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Abstract

A systematic review and economic evaluation of adalimumab and dexamethasone for treating non-infectious intermediate uveitis, posterior uveitis or panuveitis in adults

Hazel Squires,[1]* Edith Poku,[1] Inigo Bermejo,[1] Katy Cooper,[1] John Stevens,[1] Jean Hamilton,[1] Ruth Wong,[1] Alastair Denniston,[2] Ian Pearce[3] and Fahd Quhill[4]

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Background: Non-infectious intermediate uveitis, posterior uveitis and panuveitis are a heterogeneous group of inflammatory eye disorders. Management includes local and systemic corticosteroids, immunosuppressants and biological drugs.

Objectives: To evaluate the clinical effectiveness and cost-effectiveness of subcutaneous adalimumab (Humira®; AbbVie Ltd, Maidenhead, UK) and a dexamethasone intravitreal implant (Ozurdex®; Allergan Ltd, Marlow, UK) in adults with non-infectious intermediate uveitis, posterior uveitis or panuveitis.

Data sources: Electronic databases and clinical trials registries including MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and the World Health Organization's International Clinical Trials Registry Platform were searched to June 2016, with an update search carried out in October 2016.

Review methods: Review methods followed published guidelines. A Markov model was developed to assess the cost-effectiveness of dexamethasone and adalimumab, each compared with current practice, from a NHS and Personal Social Services (PSS) perspective over a lifetime horizon, parameterised with published evidence. Costs and benefits were discounted at 3.5%. Substantial sensitivity analyses were undertaken.

Results: Of the 134 full-text articles screened, three studies (four articles) were included in the clinical effectiveness review. Two randomised controlled trials (RCTs) [VISUAL I (active uveitis) and VISUAL II (inactive uveitis)] compared adalimumab with placebo, with limited standard care also provided in both arms. Time to treatment failure (reduced visual acuity, intraocular inflammation, new vascular lesions) was longer in the adalimumab group than in the placebo group, with a hazard ratio of 0.50 [95% confidence interval (CI) 0.36 to 0.70; $p < 0.001$] in the VISUAL I trial and 0.57 (95% CI 0.39 to 0.84; $p = 0.004$) in the VISUAL II trial. The adalimumab group showed a significantly greater improvement than the placebo group in the 25-item Visual Function Questionnaire (VFQ-25) composite score in the VISUAL I trial (mean difference 4.20; $p = 0.010$) but not the VISUAL II trial (mean difference 2.12; $p = 0.16$). Some systemic adverse effects occurred more frequently with adalimumab than with placebo. One RCT [HURON (active uveitis)] compared a single 0.7-mg dexamethasone implant against a sham procedure, with limited standard care also provided in both arms. Dexamethasone provided significant benefits over the sham procedure at 8 and 26 weeks in the percentage of patients with a vitreous haze score of zero ($p < 0.014$), the mean best corrected visual

acuity improvement ($p \leq 0.002$) and the percentage of patients with a ≥ 5-point improvement in VFQ-25 score ($p < 0.05$). Raised intraocular pressure and cataracts occurred more frequently with dexamethasone than with the sham procedure. The incremental cost-effectiveness ratio (ICER) for one dexamethasone implant in one eye for a combination of patients with unilateral and bilateral uveitis compared with limited current practice, as per the HURON trial, was estimated to be £19,509 per quality-adjusted life-year (QALY) gained. The ICER of adalimumab for patients with mainly bilateral uveitis compared with limited current practice, as per the VISUAL trials, was estimated to be £94,523 and £317,547 per QALY gained in active and inactive uveitis respectively. Sensitivity analyses suggested that the rate of blindness has the biggest impact on the model results. The interventions may be more cost-effective in populations in which there is a greater risk of blindness.

Limitations: The clinical trials did not fully reflect clinical practice. Thirteen additional studies of clinically relevant comparator treatments were identified; however, network meta-analysis was not feasible. The model results are highly uncertain because of the limited evidence base.

Conclusions: Two RCTs of systemic adalimumab and one RCT of a unilateral, single dexamethasone implant showed significant benefits over placebo or a sham procedure. The ICERs for adalimumab were estimated to be above generally accepted thresholds for cost-effectiveness. The cost-effectiveness of dexamethasone was estimated to fall below standard thresholds. However, there is substantial uncertainty around the model assumptions. In future work, primary research should compare dexamethasone and adalimumab with current treatments over the long term and in important subgroups and consider how short-term improvements relate to long-term effects on vision.

