical experts that there are 3 main indications in clinical practice for treating non-infectious uveitis: vitreous haze, macular oedema and worsening vision.* The treatment guideline only allows for macular oedema and there is no mention of vitreous haze or worsening vision. Worsening vision is only mentioned as an indication to stop treatment but not for commencement. 4.20 *The committee noted that disease was likely to be more severe in people with bilateral disease later in the treatment pathway. It agreed that the treatment would be more cost effective in those at higher risk of permanent legal blindness, and bilateral disease with macular oedema was a useful proxy for this.* I appreciate the need for a proxy in analysis but within clinical practice there are other clinical signs that we currently use in decision making. Other sight-threatening signs include symptomatic vitritis and occlusive retinal vasculitis. These patients	recommendation 1.2). The committee's recommendation are therefore in line with the clinical trial evidence that has underpinned the marketing authorisation granted by the regulator.

Commentator	Comment [sic]	Response
	also require disease control, which if not achieved on 'conventional therapy' then adalimumab would be on next choice in NHS Scotland. Patients with occlusive vasculitis may actually require more rapid aggressive management than those with macular oedema. I believe in NHS England anti-TNF therapy is already accessible for patients with occlusive retinal vasculitis secondary to Bechets but under these guidelines would not be available for those with occlusive retinal vasculitis of another cause. Surely this is discrimination with one rule for one group and another for another.	

Commentator	Comment [sic]	Response
Healthcare Improvement Scotland	*The committee also heard from the clinical experts and the assessment group (AG) that there is no nationally agreed pathway for treating non-infectious uveitis.* This is not case in NHS Scotland, where the Scottish Uveitis National Managed Clinical Network treatment guidelines are followed. *It heard from clinical experts that adalimumab would generally be used in people with bilateral or systemic disease or both, whereas dexamethasone is used in people with unilateral disease. The committee concluded that the general treatment pathway reflected current practice.* This does not reflect current practice within NHS Scotland. Although dexamethasone is used for unilateral disease, it is also sometimes used for bilateral disease when felt clinically appropriate. It is generally used in patients that don't tolerate, wish to avoid, or are uncontrolled on systemic steroids. It is not used as an alternative to adalimumab. At present adalimumab is used in patients requiring ongoing prednisolone therapy for disease control despite the use of two immunosuppressive agents. *4.3 The clinical and patient experts stated that treatment options are currently restricted and there was a significant unmet need for both adalimumab and dexamethasone intravitreal implant.* Thankfully this is not currently the case with NHS Scotland where patients and clinicians already have access to these therapies if there is felt to be a clinical need, as per the Scottish Uveitis National Managed Clinical Network Treatment Guidelines. 4.17 *It heard that for this reason, a maximum of 3 implants would be used consecutively in clinical practice.* This does not reflect clinical practice in NHS Scotland, where patients felt appropriate for dexamethasone implant and have received benefit from it would not have treatment stopped after the third implant. Following informed discussion with the patient further implants may be given. To stop a treatment that has proven effective does not make sense. Most patients with sight-threatening uveitis will develop cataract at some stage anyway. If glaucoma does occur and is not manageable with medical therapy then further dexamethasone would not be given.	Thank you for your comment. The recommendation for dexamethasone does not currently specify unilateral or bilateral disease. Sections 4.2 and 4.18 of the FAD have been amended to highlight that there may be variation in the use of dexamethasone and in the number of implants used in practice. Healthcare professionals starting treatment with dexamethasone should refer to the summary of product characteristics for more details on the recommended dosing intervals for dexamethasone intravitreal implant.

Commentator	Comment [sic]	Response
Healthcare Improvement Scotland	Unlike NHS England, within NHS Scotland there are nationally agreed pathways for treating patients with sight-threatening uveitis. Although these may not be evidence based, as the evidence doesn't exist, they allow a directed approach of best practice for patients within a national network. Wherever patients are now treated within Scotland they will receive a similar standard of care which reflects national consensus. The approach within NHS Scotland differs from the recommendation in that we do not restrict adalimumab to patients with bilateral disease but where deemed appropriate treat individuals with unilateral disease.	Thank you for your comment. The way NICE was established in legislation means that our guidance is officially England-only. For more details see https://www.nice.org.uk/about/who-we-are At the second appraisal committee meeting, The committee discussed the use of adalimumab when one eye is affected. The committee recognised that people with unilateral disease in the better seeing eye where the other eye has poor visual acuity were at a high risk of permanent blindness. The committee included reference to treating one eye where is it the better seeing eye in recommendation 1.1

Comments received from members of the public

Role*	Section	Comment [sic]	Response
Professor of Clinical Ophthalmology	1	1.1 Most of the time patients with NIPU respond well t corticosteroids but at high dose and the disease relapses as the dose is reduced. It is not correct to say that they have an inadequate response to corticosteroids Vision worsening with a risk of blindness may be due to a variety of causes not helped by Adalimumab eg cataract, epiretinal membranes, glaucoma. It is inflammatory causes that should be identified as the cause of the worsening vision 1.2 Indications for stopping Adalimumab - the anterior cell grade is irrelevant if you are treating NIPU - this should be removed - it applies to AU only Persistent macular oedema is a majoe reason for adding Adalimunmab in NIPU - many of these conditions may have little vitiritis eg birdshot or the vitritis is controlled. A low vitreous haze grade is therefore not relevant as a stopping indication and should be removed	Thank you for your comment. At the second appraisal committee meeting, the committee discussed whether macular oedema should be included as an essential criterion in recommendation 1.1 for adalimumab. The committee agreed that macular oedema was an example of a condition that is associated with a high risk of blindness. The committee removed macular oedema as an essential criterion in recommendation 1.1 but included it as an example of 'worsening vision with a high risk of blindness'. See sections 4.10 to 4.12 of the FAD. The committee discussed the stopping rule for adalimumab. The committee were aware that VISUAL I used 2 definitions for treatment failure, one that was used before 6 weeks and one that was used after 6 weeks. The committee agreed to use the post 6 week definition of treatment failure as part of the stopping rule for adalimumab (see recommendation 1.2). The committee's recommendation are therefore in line with the clinical trial evidence that has underpinned the marketing authorisation granted by the regulator. The committee are only able to make recommendations in line with the marketing authorisation for adalimumab "…for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid-sparing, or in whom corticosteroid treatment is inappropriate."

Role*	Section	Comment [sic]	Response
Professor of Clinical Ophthalmology	4	4.2 The low risk of IOP rise with ozurdex with multiple injections is reported in several papers using multiple injections - eg The SAFODEX study and treatment with repeat dexamethasone implants etc Tomkins-Netzer et al Ophthalmology 2014 121 (8) 1649-54 which reports patients with uveitis. Only 7 out of 38 eyes had a rise in IOP with up to 7 implants and this was easy to treat medically. There is no evidence base to suggest that more than 3 implants should not be given for this reason and no cap on repeated use should be given. The cataract risk is similarily lower - 2 cataract progression in 38 eyes - than triamcinolone which is often used when these implants are not available. If a patient is doing well with these implants there should be no reason to limit their use as the published evidence suggest this is not an issue 4.21 see above for details on why the statements - an inadequate response to steroids is not appropriate and worsening vision with a risk of blindness and anterior chamber cell grade and vitreous haze grade	Thank you for your comment. Sections 4.2 and 4.18 of the FAD have been amended to highlight that there may be variation in the use of dexamethasone and in the number of implants used in practice. Healthcare professionals starting treatment with dexamethasone should refer to the summary of product characteristics for more details on the recommended dosing intervals for dexamethasone intravitreal implant.

'No comment' was received from Department of Health

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

National Institute for Health and Care Excellence

Multiple Technology Appraisal

Adalimumab and dexamethasone for treating non-infectious uveitis [ID763]

AbbVie's Response to the Appraisal Consultation Document

Dear Meindert,

AbbVie welcome the opportunity to comment on the Appraisal Consultation Document (ACD) for the ongoing Multiple Technology Appraisal of adalimumab and dexamethasone for treating non-infectious uveitis [ID763].

Please find our comments summarised below.

With kind regards,

[redacted]

[redacted] AbbVie UK Ltd.

EXECUTIVE SUMMARY

AbbVie welcome the proposed recommendations for adalimumab as an option for treating non-infectious uveitis in the posterior segment of the eye. NICE have recognised the need for an effective and well tolerated treatment in patients with active disease at the highest risk of vision loss in whom existing treatments are inadequate, either due to lack of efficacy or adverse events.

1. Do you consider that all of the relevant evidence has been taken into account?

Yes.

2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Yes

3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

The ACD indicates that adalimumab is recommended as a treatment option in the posterior segment of the eye in adults with inadequate response to corticosteroids, only if there is:

- Active disease, that is, current inflammation in the eye, **and**
- Macular oedema, **and**
- Inadequate response to immunosuppressants, **and**
- Systemic disease or both eyes are affected, **and**
- Worsening vision with a risk of blindness.

During the committee meeting, the clinical experts mentioned that "*patients with macular oedema have a high risk of blindness*" (ACD section 4.6, page 10) and that "*people with bilateral disease or systemic disease are likely to have a higher risk of blindness compared with people with unilateral or localised disease*" (ACD section 4.6, page 11).

Given that there is uncertainty around the risk of blindness in patients with severe disease, AbbVie understand why NICE have chosen to use macular oedema as a proxy for patients at high risk of blindness (ACD section 4.20, page 17). Indeed, UK data from Durrani suggests that over one-half of vision loss in patients with uveitis is due to macular oedema. Cystoid macular oedema (CMO) was the main cause of vision loss in 26.8% of patients; other causes include a combination of CMO and cataract in 20% and macular pathology [scaring, atrophy and hole] in 8%[1].

However, AbbVie wish to highlight their concerns about the criteria for recommending adalimumab. AbbVie agree with the Committee that macular oedema and worsening vision with a risk of blindness are closely linked, in that a decrease in visual acuity is commonly associated with macular oedema. However, other eye conditions can also be associated with a decrease in visual acuity with the potential to lead to low vision or blindness, such as cataract, glaucoma and vitreous debris. Data from Durrani suggests that other causes of vision loss in people with uveitis include cataract (18%), vitreous debris (11%), glaucoma (5%) and non-glaucomatous optic neuropathy (5%)[1].

As such, it may be more clinically plausible to rephrase the recommendation to the suggestion below which would also allow treatment access to patients with worsening vision with a risk of blindness but not necessarily with concurrent macular oedema.

- Active disease, that is, current inflammation to the eye, **and**
- Inadequate response to immunosuppresants, **and**
- Systemic disease or both eyes are affected, **and**
- Worsening vision with a risk of blindness, **or**
- Macular oedema

The literature suggests that around one-third to 40% of patients with active uveitis in the posterior segment of the eye have macular oedema[2-4]. This is likely to be higher in the patient population at highest risk of vision loss. Indeed, macular oedema, as measured by optical coherence tomography (OCT) was observed in 50% of patients in VISUAL I (tables 10.1.1.3.33.M and 14.2__10.1.1.3.34.M from VISUAL I Clinical study report)[5].