Study registration: This study is registered as PROSPERO CRD42016041799.

Funding: The National Institute for Health Research Health Technology Assessment programme.

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Glossary

Active systemic disease Systemic disease that is currently requiring symptomatic treatment (in these patients, systemic treatment may be more appropriate to treat both the uveitis and the underlying disease).

Anterior chamber of the eye The fluid-filled space in the front part of the eye located between the iris and the inner surface of the cornea.

Anterior segment of the eye The part of the eye composed of the cornea, iris, lens, ciliary body and front part of the sclera (white part of the eye). In general, it forms the anterior (front) one-third of the eye.

Bilateral Uveitis affecting both eyes. For the purposes of this report, to avoid confusion, this does not relate to treatment for both eyes. In the case of local treatment, it may be for one or both eyes and will be referred to as such.

Cataract A cloudiness of the lens of the eye.

Corticosteroid-sparing therapy A single treatment or treatment regimen that allows the reduction or discontinuation of ongoing corticosteroids.

Cycloplegic drug A drug that causes relaxation of the ciliary muscle of the eye.

Extended dominance When the incremental cost-effectiveness ratio for a given treatment alternative is higher than that of the next more effective (non-dominated) comparator.

Fluorescein angiography An eye test that uses a specialised camera and a fluorescent dye to examine the circulation of the retina and choroid.

Glaucoma An eye condition characterised by damage to the optic nerve caused by intraocular pressure.

Immunosuppression Reducing or lowering the immune response with the use of drugs.

Indirect ophthalmoscope A magnifying instrument with a light source for examining the inside of the eye through the pupil, especially the space between the lens and the retina.

Intraocular pressure Pressure exerted by fluid in the eye. The normal range is between 10 and 20 mmHg and may vary in an individual at different times of the day.

Legal blindness best corrected visual acuity of $\leq$ 20/200 in the better-seeing eye and/or a visual field of $\leq 20°$.

Local treatment/local pathway Treatments that are local to the eye (may be given to one or both eyes; little effect on systemic disease).

Macula The pigmented area or 'yellow spot' near the centre of the retina.

Macular oedema Fluid collection in the region of the macula.

Meta-analysis A statistical method by which the results of a number of studies are pooled to give a combined summary statistic.

Mydriatic drug A drug instilled in the eye to dilate the pupil.

No active systemic disease Either no systemic disease related to uveitis or systemic disease that is currently controlled (in these patients, treatment local to the eye may be more appropriate).

Optic nerve A nerve that transmits visual information from the retina to the brain.

Optical coherence tomography A non-invasive technique for cross-sectional imaging of the retina and light-sensitive areas of the eye.

Posterior segment of the eye The part of the eye encompassing the vitreous, choroid, retina and optic nerve. It forms the posterior (back) two-thirds of the eye.

Relative risk The ratio of the probability of an event occurring in an exposed group relative to the probability of an event occurring in a non-exposed or control group.

Simple dominance When an intervention is less effective and more expensive than its comparator.

Systemic disease Known underlying systemic disease related to the uveitis.

Systemic treatment/systemic pathway Treatments that are given systemically (and by their nature treat both eyes and may also treat systemic disease).

Unilateral Uveitis affecting one eye. For the purposes of this report, to avoid confusion, this does not relate to treatment for one eye.

Visual acuity This refers to how well a person sees, that is, clarity of vision.

Vitreous A clear jelly-like fluid that fills the middle of the eye, between the lens and the retina.

List of abbreviations

AC	anterior chamber
ADA	adalimumab
AE	adverse event
AG	Assessment Group
AIC	Akaike information criterion
BCVA	best corrected visual acuity
BIC	Bayesian information criterion
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CPCI	Conference Proceedings Citation Index
CP(M)	current practice as provided in the MUST trial
DEX	dexamethasone
DEX 350	dexamethasone 0.35 mg
DEX 700	dexamethasone 0.7 mg
EMA	European Medicines Agency
EQ-5D	EuroQol-5 Dimensions
ETDRS	Early Treatment Diabetic Retinopathy Study
HADS	Hospital Anxiety and Depression Scale
HR	hazard ratio
HRQoL	health-related quality of life
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
IOP	intraocular pressure
ITT	intention to treat
LCP(H)	limited current practice based on the HURON trial
LCP(VI)	limited current practice based on the VISUAL I trial
LCP(VII)	limited current practice based on the VISUAL II trial
LOCF	last observation carried forward
logMAR	logarithm of the minimum angle of resolution
MD	mean difference
MeSH	medical subject heading
MUST	Multicenter Uveitis Steroid Treatment
NEI	National Eye Institute
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NSAID	non-steroidal anti-inflammatory drug
PROM	patient-reported outcome measure
PSA	probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	quality-adjusted life-year
RCT	randomised controlled trial
RR	relative risk
SAE	serious adverse event
ScHARR	School of Health and Related Research
SD	standard deviation
SF-36	Short Form questionnaire-36 items
SmPC	Summary of Product Characteristics
SUN	Standardization of Uveitis Nomenclature
TNF	tumour necrosis factor