Table 1: Minor corrections in the ACD

Section of the report	Description of the issue	Suggested change and justification of the amendment
1.1, 1.2 and 4.20	*Adalimumab is recommended as an option for treating non-infectious uveitis in the posterior segment of the eye in adults with* ***inadequate*** *response to corticosteroids* ***inadequate*** *response to immunosuppressants* We believe that for clarity inadequacy should be qualified as 'lack of efficacy or inability to tolerate adverse events'	Adalimumab is recommended as an option for treating non-infectious uveitis in the posterior segment of the eye in adults with inadequate response to corticosteroids ***defined as lack of efficacy or inability to tolerate associated adverse events*** inadequate response, ***defined as lack of efficacy or inability to tolerate adverse events****,* to immunosuppressants
4.3	*The clinical and patient experts stated that treatment options are currently restricted and there was a significant unmet need for both adalimumab and dexamethasone intravitreal implant. The committee heard from the clinical and patient experts that adalimumab and dexamethasone allow corticosteroid sparing, which is important not just for their short-term quality of life but also to avoid glaucoma, diabetes, stroke, and heart attack. The committee recognised that patients and their carers would greatly value a new treatment which prevented or delayed sight loss, particularly if it reduced the significant adverse events associated with current treatments.* At the Committee Meeting, the patient experts specifically mentioned changes in mood and behaviour associated with steroid treatment; we suggest this and other adverse events are specifically included. We have used http://www.nhs.uk/Conditions/Corticosteroid-(drugs)/Pages/Introduction.aspx to inform our suggested copy	The clinical and patient experts stated that treatment options are currently restricted and there was a significant unmet need for both adalimumab and dexamethasone intravitreal implant. The committee heard from the clinical and patient experts that adalimumab and dexamethasone allow corticosteroid sparing, which is important not just for their short-term quality of life but also to avoid glaucoma, diabetes, stroke, and heart attack. The committee recognised that patients and their caregivers would greatly value a new treatment which prevented or delayed sight loss, particularly if it reduced the significant adverse events, ***which include changes in mood, mood swings, depression, weight gain, adrenal suppression and infection*** associated with current treatments.
4.4	*The VISUAL trials compared adalimumab plus background therapy (that is, immunosuppressants with or without steroids) with placebo plus background therapy* In VISUAL I patients had a high dose steroid burst (60 mg/day) which was then tapered to 0 at week 15. In VISUAL II patients took 10-35 g/day of steroid at baseline, which was tapered to 0 by week 19	The VISUAL trials compared adalimumab plus background therapy (***a steroid burst [60 mg/day in VISUAL I and 10-35 mg/day in VISUAL II] tapered to zero with or without one immunosuppressant***) with placebo plus background therapy

	The VISUAL studies allowed patients to take one immunosuppressant and about one-third of patients in VISUAL I took concomitant immunosuppressants (mostly methotrexate, cyclosporine and mycophenolate mofetil). In VISUAL II, about one-half of patients took concomitant immunosuppressants (mostly methotrexate, cyclosporine and mycophenolate mofetil)	
4.4	*The AG advised that an indirect comparison was not appropriate because patient characteristics in VISUAL I, VISUAL II and HURON differed and there was a lack of common comparators and outcomes.* AbbVie believe that adalimumab and dexamethasone intravitreal implant should not be compared since they are not generally used in the same patient population. As stated in section 4.2 *Adalimumab would generally be used in people with bilateral or systemic disease or both, whereas dexamethasone is used in people with unilateral disease*.	The AG advised that an indirect comparison was not appropriate because patient characteristics in VISUAL I, VISUAL II and HURON differed and there was a lack of common comparators and outcomes. ***Furthermore, comparison of adalimumab and dexamethasone intravitreal implant is not clinically relevant since the agents are not generally used in the same patient population***
4.5	*It heard that because maintenance treatment with immunosuppressants and corticosteroids may control inactive disease, the next line of therapy, such as adalimumab or dexamethasone intravitreal implant may not be needed.* AbbVie believes that this sentence may be imprecise since a proportion of patients with inactive disease are unable to continue on maintenance treatment with high dose corticosteroids and immunosuppressants due to the burden of adverse events. In the Committee meeting and in their written responses, the patient experts raised the issue of intolerable adverse events with both high dose corticosteroids and immunosuppressants. Patients with inactive disease who experience a flare on treatment without adalimumab are at increased risk of vision loss. In such cases adalimumab may be required to control inflammation and disease flare and reduce the risk of vision loss. A post-hoc analysis of the VISUAL studies revealed that VISUAL II patients receiving placebo who experienced 2 or more flares in the previous 12 months had a significantly higher risk of recurrent and persistent inflammation than those with ≤1 flare (HR of 1.95 for 2 flares versus ≤1 flare and HR of 4.23 for ≥3 flares versus ≤1 flare,	AbbVie require more clarification around the optimal treatment option for patients who are not able to tolerate the adverse events associated with maintenance treatment or they do experience disease flare.

	p<0.001)[6]. Recurrent and persistent inflammation is correlated with loss of vision and the ultimate aim of controlling a uveitis flare is to preserve visual acuity and visual function.	
4.6	*The committee noted that most patients in the VISUAL trials had bilateral or systemic non-infectious uveitis.* 90% of patients in VISUAL I had bilateral disease and 95% in VISUAL II, therefore we suggest most is edited to the majority (over 90%), as per 4.8	The committee noted that ***the majority (over 90%)*** of patients in the VISUAL trials had bilateral or systemic non-infectious uveitis.
4.19	*The committee also noted that people with inactive disease would be unlikely to have treatment with adalimumab in clinical practice, because its mechanism of action suggests limited benefit.* AbbVie believes that this sentence is inaccurate since adalimumab has been shown to demonstrate clinical benefit in the VISUAL II study[7].	The committee also noted that people with inactive disease would be unlikely to have treatment with adalimumab in clinical practice, ***since adalimumab is not cost effective in such patients.***
4.20	*Taking all of this into account, itrecommended* Insert space	*Taking all of this into account, it recommended*
4.20	*The committee also agreed that a stopping rule should be included, which reflected the strict criteria for defining treatment failure in the VISUAL I trial. Based on these criteria, it concluded that treatment should be stopped if there is evidence of 1 of the following:* *Stop adalimumab for non-infectious uveitis in the posterior segment of the eye in adults with inadequate response to corticosteroids if there is 1 of the following:* • *new active inflammatory chorioretinal or inflammatory retinal vascular lesions or both* • *anterior chamber cell grade of 0.5+ or less* • *vitreous haze grade of 0.5+ or less* • *worsening of best corrected visual acuity by 3 or more lines or 15 letters.*	AbbVie require more clarification around the stopping criteria in order to reflect clinical practice.
4.22	*1.1* ***Error! Reference source not found****. to 1.3*	To be corrected

Table 2: Minor corrections in the committee papers

Section of the report	Description of the issue	Suggested change and justification of the amendment
"Assessment Group response to consultation [AIC] and [redacted]" documents, page 2, Issue 7: Age at start, 4th line	It is stated that "*base case was reduced from £99,506 to £94,126*" The correct base case ICER for the active population and 42.7 average age at start is £95,506	Base case ICER for the active population to be corrected
"Assessment Group response to consultation [AIC] and [redacted]" documents, page 2, Issue 7: Age at start, 6th line	It is stated that "*the base case was reduced from £321,405 to £314,726*" when the average age of VISUAL II trial (i.e. 42.5) is used. However, when using the age of 42.5, the ICER for the inactive population reduces to £314,134.	Reduced base case ICER for the inactive population to be corrected

References

1. Durrani OM, Tehrani NN, Marr JE, Moradi P, Stavrou P, Murray PI. Degree, duration, and causes of visual loss in uveitis. *British Journal of Ophthalmology* 2004; **88**(9): 1159-62.

2. Karim R, Sykakis E, Lightman S, Fraser-Bell S. Interventions for the treatment of uveitic macular edema: a systematic review and meta-analysis. *Clinical ophthalmology (Auckland, NZ)* 2013; **7**: 1109-44.

3. Kempen JH, Altaweel MM, Holbrook JT, Jabs DA, Sugar EA. The multicenter uveitis steroid treatment trial: rationale, design, and baseline characteristics. *American journal of ophthalmology* 2010; **149**(4): 550-61.e10.

4. Rothova A, Suttorp-van Schulten MS, Frits Treffers W, Kijlstra A. Causes and frequency of blindness in patients with intraocular inflammatory disease. *The British journal of ophthalmology* 1996; **80**(4): 332-6.

5. AbbVie Limited. A Multicenter Study of the Efficacy and Safety of the Human Anti-TNF Monoclonal Antibody Adalimumab as Maintenance Therapy in Subjects Requiring High Dose Corticosteroids for Active Non-infectious Intermediate Uveitis, Posterior Uveitis, or Panuveitis – Including a Sub-study in Japanese Patients AbbVie Inc. (AbbVie) Clinical Study Report R&D/14/0730 Adalimumab/Protocol M10-877, 2015.

6. Merrill PT, Lim L, Song AP, et al. Predictors for Recurrent or Persistent Inflammation in Patients with Active and Inactive Non-Infectious Uveitis (presentation PO434). American Academy of Opthalmology; 2016; Chicago, IL

7. Nguyen QD, Merrill PT, Jaffe GJ, et al. Adalimumab for the prevention of uveitic flare in patients with inactive non-infectious uveitis requiring corticosteroids: a multicenter, double-masked, placebo-controlled phase 3, randomised controlled trial *Lancet* 2016; **Online first**.

Allergan comments on the appraisal consultation document for the NICE appraisal of dexamethasone intravitreal implant and adalimumab for the treatment of non-infectious uveitis [ID 763]

Submitted on: 31st March 2017

Allergan welcomes the recommendation of the dexamethasone intravitreal implant for use in patients with non-infectious posterior segment uveitis. Allergan's comments on the ACD are set out under the headings outlined in NICE's appraisal consultation document.

Has all of the relevant evidence been taken into account?

1. Restriction to patients with macular oedema and duration of treatment effect

Allergan welcomes the recommendation of the dexamethasone intravitreal implant as a treatment option for patients with non-infectious posterior segment uveitis who have macular oedema but considers that the clinical and cost effectiveness evidence also support its use in patients without macular oedema.