VCM	Vision Core Measure	WHO	World Health Organization
VFQ-25	25-item Visual Function Questionnaire	WPAI	Work Productivity and Activity Impairment
VH	vitreous haze	WTP	willingness to pay
VKH	Vogt–Koyanagi–Harada disease		

Plain English summary

Non-infectious intermediate uveitis, posterior uveitis and panuveitis are a group of conditions causing inflammation in the eye, which if untreated may lead to sight loss. Treatment may include injections or implants into the eye or medicines taken by mouth or via injection.

This assessment evaluated whether adalimumab (as an injection under the skin) (Humira®; AbbieVie Ltd, Maidenhead, UK) or dexamethasone (as an implant in the eye) (Ozurdex®; Allergan Ltd, Marlow, UK) improved patients' eye inflammation, vision and quality of life. We also examined the harmful effects of treatment as well as the associated costs. Data were combined from published sources in an economic model to estimate the cost-effectiveness of adalimumab and dexamethasone compared with current treatment.

Evidence from three studies showed that adalimumab and dexamethasone were each better than placebo at improving eye inflammation, vision and quality of life. In terms of safety, adalimumab resulted in more generalised effects such as infections and injection site reactions. The dexamethasone implant resulted in more eye-related complications such as raised pressure in the eye and cataracts.

For dexamethasone, the additional cost for each additional year of life in full health (cost per quality-adjusted life-year gained) was estimated as £19,509 compared with current practice. The equivalent figure for adalimumab was estimated to be > £90,000, which is higher than the values reported by the National Institute for Health and Care Excellence as thresholds for a treatment to be considered cost-effective. There is substantial uncertainty around the evidence, in particular with regard to the impact of the interventions on patient blindness and differences between trial evidence and clinical practice.

Scientific summary

Background

Uveitis describes a group of conditions characterised by inflammation of the uveal tract. The underlying cause may be infectious or non-infectious. In the UK and the developed world, uveitis is most commonly non-infectious and likely autoimmune in origin, either isolated to the eye or associated with systemic autoimmune disorders. This study covers the most sight-threatening forms of non-infectious uveitis, those affecting the posterior structures of the eye, termed intermediate uveitis (vitreous humour and posterior ciliary body), posterior uveitis (retina and choroid) and panuveitis (front and back of the eye). It does not cover anterior uveitis (iris and anterior ciliary body). Symptoms include blurred vision, floaters and sometimes pain and redness. Consequences leading to potential vision loss include early complications such as cystoid macular oedema (retinal swelling) and vitreous haze (VH) (inflammatory cell debris in the vitreous) and late complications such as cataracts (lens cloudiness), glaucoma [optic nerve damage from increased intraocular pressure (IOP)] and irreversible retinal damage. Between 3 and 16 in 100,000 people are estimated to have non-infectious posterior segment-involving uveitis. Uveitis generally presents in working-age people, is the fifth leading cause of visual impairment in developed countries and accounts for 10% of cases of legal blindness.

Current treatment includes corticosteroids (systemic or local injection or implant) as first-line treatment and immunosuppressive drugs (such as methotrexate, mycophenolate mofetil, ciclosporin, tacrolimus and azathioprine) as second-line treatment for uveitis unresponsive to corticosteroids or which recurs on steroid tapering. Tumour necrosis factor (TNF)-alpha inhibitors are considered a third-line option. The majority of these treatments are not currently licensed. The technologies assessed in this study were adalimumab (ADA) (Humira®; AbbVie Ltd, Maidenhead, UK), a monoclonal antibody TNF-alpha inhibitor, and dexamethasone (DEX) (Ozurdex®; Allergan Ltd, Marlow, UK), a corticosteroid intravitreal implant.