1.1 Duration of treatment effect for patients with macular oedema

In the post-authorisation long-term safety study (CONSTANCE), 22.3% of the eyes treated with dexamethasone intravitreal implants for non-infectious posterior segment uveitis did not have macular oedema (1). Within this study, eyes without macular oedema had a mean time to retreatment of 44 weeks compared with 35 weeks in eyes with macular oedema. The longer time to retreatment will decrease the ICER to a level that may be considered cost-effective even when a lower risk of blindness is included in the model. Using the committee's preferred utility for blindness (0.57) and increasing the duration of dexamethasone treatment effect from 30 weeks to 44 weeks decreases the deterministic ICER from £25,257 to £14,016 per QALY gained vs limited current practice (LCP). Following the committee's reasoning that the risk of blindness is lower in patients without macular oedema, changing the annual rate of blindness to 0 (i.e. no risk of blindness), results in an ICER of £30,898 per QALY gained vs LCP. In a scenario analysis using the 44 weeks treatment duration, the committee's preferred utility of 0.57 for blindness and the low background rate of blindness from Tomkins Netzer et al. results in an ICER of £19,658 per QALY gained. Allergan considers that there is likely to be a risk of blindness for patients without macular oedema, albeit smaller than for patients with macular oedema, and that the ICER is therefore likely to be within the range normally considered a cost-effective use of NHS resources.

Allergan considers that the prolonged time to retreatment in patients without macular oedema compared to those with, and the improvement in ICER that results from extended duration of treatment effect in the model, means that both the clinical and cost-effectiveness evidence supports use in all patients with active posterior segment uveitis, not just those patients with macular oedema. The clinical effectiveness of dexamethasone in patients without macular oedema is supported by the HURON study. Patients in the HURON study did not have macular oedema as entry criteria and the Central Macular Thickness in the DEX 700 group was modestly raised at 344 µm at entry.

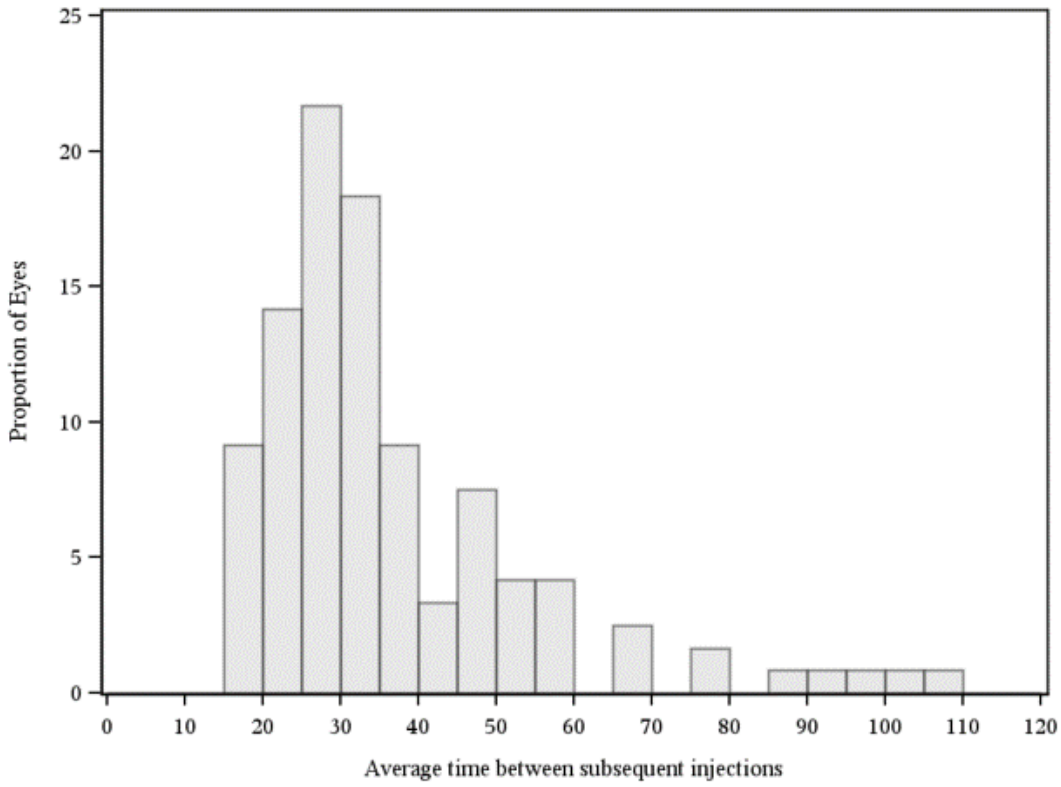
1.2 Duration of treatment effect for all patients

Section 4.17 of the ACD includes description of the assessment group opinion "that dexamethasone would only provide a treatment benefit for around 6 months". Allergan considers that the 30-week treatment effect assumption gives a higher ICER for the dexamethasone intravitreal implant than would be the case if a longer treatment effect were to be modelled. In the CONSTANCE study, the mean time between injections for all patients with non-infectious posterior segment uveitis who received at least two injections, excluding patients with remission after a single implant, was 36.77 weeks (SD 18.218 weeks; median [range] 31.14 weeks [15.14-106.29 weeks]). Analysis of the

distribution of average time between subsequent injections demonstrated that approximately 55% of eyes had a longer average time between subsequent injections than the modelled 30-week duration of effect, as shown in Figure 1. The modelled 30-week duration of effect is therefore likely to overestimate the ICER since increasing the duration of treatment in the assessment group model leads to improved ICERs for dexamethasone intravitreal implants vs LCP.

Allergan therefore considers that clarification should be made of the potential for substantially longer duration of treatment effect with dexamethasone intravitreal implants. These data on time to retreatment do not take account of patients who achieve long term control with a single implant. The assessment group model does not account for the benefits of any patients achieving long term control ("remission") on the dexamethasone intravitreal implant.

Figure 1: Distribution of average time between subsequent injections in eyes treated with at least two injections in the CONSTANCE study (all patients with non-infectious posterior segment uveitis)



2. Number of injections per eye

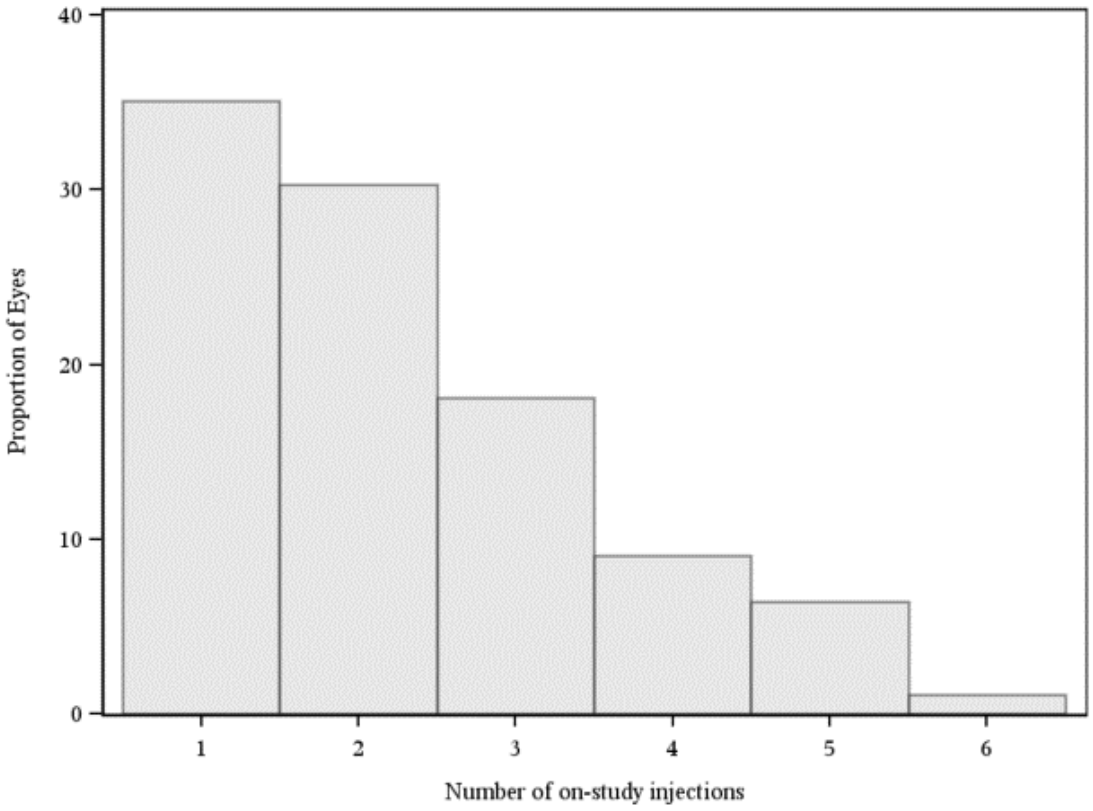
Section 4.17 of the ACD refers to the opinion of clinical experts that "a maximum of 3 implants would be used consecutively in clinical practice". Allergan acknowledges that the consideration for retreatment should be based on the ophthalmologist's opinion regarding whether the patient may benefit from retreatment without being exposed to significant risk. There are observational data to indicate that patients with non-infectious posterior segment uveitis receive more than 3 consecutive implants in the same eye. Among all patients receiving dexamethasone intravitreal implants for non-infectious posterior segment uveitis in the long-term safety study (CONSTANCE), the mean number of injections per study eye was 2.2 (standard deviation (SD) 1.26), with a median number of injections of 2.0 (range 1-6) (1). Analysing the distribution of number of injections per study eye in this cohort

demonstrates that 16.48% of eyes received more than 3 implants (Figure 2). Allergan considers that it is probable that a non-negligible proportion of patients may continue to benefit from treatment with dexamethasone intravitreal implants beyond a potential imposed limit of 3 implants.

This analysis also demonstrates that 35.11% of eyes received one implant, which will include a proportion of patients who enter remission, with appropriate and lasting control of their condition, after a single implant.

Allergan concludes that some patients may require more than 3 implants in the same eye and that it would be inappropriate to restrict access in clinical practice to a maximum number of implants per eye on cost grounds as the budget impact will be low.

Figure 2: Distribution of number of on-study injections per treated eye (all patients with non-infections posterior segment uveitis)



Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

1. Cost of blindness

Section 4.22 of the ACD states "the reduction (that is, improvement) in ICERs resulting from overestimated costs of blindness were likely to be at least partly offset by the low rate of background blindness in this high-risk group." Allergan considers that the term "partly offset" implies a comparable impact on the modelled ICER when in fact, changing the source for the background rate of blindness has a far greater impact than changing the cost of blindness. Allergan therefore considers that this should be rephrased to "the reduction (that is, improvement) in ICERs resulting from overestimated costs of blindness were likely to be offset by the low rate of background blindness in this high-risk group".

2. Wording regarding general usage of dexamethasone

Section 4.2 notes that the committee "heard from clinical experts that adalimumab would generally be used in people with bilateral or systemic disease or both, whereas dexamethasone is used in people with unilateral disease." Allergan considers that reference to dexamethasone should include the wording "generally be used" in the same way that this wording is applied to adalimumab. Therefore, Allergan proposes that this sentence should be revised to indicate that the committee "heard from clinical experts that adalimumab would generally be used in people with bilateral or systemic disease or both, whereas dexamethasone would generally be used in people with unilateral disease."