Aims

The aims of this study were to:

- evaluate the clinical effectiveness and safety of ADA (via subcutaneous injections) and a DEX intravitreal implant within their marketing authorisations for non-infectious intermediate uveitis, posterior uveitis or panuveitis in adults
- estimate the incremental cost-effectiveness of ADA and a DEX intravitreal implant for non-infectious intermediate uveitis, posterior uveitis or panuveitis compared with each other and current treatment
- estimate the expected overall cost of ADA and DEX treatment in England
- identify areas for primary research.

Methods

Searches of nine databases to June/October 2016 including MEDLINE, EMBASE, Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE) and Cumulative Index to Nursing and Allied Health Literature (CINAHL) identified randomised controlled trials (RCTs) of ADA, DEX implants and relevant comparators. Study quality was assessed using the Cochrane risk-of-bias tool. Results were synthesised using narrative synthesis. The use of a network meta-analysis (NMA) was explored.

Searches were undertaken for existing cost-effectiveness studies in non-infectious uveitis. A de novo Markov model was developed by the Assessment Group (AG) to assess the cost-effectiveness of DEX and ADA, each compared with (limited) current practice, from a NHS and Personal Social Services (PSS) perspective over a lifetime horizon. The two interventions were not compared directly as they are often used in different patient scenarios and, when comparison would be clinically appropriate, there was insufficient trial evidence. The cost-effectiveness of ADA was assessed separately for active and inactive uveitis and the cost-effectiveness of DEX was assessed only for active uveitis. The model included five health states: (1) treatment: no permanent blindness, (2) treatment failure: no permanent blindness, (3) permanent blindness, (4) remission and (5) death. Effectiveness was modelled using EuroQol-5 Dimensions (EQ-5D) utility data from the ADA trials and by regression analysis, mapping scores from the 25-item Visual Function Questionnaire (VFQ-25) reported within the DEX trial to EQ-5D utilities. Health-related quality of life (HRQoL) (VFQ-25 or EQ-5D) could be improved by a reduction in inflammation, improvements in vision or a reduction in adverse events (AEs). Treatment may reduce the risk of permanent damage to the eye, resulting in a decreased risk of legal blindness. Given the uncertainties around the comparators and long-term outcomes, substantial exploratory and sensitivity analyses were undertaken.

Results

Of the 134 full-text articles screened, three studies (four articles) were included in the clinical effectiveness review. Two RCTs compared ADA (40 mg every 2 weeks by subcutaneous injection) with placebo: VISUAL I (active uveitis, $n = 223$) and VISUAL II (inactive uveitis, $n = 229$). Over 90% of patients had bilateral uveitis. As ADA is a systemic treatment, both eyes were treated. All patients were on high-dose corticosteroids at baseline and patients in the VISUAL I trial received an initial high-dose steroid burst; steroids were then tapered in both studies. One concomitant immunosuppressant was received by 30% of participants in the VISUAL I trial and 47% of participants in the VISUAL II trial. Follow-up was carried out up to 80 weeks or until treatment failure and outcomes were measured from the best response following the steroid burst (VISUAL I) or from baseline (VISUAL II) to treatment failure or the study end. One RCT of DEX implants (HURON, $n = 229$) compared a dose of 0.7 mg (DEX 700) or 0.35 mg (DEX 350) with a sham procedure over 26 weeks. This assessment was limited to the licensed DEX 700 group compared with the sham group. One eye per patient received a single implant (right eye if bilateral; worse-seeing eye in 84% of all patients). Systemic therapies were received by 25% of participants at baseline and could be continued throughout the trial. The proportion of bilateral cases was not recorded. Thirteen additional trials of clinically relevant comparator treatments [vs. placebo or one another as per the National Institute for Health and Care Excellence (NICE) scope] were identified. However, pairwise meta-analysis and NMA were not feasible because of clinical heterogeneity, lack of common comparators (the network was disconnected) and differences in reported outcomes.