3. Spelling mistake

In section 4.21 of the ACD "macula oedema" should be amended to "macular oedema".

Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

As described above, Allergan considers that there is reasonable justification for extension of the recommendation for the dexamethasone intravitreal implant to include patients without macular oedema. Allergan also considers that the current wording of Section 4.17 of the ACD may limit use of dexamethasone intravitreal implant to three consecutive implants at a retreatment interval of 6 months, despite evidence of clinical effectiveness and cost-effectiveness beyond this number of implants. There is evidence that a substantial proportion of patients experience a much longer duration of effect, and there is likely to be a proportion of patients for whom adequate control of their condition is achieved with a single injection.

References

1. Allergan. Post-authorisation Safety Study (PASS) Observational Clinical Study Report CONSTANCE 206207-025 2016.

NICE Appraisal Consultation Document, adalimumab and dexamethasone for treating non-infectious uveitis: comments from Birdshot Uveitis Society

We welcome NICE's recommendations that adalimumab injection and dexamethasone intravitreal implants should be made available for treating non-infectious uveitis.

However, we have suggested some amendments to both the start criteria and the stop criteria for adalimumab to correct errors made in the proposed recommendations and to provide further clarity.

We have also suggested revisions to the recommendations for dexamethasone.

Adalimumab

<table>
<tr><td></td><td colspan="2">START CRITERIA</td></tr>
<tr><td></td><td colspan="2">Comment 1: start criteria should not be 'all of the following' but should be 'one of the following' because:

• macular oedema is only one of the causes of loss of vision due to inflammation in uveitis. Given that the rationale for these recommendations is visual impact, then worsening vision, from whatever cause, in uveitis which is active despite treatment with corticosteroids and immunosuppressants, should be sufficient indication to start treatment with adalimumab.

Thus

• the recommendations relating to 'macular oedema' and 'worsening vision with a risk of blindness' should be combined to read: 'worsening vision relating to the uveitis (eg, from macular oedema) with a risk of blindness.'

Comment 2: the appraisal is based on the ICER of who has the most to gain from treatment due to visual impact, and not on considering those in whom treatment will be the most effective. This raises two inequality issues:

• there may be some patients with unilateral non-infectious uveitis who need to have access to systemic therapies, especially those in whom local therapies, such as dexamethasone implants, are contraindicated (eg, those who have had previous steroid-induced raised intraocular pressure);

• there will also be some patients with unilateral non-infectious uveitis who already have reduced vision in their other eye for whatever reason (eg, amblyopia, previous injury or unrelated eye disease) and who require systemic treatment to preserve vision in their uveitic eye.</td></tr>
<tr><td></td><td>Current wording</td><td>Suggested amended wording</td></tr>
<tr><td></td><td>Adalimumab is recommended as an option for treating non-infectious uveitis in the posterior segment of the eye in adults with inadequate response to corticosteroids, only if there is:</td><td>Adalimumab is recommended as an option for treating non-infectious uveitis in the posterior segment of the eye in adults with inadequate response to corticosteroids if there is one of the following:</td></tr>
</table>

	• macular oedema active disease, that is, current inflammation in the eye • inadequate response to immunosuppressants • systemic disease or both eyes are affected and • worsening vision with a risk of blindness.	• active disease, that is, current inflammation in the eye • inadequate response to immunosuppressants • systemic disease or both eyes are affected * • worsening vision relating to the uveitis (eg, from macular oedema) with a risk of blindness * active disease involving only one eye may be treated where this eye is the better seeing eye and local therapies are contraindicated or ineffective.

STOP CRITERIA

Comment 1: the stop criteria in the appraisal consultation document are ambiguous and do not harmonise either with the VISUAL studies or the criteria set out in the Interim Clinical Commissioning Policy Statement: Adalimumab for Severe Refractory Uveitis https://www.england.nhs.uk/wp-content/uploads/2017/03/clin-com-pol-statment-170010ps.pdf.

The stop criteria should read:

- Failure to reduce to 0.5+ or less for anterior chamber cells
- Failure to reduce to 0.5+ or less for vitreous haze.

Comment 2: anterior chamber activity alone should not be used as a reason for switching systemic medication for posterior uveitis. A flare which shows anterior chamber activity has little implication for vision. It can be safely treated with drops.

Current wording	**Suggested amended wording**
Stop adalimumab for non-infectious uveitis in the posterior segment of the eye in adults with inadequate response to corticosteroids if there is 1 of the following:	Stop adalimumab for non-infectious uveitis in the posterior segment of the eye in adults with inadequate response to corticosteroids if there is one of the following:
• new active inflammatory chorioretinal or inflammatory retinal vascular lesions or both	• new active inflammatory chorioretinal or inflammatory retinal vascular lesions or both
• anterior chamber cell grade of 0.5+ or less	
• vitreous haze grade of 0.5+ or less	• failure to reduce to (or maintain) vitreous haze grade of 0.5+ or less
• worsening of best corrected visual acuity by 3 or more lines or 15 letters	• worsening of best corrected visual acuity by 3 or more lines or 15 letters.

Alternatively, see the NHS England interim policy https://www.england.nhs.uk/wp-content/uploads/2017/03/clin-com-pol-statment-170010ps.pdf :

'Adults who respond to treatment with adalimumab will continue treatment for 18 months at which time a trial of treatment withdrawal will be undertaken. If relapse occurs, restarting adalimumab will be considered using the start criteria stated in this policy. Response to treatment with adalimumab is defined as achieving one or more of the following criteria:

• Reduction in daily oral prednisolone dose by 5mg, or to ≤10mg

• Reduction in conventional second-line immunosuppressive treatment

• For eyes with impaired visual acuity, an improvement in visual acuity by ≥5 LogMAR letters (0.1 log units)

	• For eyes with reduced visual field, an improvement in visual field based on an assessment using Humphrey, Goldmann or Octopus perimetry • For eyes with increased central macular thickness, a ≥10% reduction in central macular thickness.' **Stop criteria would then be:** 'Adalimumab for the treatment of uveitis is stopped using following criteria: 1. Failure to achieve the response criteria defined above after 3 months of treatment 2. Adverse reaction to adalimumab.'

Dexamethasone

We believe that the recommendations unfairly discriminate against patients with uveitis refractory to other treatments (or for whom other treatments are contraindicated) and who do not have macular oedema, but whose vision is worsening due to active inflammation.

Dexamethasone implant - suggested amended wording:	
	Dexamethasone intravitreal implant is recommended as an option for treating non-infectious uveitis in the posterior segment of the eye in adults, only if there is: • active disease, that is, current inflammation in the eye and • worsening vision relating to the uveitis (eg, from macular oedema) with a risk of blindness.

Comments and observations on appraisal committee discussions:		
4.2 4.6 4.21	4.2 '…whereas dexamethasone is used in people with unilateral disease.' 4.6 '…current clinical practice preferred dexamethasone for unilateral disease.' 4.21 '…people who have dexamethasone in current clinical practice are likely to have disease affecting only one eye…'	The statement at 4.2 is an incorrect extrapolation of those at 4.6 and 4.21. For patients with uveitis affecting only one eye, a clinical choice, ie, a treatment option, would be to treat only the affected eye with a dexamethasone intravitreal implant rather than treating the whole person with systemic steroids. Both eyes may be affected by the disease, but one eye may be more badly affected than the other and require an implant.
4.3	'…adalimumab and dexamethasone allow corticosteroid sparing…	This should read …'adalimumab and dexamethasone allow <u>systemic</u> corticosteroid sparing…'
4.17	'…a maximum of 3 implants would be used consecutively in clinical practice.'	We disagree that a maximum of 3 implants would be used consecutively in clinical practice. This was a clinician's personal view given at the first appraisal committee meeting. Clinical experience on repeat administration of dexamethasone implants in uveitis will accrue over time. See Statement of Product Characteristics for Ozurdex https://www.medicines.org.uk/emc/print-document?documentid=23422
5.	<u>Implementation</u>	Treatment recommendations for the use of adalimumab and dexamethasone intravitreal implant in non-infectious uveitis for patients in Scotland and Northern Ireland should be noted here.

Comments on Committee Papers ID763 uveitis ACD_cmtepapers_Mar 17.pdf:	
Page 33	'The AG assumed that the treatments were only effective whilst they were being given. Therefore, patients who are no longer being treated with adalimumab, and patients who received the dexamethasone implant more than 6 months ago, will accrue no additional health gains'. We disagree with this statement. The goal of treatment for non-infectious uveitis is attaining a state of clinical remission and maintaining it after stopping treatment. For patients achieving this goal, the continuing 'additional health gains' are considerable.

Appraisal Consultation Document. ID 763 Uveitis.

Comments by **Olivia's Vision.**

We thank the committee for its decision to recommend both technologies and we look forward to the publication of clinical guidelines which will allow uveitis specialists to increase the number of therapies available to their sight threatened patients.

We thank you for the opportunity to comment on your draft recommendations.

Recommendations.

1.1 Adalimumab

Bullets 1 and 3 are problematic for us. We are concerned that the recommendation does not adequately reflect the clinical need for adalimumab as a treatment option. This seems to arise from comments found in 4.5 and 4.19:

'The committee also noted that people with inactive disease would be unlikely to have treatment with adalimumab in clinical practice, because its mechanism of action suggests limited benefit. Therefore, it concluded that adalimumab could not be recommended for treating inactive non-infectious uveitis.'

This does not recognise that the disease may be inactive because it is controlled by an immunosuppressant, the side effects of which are not tolerated by the patient. We would like bullet 3 altered to read:

'inadequate response to, or intolerance of, an immunosuppressant(s).'

Bullet 4 also concerns us. In the Summary of Appraisal Committee's Key Conclusions, page 22, the following comment appears:

'The committee heard from clinical experts that adalimumab would **generally** be used in people with bilateral or systemic disease, whereas dexamethasone is used in people with unilateral disease.'

The word, 'generally' is important here and we would like bullet 4 to include unilateral uveitis without systemic disease. A severity of disease and threat to vision, in such cases, will have been established through the initiation of second line therapy with immunosuppressants. When this fails to control inflammation, or is not tolerated, therapy with dexamethasone may be contraindicated through the associated risk of additional ocular morbidity.

It is not clear whether all these criteria should be met for adalimumab to be prescribed. We feel meeting two of the criteria is sufficiently indicative of a need for biologic therapy.

1.2

We appreciate that strict criteria to determine treatment failure are required in clinical trials and the ideal outcome is drug induced remission. However, clinical practice is different with a long-term goal of preserving as much vision as possible for as long as possible. While bullets 1 and 4 strongly suggest treatment failure, bullets 2 and 3 may not be so indicative of this, especially at the lower end of the

grades specified. Low grade anterior cells are managed, often easily and successfully, with topical steroid and vitreous haze, at lower grades, depending on location, may have minimal impact on vision. Furthermore, the vitreous contains no structure critical to vision which may be damaged by inflammation.

We note that on page 12 of the Pre-meeting briefing, Adalimumab and dexamethasone for treating non-infectious uveitis, clinical experts stated:

(The) Most important outcome measure and the most important sight threatening complication of non-infectious posterior uveitis is cystoid macular oedema,

but the

'main outcome in clinical trials is vitreous haze and a 2-step improvement may be considered clinically significant.'

We further note that neither of these measurements are included in the criteria which describe treatment failure in the NHS Interim Policy, 2017. We would prefer that they are removed from the 'Stop' criteria.

1.3 Dexamethasone

We are not clear whether the wording of this recommendation means people must have both active disease and macular oedema.

If this isn't the case, the use of 'and/or' would provide clarity.

If both active disease and macular oedema must be present, there are some groups of patients who would benefit from the therapy but be denied it. These include patients for whom systemic therapy is contraindicated such as pregnant women or those who have received, or are being treated for cancer.

Some of these patients may have bi-lateral disease and also require more than the three consecutive implants the clinical experts stated were likely to be employed in clinical practice. (4.17, page 16).

The Royal College of Ophthalmologists' (RCOphth) response to NICE's Multiple Technology Appraisal (MTA)Adalimumab and dexamethasone for treating non-infectious uveitis [ID763] Appraisal Consultation Document

1. Introduction

1.1 The Royal College of Ophthalmologists welcomes the opportunity to respond to this consultation.

1.2 The Royal College of Ophthalmologists is the professional body for ophthalmologists and we champion excellence in the practice of ophthalmology on behalf of our members to optimise care for patients. We set the curriculum and examinations for trainee ophthalmologists, provide training in eye surgery, maintain standards in the practice of ophthalmology, and promote research and advance science in the specialty.

1.3 We work with leaders across the eye health sector to help shape eye services for the benefit of patients.

2. START/INCLUSION CRITERIA

2.1 It is not clear whether inclusion requires all the listed criteria to be met. This needs to be elucidated. There are several points where points:

a) Macular oedema should not be an essential criterion. We understand and support the NICE MTA in its aim to direct and limit Adalimumab to those at most risk of visual loss, however this is already highlighted in the criterion 'worsening vision relating to uveitis with a risk of blindness'. The presence of macular oedema is only one of reversible inflammation-induced vision loss the causes of loss of vision due to inflammation in uveitis, but it is not the only cause of and there is no data from any of the trials to suggest that patients who are losing vision due to active inflammation without macular oedema would be any less likely to benefit. We would suggest that the sentence pertaining to macular oedema be removed.

b) There may be the rare cases where adalimumab would be considered in unilateral disease (assuming all other criteria have been fulfilled). This could occur in the situation where a patient is contraindicated from local therapy (e.g. due to known steroid-induced ocular hypertension/glaucoma), had failed local therapy or had already lost the other eye to other disease. The cost effectiveness argument would be equally valid in a patient with unilateral disease in their better seeing/only eye as in the patient with bilateral disease. NICE may wish to provide some provision for this within their recommendations such as a footnote to the effect that "*active disease involving only one eye may be treated where this is the better seeing eye

and/or local therapies and or systemic therapies are contraindicated or have been ineffective"

3. STOPPING CRITERIA

3.1 The stopping criteria state that they are based on the VISUAL trials. This was based on detecting 'Treatment Failure' as a trial endpoint and is not the same as 'Treatment Failure' in clinical practice. A systemic treatment would rarely be discontinued at the first sign of breakthrough inflammation as is suggested by the application of the VISUAL criteria. For example if a patient had been having flares of inflammation every month on their previous treatment regimen, and then had complete remission for six months on adalimumab, it would seem wrong to withdraw adalimumab due to a minor flare of disease affecting one domain (e.g. 1+ Anterior Chamber cells) which could be adequately controlled with either topical or local therapy PROVIDED that the adalimumab was continued. It is however appropriate that adalimumab should indeed be stopped where it is clear that it is not being effective.

3.2 Considering all available evidence reviewed by NICE, and current delivery of care we would recommend that the NICE recommendations should align with those of the continuation and stopping criteria of the NHSE Interim policy, namely:

> *"Adults who respond to treatment with adalimumab will continue treatment for 18 months at which time a trial of treatment withdrawal will be undertaken. If relapse occurs, restarting adalimumab will be considered using the start criteria stated in this policy. Response to treatment with adalimumab is defined as achieving one or more of the following criteria:*
>
> - *Reduction in daily oral prednisolone dose by 5mg, or to ≤10mg*
> - *Reduction in conventional second-line immunosuppressive treatment*
> - *for eyes with impaired visual acuity, an improvement in visual acuity by ≥5 Log MAR letters (0.1 log units)*
> - *For eyes with reduced visual field, an improvement in visual field based on an assessment using Humphrey, Goldmann or Octopus perimetry*
> - *For eyes with increased central macular thickness, a ≥10% reduction in central macular thickness*
>
> *Stop Criteria*
> *Adalimumab for the treatment of uveitis is stopped using following criteria:*
> *1. Failure to achieve the response criteria defined above after 3 months of treatment*
> *2. Adverse reaction to adalimumab"*

3.3 Furthermore the stopping criteria provided by NICE are mis-quoted (or mis-adapted) from the VISUAL trials. Where it states 'AC cells of 0.5+ or less' and 'vitreous haze grade of

0.5+ or less' it should read 'failure to reduce to AC cells/vitreous haze grade of 0.5+ or less'. This issue would be superseded if our recommendation in point 2a were followed.

3.4 Additional thoughts about the macular oedema for ozurdex - again as per previous discussion around adalimumab you might suggest that this is an unfair discrimination against patients with uveitis refractory to other treatments who do not happen to have macular oedema but are getting worsening vision due to active inflammation which would respond to ozurdex therefore you recommend that the criteria are as follows (which also harmonises with those for adalimumab)

3.5 In line with our discussion in 1a, it is not clear whether all criteria on the inclusion criteria for dexamethasone implant are meant to be essential. If they are, then we disagree with the inclusion of macular oedema as an essential criterion. In line with our comments above we would recommend that this be amended to:

> *Dexamethasone intravitreal implant is recommended as an option for treating non-infectious uveitis in the posterior segment of the eye in adults, only if there is:*
> - *active disease, that is, current inflammation in the eye and*
>
> - *worsening vision with a risk of blindness (e.g. from macular oedema)*

3.6 Although in many patients the option of Adalimumab as 1st choice may be correct there may be circumstance where bilateral Ozurdex for patients with bilateral uveitis is a preferred treatment particularly where there is no systemic disease or there has been no response or an adverse affect to Adalimumab or other systemic therapies.

3.7 We do not agree that there should be a limit on how long Ozurdex can be used for. The guidance should say not more than 3 injections in 12 months. We believe it should be re-usable for as long as necessary, as long as the patient benefits, and there are no adverse events. There is concern about using Ozurdex for bilateral uveitis however we do not share these concerns. There are valid indications for bilateral treatment. There is concern about using more than three implants in one eye consecutively. However, members have reported experience with patients who have had no cumulative harm from repeated implants, many more than three, for multiple indications including uveitis.

4 April 2017

RNIB Supporting people with sight loss

Appraisal consultation document response: adalimumab and dexamethasone for treating non-infectious uveitis

RNIB welcomes the committee's recommendation that adalimumab and dexamethasone become treatment options for non-infectious uveitis.

However we believe that the eligibility criteria outlined in the recommendations are restrictive, denying patients at risk of sight loss effective and appropriate treatment options.

Adalimumab

Recommendations: 1.1 outlines five start criteria for treatment with adalimumab.

i) We do not agree that macular oedema should be listed as stand-alone start criteria. Macular oedema is not present in all patients who have worsening vision with the risk of blindness. Patients without macular oedema but with worsening vision and at risk of blindness should be able to access the treatment option of adalimumab.

   RNIB recommends that macular oedema is removed from the start criteria or alternatively be listed as an 'or' alongside worsening vision with risk of blindness.

ii) We do not agree that start criteria should be limited to a bilateral indication. This restriction rules out any patient with non-infectious uveitis in one eye who has already lost vision to a greater extent in the other eye as a result of any sight loss condition or event. Excluding patients with a unilateral indication in these circumstances could result in the loss of remaining useful vision. This would have a huge impact on quality of life for the individual as highlighted in our original submission. While this would only represent a small number of patients it is a significant exclusion.

Royal National Institute of Blind People

Patron: Her Majesty The Queen • President: Dame Gail Ronson DBE • Chair: Kevin Carey • Acting Chief Executive: Sally Harvey • Principal address: 105 Judd Street, London WC1H 9NE • Registered charity number: 226227 (England and Wales) and SC039316 (Scotland) • Incorporated by Royal Charter Registered in England no. RC000500

This limitation would also rule out anyone with unilateral disease for whom local therapies are not appropriate due to increased IOP.

Additionally, the current criteria means that a patient with a severe unilateral indication and no access to adalimumab could be at risk of losing sight in one eye. This would likely have a significant impact on the patient's life, for example the ability to drive or carry out certain types of employment. While this would only represent a small number of patients it is a significant exclusion.

RNIB recommends that patients with unilateral disease who have poorer vision in their other eye be considered in the start criteria to preserve remaining sight.

RNIB recommends that patients with unilateral disease and a contraindication such as IOP be considered in the start criteria to preserve bilateral vision.

RNIB recommends that patients with unilateral disease who have worsening vision with the risk of blindness in that eye be considered in the start criteria to preserve bilateral vision.

iii) Recommendation 1.2 outlines the stop criteria for treatment with adalimumab.

We do not agree that a single flare of inflammation is justification for withdrawing treatment of adalimumab. This would deny a viable treatment option to patients who had achieved greater stability in terms of their condition through treatment with adalimumab.

RNIB recommends consideration of the stopping criteria outlined in the NHS England interim policy: https://www.england.nhs.uk/wp-content/uploads/2017/03/clin-com-pol-statment-170010ps.pdf

Dexamethasone

We note that in section 4.2, dexamethasone is recommended for unilateral use only. However it would be possible to treat bilateral non-infectious uveitis with dexamethasone. As a localised therapy this would circumvent the impact of systemic steroids on the patient's quality of life. The ACD recognises the impact of systemic steroids and the benefits of sparing for the patient in section 4.3.

RNIB requests that bilateral use of dexamethasone is considered to lessen the impact of treatment on the patient's quality of life.

NHS England Response to NICE ACD – Uveitis (non-infectious) - adalimumab and dexamethasone [763]

Please find NHS England's response to the ACD – Uveitis (non-infectious) - adalimumab and dexamethasone [763] which has been reviewed by the Specialised Ear and Ophthalmology CRG

Has all of the relevant evidence been taken into account?
Yes – the key RCTs in this area have been identified (the two VISUAL studies and the HURON study); there is much more limited evidence to support the cost effectiveness assessments, but the best available evidence has been considered.
Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
Yes. The clinical evidence is reasonably well defined now post the VISUAL and HURON studies. The cost effectiveness evidence is limited and therefore the estimates are necessarily imprecise, however we would agree with the baseline estimates used.
Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
The recommendations are largely sound but there is one significant error (which may be typographical – see 1.2B below) and there are a number of places where the recommendations (1.1-3) would benefit from clarification. Specifically: **1.1 START/INCLUSION CRITERIA** It is not clear whether inclusion requires all the listed criteria to be met, but our assumption is that this is what is expected (given the discussion of cost effectiveness and the aim to direct to those patients where there is most to gain). This should be clarified, but also we disagree with two points: 1.1A) Macular oedema should not be an essential criterion. We support the NICE MTA in its aim to direct and limit Adalimumab to those at most risk of visual loss, however this is already captured in the criterion 'worsening vision relating to uveitis with a risk of blindness'. The presence of macular oedema is indeed one of the causes of loss of vision due to inflammation in uveitis, but it is not the only cause of reversible inflammation-induced sight-loss and there is no data from any of the trials to suggest that patients who are losing vision due to active inflammation without macular oedema would be any less likely to benefit. We would suggest that the line relating to macular oedema is removed. 1.1B) There may be rare cases where adalimumab would be considered in unilateral disease (assuming all other criteria have been met). This would occur in the unusual situation where a patient is contraindicated from local therapy (e.g. due to known steroid-induced ocular hypertension/glaucoma), had failed local therapy or had already lost the other eye to other disease. The cost effectiveness argument would be equally valid in a patient with unilateral disease in their better seeing/only eye as in the patient with bilateral disease. NICE may wish to provide some provision for this within their recommendations such as a footnote to the effect that "*active disease

involving only one eye may be treated where this is the better seeing eye and/or local therapies are contraindicated or ineffective”

1.2 STOPPING CRITERIA

1.2A) The stopping criteria state that they are based on the VISUAL trials. This was based on detecting ‘Treatment Failure’ as a trial endpoint and is not the same as ‘Treatment Failure’ in clinical practice. We would almost never stop treatment with a systemic agent at the first sign of breakthrough inflammation as is suggested by the application of the VISUAL criteria. For example if a patient had been having flares of inflammation every month on their previous treatment regimen, and then had complete remission for six months after stopping adalimumab, it would seem wrong to withdraw adalimumab due to a minor flare of disease affecting one domain (eg 1+ Anterior Chamber cells) which could be adequately controlled with either topical or local therapy PROVIDED that the adalimumab was continued. It is however appropriate that adalimumab should indeed be stopped where it is clear that it is not being effective,

Considering all available evidence reviewed by NICE, and current delivery of care we would recommend that the NICE recommendations should align with those of the continuation and stopping criteria of the NHS England Interim policy, namely:

"Adults who respond to treatment with adalimumab will continue treatment for 18 months at which time a trial of treatment withdrawal will be undertaken. If relapse occurs, restarting adalimumab will be considered using the start criteria stated in this policy. Response to treatment with adalimumab is defined as achieving one or more of the following criteria:

- *Reduction in daily oral prednisolone dose by 5mg, or to ≤10mg*
- *Reduction in conventional second-line immunosuppressive treatment*
- *For eyes with impaired visual acuity, an improvement in visual acuity by ≥5 LogMAR letters (0.1 log units)*
- *For eyes with reduced visual field, an improvement in visual field based on an assessment using Humphrey, Goldmann or Octopus perimetry*
- *For eyes with increased central macular thickness, a ≥10% reduction in central macular thickness*

Stop Criteria
Adalimumab for the treatment of uveitis is stopped using following criteria:
1. Failure to achieve the response criteria defined above after 3 months of treatment
2. Adverse reaction to adalimumab "

1.2B) Furthermore the stopping criteria provided by NICE are mis-quoted (or mis-adapted) from the VISUAL trials. Where it states ‘AC cells of 0.5+ or less’ and ‘vitreous haze grade of 0.5+ or less’ it should read ‘failure to reduce to AC cells/vitreous haze grade of 0.5+ or less’ . This issue would be superseded if our recommendation in point 1.2A is followed.

Any other comments

Whilst NHS England is not the responsible commissioner for ozurdex (which falls to CCGs), we have included comments based on how the use of ozurdex aligns with the indications in the NHS England interim policy. As per previous discussion around adalimumab you might suggest that this is an unfair discrimination against patients with uveitis refractory to other treatments who do not happen to have macular oedema but are getting worsening vision due to active inflammation which would respond to ozurdex therefore you recommend that the crtiera are as follows (which also harmonises with those for adalimumab) 1.3 In line with our discussion in 1.1, it is not clear whether all criteria on the inclusion criteria for dexamethasone implant are meant to be essential. If they are, then we disagree with the inclusion of macular oedema as an essential criterion. In line with our comments above we would recommend that this is amended to: *Dexamethasone intravitreal implant is recommended as an option for treating non-infectious uveitis in the posterior segment of the eye in adults, only if there is:* *active disease, that is, current inflammation in the eye and* *worsening vision with a risk of blindness (e.g. from macular oedema)* Given the lack of current evidence NICE may wish to consider a requirement to collect such data as part of its recommendations. This is a requirement of the NHS England interim commissioning policy

Contact details

Title (e.g. Dr, Mr, Ms, Prof)	[redacted]
Name	[redacted]
Job title or role	[redacted]
Email address	[redacted]

Healthcare Improvement Scotland

NICE HEALTH TECHNOLOGY APPRAISAL COMMENT ON ACD FOR Uveitis (posterior segment, non-infectious) - dexamethasone and adalimumab	
TO: NICE	FROM: Healthcare Improvement Scotland 03 April 2017

Comment provided to HIS by [redacted], Consultant Opthalmic Physician, [redacted]

Question	Response
Has all the relevant evidence been taken into account?	Yes. As far as I am aware all RCTs have been included. There are many case series and advisory papers in the literature that have been beneficial in guiding current clinical practice but these are the only RCTs.
Has the analysis of clinical and cost effectiveness used an appropriate comparator which reflects Scottish practice?	Yes and no. I believe the analysis to be appropriate for the information available. However although it may be useful, at a specific time point, to differentiate between unilateral and bilateral disease from an economic point of view, it is often not possible to differentiate who will in future develop second eye involvement. To make a decision not to treat a patient with unilateral disease and potentially result in irreversible vision loss, may make health economic sense at the time. This decision makes assumptions that patients need only one eye to function and if the other eye were involved then it would be possible to get disease control with treatment. This is not always possible and inflammatory eye disease is often asymmetrical in its disease process and the response to treatment. I would have concerns for rationing treatment with adalimumab to those with bilateral disease at this time point, as this could have significant long term implications for individuals and does not reflection current NHS Scotland practice.
Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?	I would agree with the committee's conclusion that fewer young blind individuals enter residential care than their older comparators. However blindness is generally for life. It is therefore likely that although the majority blind or visually impaired due to sight

	threatening uveitis will be younger and not require residential care at point of registration, as they age they are likely to require residential care at an earlier stage than those without visual impairment. I would therefore suggest that the model may be an underestimate. I am not a health economist however and would not begin to suggest I understand the modelling but would be grateful for clarification.
Are the provisional recommendations of the Appraisal Committee reasonable?	I appreciate from the data presented that in inactive disease there is insufficient QALY to warrant the use of adalimumab. However it is not always as straight forward in clinical practice to define inactive disease. Does this term mean inactive disease off treatment or inactive disease off prednisolone? With sight-threatening uveitis, hopefully once disease control has been achieved, the intention is to taper therapy dependent on disease activity. Often patients are on a combination of systemic steroids and two systemic immunosuppressive agents at the time of commencing adalimumab. The primary aim of biologic therapy in these patients can be to get the prednisolone to as low a level as possible. Patients have often already been on a moderately high dose of prednisolone for a minimum of 6 months by this stage but often longer. They will possibly have osteoporosis, be cushingoid, iatrogenic adrenal suppression, weight gain, hypertension and diabetes. These are just a few of the side effects our patients experience on their journey toward adalimumab. During this time they will have had visual difficulties that create problems undertaking daily activities including driving and working. They also require regular hospital clinic attendance, which, in this often young patient group, require taking more time off work. However as the document reads at present the only patients with sight-threatening uveitis who would qualify for treatment with adalimumab would be those with worsening vision with a risk of blindness due to bilateral active intraocular inflammation in the presence of macular oedema, not responding to immunosuppression, with an underlying systemic disease that is, current inflammation in the eye macular oedema inadequate response to

	immunosuppressants systemic disease or both eyes are affected and worsening vision with a risk of blindness. 1.2 'Stop adalimumab for non-infectious uveitis in the posterior segment of the eye in adults with inadequate response to corticosteroids if there is 1 of the following': • new active inflammatory chorioretinal or inflammatory retinal vascular lesions or both • anterior chamber cell grade of 0.5+ or less • vitreous haze grade of 0.5+ or less • worsening of best corrected visual acuity by 3 or more lines or 15 letters. By these criteria any patient with active chorioretinal or retinal lesions should have treatment stopped, however these lesions are not mentioned in treatment commencement guidelines. Also when you have control of the anterior chamber or vitreous activity you are obliged to stop the treatment. Although the data does not support the commencement of adalimumab in patients with inactive disease, what this recommendation is actually referring to is maintenance therapy once disease control has been achieved. I believe this approach will greatly increase burden for the patient and the service. In other areas where adalimumab is used, for example rheumatoid arthritis, this is not an approach that has been found to provide clinical efficiency and cost effectiveness. Although I am not aware that this data exists at present for the management of patients with uveitis I would suspect a similar outcome would arise for those requiring anti-TNF therapy. Although the letter loss was defined by the trials, I feel that a loss of 3 lines or 15 letters is too long to wait and I would be looking to stop and change therapy before this stage. Patients would struggle to continue normal activities if they had lost this level of vision before a decision to change treatment had been made.

	I am not sure why worsening macular oedema has not been included in the stopping criteria when it was included as a major commencement criteria. With the recommendations as they are currently any patient without macula oedema despite sight-threatening uveitis (eg occlusive retinal vasculitis, severe vitritis) would not qualify for either adalimumab or dexamethasone. *Recommended dose and schedules* *'Repeat doses should be considered when a patient experiences a response to treatment followed subsequently by a loss in visual acuity and in the physician's opinion may benefit from retreatment without being exposed to significant risk'.* Visual acuity is not one of the indications for commencing treatment and am therefore unsure why is it in the retreatment criteria. *4.2 The committee heard from the clinical experts that there are 3 main indications in clinical practice for treating non-infectious uveitis: vitreous haze, macular oedema and worsening vision.* The treatment guideline only allows for macular oedema and there is no mention of vitreous haze or worsening vision. Worsening vision is only mentioned as an indication to stop treatment but not for commencement. 4.20 *The committee noted that disease was likely to be more severe in people with bilateral disease later in the treatment pathway. It agreed that the treatment would be more cost effective in those at higher risk of permanent legal blindness, and bilateral disease with macular oedema was a useful proxy for this.*

	I appreciate the need for a proxy in analysis but within clinical practice there are other clinical signs that we currently use in decision making. Other sight-threatening signs include symptomatic vitritis and occlusive retinal vasculitis. These patients also require disease control, which if not achieved on 'conventional therapy' then adalimumab would be on next choice in NHS Scotland. Patients with occlusive vasculitis may actually require more rapid aggressive management than those with macular oedema. I believe in NHS England anti-TNF therapy is already accessible for patients with occlusive retinal vasculitis secondary to Bechets but under these guidelines would not be available for those with occlusive retinal vasculitis of another cause. Surely this is discrimination with one rule for one group and another for another.
Are the patient pathways and treatment options described in the NICE assessment applicable to NHS Scotland?	*The committee also heard from the clinical experts and the assessment group (AG) that there is no nationally agreed pathway for treating non-infectious uveitis.* This is not case in NHS Scotland, where the Scottish Uveitis National Managed Clinical Network treatment guidelines are followed. *It heard from clinical experts that adalimumab would generally be used in people with bilateral or systemic disease or both, whereas dexamethasone is used in people with unilateral disease. The committee concluded that the general treatment pathway reflected current practice.* This does not reflect current practice within NHS Scotland. Although dexamethasone is used for unilateral disease, it is also sometimes used for bilateral disease when felt clinically appropriate. It is generally used in patients that don't tolerate, wish to avoid, or are uncontrolled on systemic steroids. It

	is not used as an alternative to adalimumab. At present adalimumab is used in patients requiring ongoing prednisolone therapy for disease control despite the use of two immunosuppressive agents. *4.3 The clinical and patient experts stated that treatment options are currently restricted and there was a significant unmet need for both adalimumab and dexamethasone intravitreal implant.* Thankfully this is not currently the case with NHS Scotland where patients and clinicians already have access to these therapies if there is felt to be a clinical need, as per the Scottish Uveitis National Managed Clinical Network Treatment Guidelines. 4.17 *It heard that for this reason, a maximum of 3 implants would be used consecutively in clinical practice.* This does not reflect clinical practice in NHS Scotland, where patients felt appropriate for dexamethasone implant and have received benefit from it would not have treatment stopped after the third implant. Following informed discussion with the patient further implants may be given. To stop a treatment that has proven effective does not make sense. Most patients with sight-threatening uveitis will develop cataract at some stage anyway. If glaucoma does occur and is not manageable with medical therapy then further dexamethasone would not be given.
Is the provisional guidance as valid in Scotland as it is in England and Wales?	**Please see below**

Please add any other information which you think would be useful to the Appraisal Committee, or helpful to us in guiding the Scottish response to this assessment.	Unlike NHS England, within NHS Scotland there are nationally agreed pathways for treating patients with sight-threatening uveitis. Although these may not be evidence based, as the evidence doesn't exist, they allow a directed approach of best practice for patients within a national network. Wherever patients are now treated within Scotland they will receive a similar standard of care which reflects national consensus. The approach within NHS Scotland differs from the recommendation in that we do not restrict adalimumab to patients with bilateral disease but where deemed appropriate treat individuals with unilateral disease.

Srilakshmi Sharma
Comments on draft Guidance
ID763 uveitis
31 March 2017

Dear Committee Members,

Thank you for permitting me to contribute to the appraisal process for dexamethasone and and adalimumab. My comments may be found from pages 2-8 of this document.

I would like to bring to the attention of the committee thatthe NIHR/NHSE is currently evaluating proposal sent in response to a commissioned call for research into biologic therapies for rare autoimmune diseases. One of the shortlisted research projects is a clinical trial to evaluate the effectiveness and cost-effectiveness of adalimumab compared to standard immunosuppressant therapy. A key research output of this trial will be evidence-based commissioning criteria for adalimumab for the NHS. This research will also provide evidence relevant to the scope of this NICE appraisal (section 4.4 Clinical Evidence), including information about criteria for stopping adalimumab. In addition, information concerning long term remission or clinical response following cessation of adalimumab will be obtained. In the interests of full disclosure, I would like to inform the committee that I am Co-Chief Investigator for this trial. The relevant NIHR funding board has already reviewed the proposal and I anticipate that a funding decision will be communicated in early May. The trial team would be willing to provide the committee with a copy of the trial design should the committee wish to review this.

I am grateful to the committee for consideration of my comments.

Yours sincerely,

Srilakshmi Sharma

Srilakshmi Sharma
Comments on draft Guidance
ID763 uveitis
31 March 2017

Has all the relevant evidence been taken into account? Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence

Please see the below corrections/ comments

1. **Section 4.4** National Institute for Health and Care Excellence Page 10 of 28 Appraisal consultation document – Adalimumab and dexamethasone for treating non-infectious uveitis Issue date: March 2017 *"evidence for adalimumab came from the VISUAL I and VISUAL II trials and the evidence for dexamethasone intravitreal implant came from the HURON trial. The VISUAL trials compared adalimumab plus background therapy (that is, immunosuppressants with or without steroids) with placebo plus background therapy and HURON compared dexamethasone plus background therapy with a sham procedure plus background therapy. "*

Response:
In the VISUAL trials, approximately 70% of comparator participants were on sham treatment and no corticosteroids; 30% were on sham treatment plus another immunosuppressant. Post hoc analysis to examine the effects of immunosuppressant therapy was either not made available or not calculated in this industry-sponsored trial.

The HURON and VISUAL trials had similar inclusion criteria is non infectious uveitis. The HURON trial was not exclusively for cystoid macular oedema.

2. ***Section 4.4*** *National Institute for Health and Care Excellence Page 10 of 28 Appraisal consultation document – Adalimumab and dexamethasone for treating non-infectious uveitis Issue date: March 2017*

"The committee agreed that there was a lack of evidence on therapy for non-infectious uveitis, with varied and often limited current treatments available. However, the available clinical evidence was adequate for decision-making.
the available clinical evidence was adequate for decision-making"

Response:

There is now adequate evidence for biological effect of adalimumab in uveitis to support decision making but inadequate direct evidence to support commissioning criteria proposed. There is, in fact, randomized controlled trial evidence to support other immunosuppressive therapies (eg mycophenolate, methotrexate

and tacrolimus) in uveitis. However, there is no direct comparison between adalimumab and a comparator. See comment 1. (above)

3. ***Section 4.20*** *National Institute for Health and Care Excellence Page 17 of 28 Appraisal consultation document – Adalimumab and dexamethasone for treating non-infectious uveitis Issue date: March 2017*

“

“treatment would be more cost effective in those at higher risk of permanent legal blindness, and bilateral disease with macular oedema was a useful proxy for this
risk of permanent legal blindness, and bilateral disease with macular oedema was a useful proxy for this.”

a/
Not all forms of sight threatening inflammation cause cystoid macular oedema although a significant proportion does. For example, vitreous inflammation or an ischaemic retinal vasculitis can cause loss of sight where there is no macular oedema. Therefore, bilateral disease affecting the posterior segment of the eye alone is likely to be a useful proxy and ‘bilateral disease with macular oedema’, too restrictive.

b/
In situations where the eye with unilateral posterior/pan or intermediate uveitis is the only eye eg the other eye is lost due to trauma or another ocular problem eg amblyopia the risk of legal blindness is equally high. I appreciate that worsening vision with a risk of blindness is a useful criterion which could potentially capture this group.

4. **Could the draft policy exclude from full consideration any people protected by the equality legislation who fall within the patient population for which non- infectious Uveitis will be licensed?**

No, not that I am aware of

Could the draft policy 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

No such selective restrictions are anticipated.

Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

No, I do not think a person with a specific disability will be adversely affected.

Srilakshmi Sharma
Comments on draft Guidance
ID763 uveitis
31 March 2017

Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

1 Adalimumab is recommended as an option for treating non-infectious uveitis in the posterior segment of the eye in adults with inadequate response to corticosteroids, only if there is:

A. active disease, that is, current inflammation in the eye

B. macular oedema

C. inadequate response to immunosuppressants

D. systemic disease or both eyes are affected and

E. *worsening vision with a risk of blindness.*

A	Active disease, that is, current inflammation in the eye	This is appropriate for most patients. However, it needs to be understood that those who are finding they cannot continue the medication because of side effects would have to stop the medication they are struggling to tolerate. Then, they would have to wait until inflammation relapses, following which they would be eligible to start adalimumab. Clinicians should have the flexibility to prescribe adalimumab straight away in patients of high risk of visual loss once they stop a standard immunosuppressant which is not being well- tolerated.
B	Macular oedema	Not all forms of sight threatening inflammation cause cystoid macular oedema although a significant proportion does. For example, vitreous inflammation or an ischaemic retinal vasculitis can cause loss of sight where there is no macular oedema. However, it is correct to state that macular oedema does indicate therapy.
C	Inadequate response to immunosuppressants	It would be helpful to ensure there is clarification about whether inadequate response to immunosuppression also encompasses intolerance to existing immunosuppressant medication. This is a common problem
D	Systemic disease	This recommendation excludes unilateral disease which is autoimmune and restricted to the eye (50%-60% of all cases) where there is no systemic disease. Thus, this policy would discriminate against those with autoimmune, idiopathic uveitis.

		Dexamethasone implants are not appropriate for all patients with unilateral uveitis: Patients with uveitis prior to implants may have ocular hypertension, glaucoma, high pressure in the eye secondary to topical /oral steroid therapy . Other patients may have a history of complications secondary to dexamethasone eg infection. Also, some patients find it difficult to tolerate a 4 monthly implant procedure into the eye. Patients have the right to refuse a treatment during the informed consent process since the risks of infection, cataract, glaucoma or retinal detachment following the may be perceived as too high. In all of the above circumstances, adalimumab should be offered according to the judgement of the clinician.. Equally, some patients with systemic bilateral disease may require dexamethasone implants e.g. if compliance with monitoring of immunosuppression is an issue . This is not a common situation but does exist.

2. *Stop adalimumab for non-infectious uveitis in the posterior segment of the eye in adults with inadequate response to corticosteroids if there is 1 of the following:*

   A. *new active inflammatory chorioretinal or inflammatory retinal vascular lesions or both*

   B. *anterior chamber cell grade of 0.5+ or less*

   C. *vitreous haze grade of 0.5+ or less*

   D. *worsening of best corrected visual acuity by 3 or more lines or 15 letters.*

2.		The statement is unclear. It would be helpful to rephrase. In particular it is difficulty to understand what ‘inadequate responses to corticosteroid ‘means in this context. Would it be simpler to state adalimumab should be stopped in the following condtions if a trial of

		corticosteroids and optimisation of immunosuppressants have failed?
B	anterior chamber cell grade of 0.5+ or less	An anterior chamber cellular activity may usually be treated with topical steroids which are low cost and have little appreciable toxicity in the vast majority. The consequences of isolated anterior chamber inflammation is rarely vision loss. The VISUAL trial's criterion for failure in this regard was too stringent and does not reflect usual clinical practice. I recommend removing this statement
C	Vitreous haze grade of 0.5 or less	Viteous haze is graded 0 – 5. Vitreous haze of 0 or 0.5+ would be considered treatment success, not failure. A stopping criterion of vitreous haze grade of 0.5+ would be very restrictive. A vitreous haze grade 0.5+ can arise due to progression of cataract alone or a posterior vitreous detachment; neither of which are related to worsening inflammation. Sight may also be very good with vitreous haze of 0.5 and it may be that vitreous inflammation never improves beyond grade 0.5+, if it started at a much higher score. This is because vitreous cells often do not resolve completely and may remain in the vitreous. A more suitable stopping criterion may be " worsening vitreous inflammation, causing reduction in vision"
	Stopping criterion additional suggestion.	TNFalpha therapy can be associated with demyelination. Thus if demyelination is detected after commencing treatment, then adalimumab should be stopped. (demylelination is a relative contraindication to adalimumab therapy)

3. *Dexamethasone intravitreal implant is recommended as an option for treating non-infectious uveitis in the posterior segment of the eye in adults, only if there is:*

- *active disease, that is, current inflammation in the eye and*
- *macular oedema.*

This reflects current practice. It would be helpful to define a cut-off for the degree of macular oedema . Very mild macular oedema may be improved with topical steroid.

4. This guidance is not intended to affect the position of patients whose treatment with adalimumab or dexamethasone was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

This is appropriate.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	NHS Professional
Other role	Professor of Clinical Ophthalmology
Organisation	[redacted]
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	1.1 Most of the time patients with NIPU respond well t corticosteroids but at high dose and the disease relapses as the dose is reduced. It is not correct to say that they have an inadequate response to corticosteroids Vision worsening with a risk of blindness may be due to a variety of causes not helped by Adalimumab eg cataract, epiretinal membranes, glaucoma. It is inflammatory causes that should be identified as the cause of the worsening vision 1.2 Indications for stopping Adalimumab - the anterior cell grade is irrelevant if you are treating NIPU - this should be removed - it applies to AU only Persistent macular oedema is a majoe reason for adding Adalimunmab in NIPU - many of these conditions may have little vitiritis eg birdshot or the vitritis is controlled. A low vitreous haze grade is therefore not relevant as a stopping indication and should be removed
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	4.2 The low risk of IOP rise with ozurdex with multiple injections is reported in several papers using multiple injections - eg The SAFODEX study and treatment with repeat dexamethasone implants etc Tomkins-Netzer et al Ophthalmology 2014 121 (8) 1649-54 which reports patients with uveitis. Only 7 out of 38 eyes had a rise in IOP with up to 7 implants and this was easy to treat medically. There is no evidence base to suggest that more than 3 implants should not be given for this reason and no cap on repeated use should be given. The cataract risk is similarily lower - 2 cataract progression in 38 eyes - than triamcinolone which is often used when these implants are not available. If a patient is doing well with these implants there should be no reason to limit their use as the published evidence suggest this is not an issue 4.21 see above for details on why the statements - an inadequate response to steroids is not appropriate and worsening vision with a risk of blindness and anterior chamber cell grade and vitreous haze grade

Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Adalimumab and dexamethasone for treating non-infectious intermediate, posterior or pan uveitis in adults: Assessment Group response to ACD consultation

The purpose of this document is to outline the Assessment Group (AG) response to the new analysis and incremental cost-effectiveness ratios (ICERs) submitted by Allergan as part of the Appraisal Consultation Document (ACD).

Allergan suggest that the recommendation for the dexamethasone implant should not be limited to patients with macular oedema. As such they use the AG economic model with some alternative assumptions, with the intention of representing patients without macular oedema, to assess the impact upon the model results. The company use the committee's preferred utility for blindness from Brown 1999 (0.57), and in order to represent patients without macular oedema they:

- Increase the duration of dexamethasone treatment effect from 30 weeks to 44 weeks based on the CONSTANCE study;
- Change the annual rate of blindness to the lower rate used within the AG's exploratory analyses based on a study by Tomkins-Netzer *et al.* (0.0038) and also to zero, suggesting it would be somewhere between the two.

The deterministic ICERs produced by the company using the rate of blindness from Tomkins-Netzer and no risk of blindness are £14,016 and £30,898 per QALY gained respectively, versus limited current practice. The AG has been able to reproduce the ICERs that Allergan have produced and can verify that they are technically correct.

The AG questions the company's assumption that in patients with macular oedema the treatment effect would increase from 30 weeks to 44 weeks. The AG does not believe that the results of the CONSTANCE study that Allergan refer to are in the public domain; as such it is not possible to verify these findings. Moreover, there is no justification from the company for using the results of this study over any other available evidence.

However, for the underlying rate of blindness, the AG believes that the papers by Dick *et al.*, Durrani *et al.* and Tomkins-Netzer *et al.* include patients with and without macular oedema (although this is not explicit in all of the papers), so the rate of blindness used in the model is based on a combination of people with and without macular oedema. Also the AG understands that the HURON trial includes people with and without macular oedema, and hence the effectiveness data used in the model represents that across a proportion of those with and without macular oedema.

Thus, the committee should consider whether it is appropriate to consider the subgroup without macular oedema separately to those with macular oedema. If so, the ICER may be higher than predicted by Allergan for this subgroup due to the assumption about duration of treatment effect. However, the clinical evidence that we currently have does not differentiate between the two groups, and hence neither do the AGs base case ICERs. In addition, clinical advice suggests that there may be patients who do not have macular oedema but whose vision is worsening due to active inflammation and in whom it would be appropriate to use the dexamethasone implant.

Medical Affairs Dept
AbbVie Ltd
Abbvie House
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17th April 2017

Dear [redacted]

Thank you for your questions, Abbvie would like to offer the response below.

The VISUAL study is a time to event (Treatment Failure) trial design. The definition of treatment failure was modified to account for the degree of inflammation within the eye relative to the steroid burst.

At week six, to assess treatment failure, the degree of ocular inflammation was first reduced with a steroid burst in both Humira and placebo groups, and then assessed at 6 weeks to ensure a state of disease quiescence had been achieved. Treatment failure at six weeks was then an inability to achieve quiescence, or worsening visual acuity defined as:

- New inflammatory lesions relative to baseline, (i.e. active inflammatory activity, thus inability to achieve quiescence)
- Anterior chamber cell or vitreous haze grade that did not decrease to 0.5+ or lower, (i.e. quiescence is defined as AC or VH ≤0.5, therefore AC/VH grade that could not decrease to 0.5 or lower reflects inability to achieve quiescence and continued active inflammation)
- Worsening of best corrected visual acuity by 15 or more letters on the Early Treatment Diabetic Retinopathy Study chart, relative to the best state previously achieved.

The rationale behind selecting these criteria is that baseline quiescence must first be achieved before time to treatment failure could be measured. If subjects could not achieve quiescence at week six, or visual acuity worsened, they exited the study.

After six weeks, all subjects remaining in the study begun at the same quiescent baseline and from this point the time to significant new inflammation, or worsening vision could be assessed. This time the definition of treatment failure was modified to take account worsening inflammatory parameters compared to quiescent baseline as defined by:

- New inflammatory lesions relative to baseline, (i.e. active inflammatory activity)
- Two step increase of anterior chamber cell or vitreous haze grade relative to best state achieved, (i.e. 2-step increase in inflammatory parameters is considered significant worsening of inflammation)
- Worsening of best corrected visual acuity by 15 or more letters on the Early Treatment Diabetic Retinopathy Study chart, relative to the best state previously achieved.

Thus it was mandatory, for the two definitions of treatment failure at week six and after week six, to be different.

In contrast, all subjects in VISUAL 2 (inactive uveitis) had by definition disease quiescence at study entry. Therefore, an initial 6 week period to reduce inflammation was not required, nor two different definitions of treatment failure. Rather time to treatment failure could be measured from the outset and as defined by the same definition of treatment failure '*after six weeks'* in VISUAL 1.

If you have any further questions please do not hesitate to contact Abbvie.

Best wishes,

[redacted]

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Adalimumab and dexamethasone for treating non-infectious intermediate, posterior or pan uveitis in adults: Assessment Group's additional analyses post-CM2

The purpose of this document is to provide the results of the exploratory analyses for adalimumab versus limited current practice (LCP) in patients with active uveitis for different rates of remission and relative risks (RRs) of blindness until treatment failure based on the utility of blindness as reported by the committee-preferred source (Brown 1999[1]) instead of the one used in the Assessment Group's (AG) base case (Czoski-Murray *et al.*[2]). **Error! Reference source not found.** and Table 2 show the incremental cost-effectiveness (ICERs) ratios for adalimumab versus LCP in terms of the cost per quality-adjusted life year (QALY), based on the rate of blindness reported by the committee-preferred Durrani *et al.*[3] and the source used in the AG base case (Dick *et al.*[4]), respectively.

Table 1: Exploratory analysis showing the ICERs of adalimumab versus LCP using the utility of blindness from Brown 1999[1] and the blindness rate reported by Durrani *et al.*[3] and assuming different RRs of blindness and remission rates

Rate of remission*	RR of blindness until treatment failure				
	0	0.25	0.5	0.75	1
0	£48,876	£63,923	£86,679	£124,952	£202,592
0.05	£37,279	£51,345	£72,358	£107,418	£178,191
0.1	£30,835	£44,041	£63,711	£96,456	£162,462
0.2	£23,688	£35,662	£53,486	£83,140	£142,883
1	£10,281	£19,280	£32,709	£55,091	£100,230

*Annual rate of patients going into remission and discontinuing treatment whilst maintaining the benefit, if remaining on treatment at 2 years

Table 2: Exploratory analysis showing the ICERs of adalimumab versus LCP using the utility of blindness from Brown 1999[1] and the blindness rate reported by Dick *et al.*[4] and assuming different RRs of blindness and remission rates

Rate of remission*	RR of blindness until treatment failure				
	0	0.25	0.5	0.75	1
0	£119,012	£132,539	£148,886	£169,031	£194,471
0.05	£96,468	£108,333	£122,657	£140,293	£162,547
0.1	£83,943	£94,777	£107,852	£123,947	£144,253
0.2	£70,049	£79,647	£91,230	£105,488	£123,473
1	£43,987	£51,057	£59,591	£70,098	£83,353

* Annual rate of patients going into remission and discontinuing treatment whilst maintaining the benefit, if remaining on treatment at 2 years

References

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