Clinical effectiveness

The primary outcome for the VISUAL trials of ADA was treatment failure, defined as worsening of any of the following in either eye: anterior chamber (AC) cell grade, VH grade, best corrected visual acuity (BCVA) or new inflammatory lesions. In the VISUAL I trial (active uveitis), the median time to treatment failure was 5.6 months in the ADA arm compared with 3.0 months in the placebo arm [hazard ratio (HR) 0.50, 95% confidence interval (CI) 0.36 to 0.70; $p < 0.001$]. In the VISUAL II trial (inactive uveitis), the median time to treatment failure was not estimable in the ADA arm and was 8.3 months in the placebo arm [HR 0.57, 95% CI 0.39 to 0.84; $p = 0.004$). The VISUAL I trial reported significant benefits for ADA compared with placebo for changes in the following (averaged across both eyes): visual acuity [mean difference (MD) –0.07; $p = 0.003$), VH (MD –0.27; $p < 0.001$), AC cell grade (MD –0.29; $p = 0.011$), macular oedema (percentage change in central retinal thickness: MD –11.4%; $p = 0.020$), VFQ-25 composite score (MD 4.20; $p = 0.010$) and EQ-5D score (MD 0.04; $p = 0.044$). In the VISUAL II trial, differences were not significant for ADA compared with placebo for changes in any of visual acuity (MD –0.04; $p = 0.096$), VH (MD –0.13; $p < 0.070$), AC cell grade (MD –0.14; $p = 0.218$), macular oedema (percentage change in central retinal thickness: MD –2.3%; $p = 0.451$), VFQ-25 composite score (MD 2.12; $p = 0.160$) or EQ-5D score (MD 0.00; $p = 0.836$).

Secondary outcomes in the VISUAL I and II trials were measured only to treatment failure or the study end and, as treatment failure occurred in more patients on placebo than on ADA, the last observation carried forward method may have introduced bias as data post treatment failure were not missing at random.

In the HURON trial there were significant benefits of DEX 700 compared with the sham procedure for the following (measured in the study eye only): percentage of patients with a VH score of zero at 8 weeks (MD 34.9%; $p < 0.001$) and 26 weeks (MD 16.7%; $p = 0.014$), percentage with a VH improvement of ≥ 2 units at 8 weeks (MD not reported; $p < 0.001$) and 26 weeks (MD not reported; $p = 0.001$), percentage with a BCVA improvement of three or more lines at week 26 (MD 24.5%; $p < 0.001$), mean BCVA improvement over weeks 3–26 (no values reported; $p \leq 0.002$), decrease in central retinal thickness at 8 weeks (MD –87.0 µm; $p = 0.004$) although not at 26 weeks (MD –14.7 µm; $p = 0.58$), change in VFQ-25 composite score at 8 weeks (MD 5.4; $p = 0.007$) and 26 weeks (MD 7.3; $p = 0.001$) and percentage of patients with a ≥ 5-point improvement in VFQ-25 score at 8 weeks (54.8% vs. 27%; $p < 0.001$) and 26 weeks (57.5% vs. 32.4%; $p < 0.05$). Rescue medications (corticosteroid injections or new/increased use of systemic therapies) were required in 22% of the DEX 700 group compared with 38% of the sham group ($p = 0.030$).

As ADA affects the immune system, potential risks of treatment include infections and malignancy. Serious infections were higher in the ADA group than in the placebo group in the VISUAL I trial (4.5% vs. 1.8%) but not in the VISUAL II trial (1.7% vs. 1.8%). Across both trials, malignancies and chronic renal failure each occurred in three patients in the ADA group, with no cases in the placebo group. Systemic AEs that had a higher rate in the ADA group than in the placebo group in at least one RCT included infections, injection site reactions, fatigue, arthralgia, myalgia, paraesthesia, hypertension and elevated levels of liver enzymes. Anti-ADA antibodies occurred in 2.7% of participants in the VISUAL I trial and 5% of participants in the VISUAL II trial. There was little difference in ocular AEs between the groups.

In the HURON trial, the following AEs were reported: raised IOP (DEX 700 25% vs. sham 7%), IOP of ≥ 25 mmHg (DEX 700 7.1% vs. sham 1.4%), glaucoma (DEX 700 0% vs. sham 2.7%), cataracts in phakic eyes (DEX 700 15% vs. sham 7%), endophthalmitis (severe eye infection) (DEX 700 1.3% vs. sham 0%) and conjunctival haemorrhage (DEX 700 30% vs. sham 21%). No systemic AEs had a significantly higher rate in the DEX 700 group than in the sham group.

No patients required incisional surgery, 2.6% of participants in the DEX 700 group required a laser iridotomy and, at any one time, up to 23% of participants in the DEX 700 group required IOP-lowering medication (not reported for the sham group). Cataract surgery was required in 1.6% of participants in the DEX 700 group compared with 3.6% of participants in the sham group.

Cost-effectiveness

The base-case analysis undertaken by the AG estimated the incremental cost-effectiveness ratio (ICER) of one DEX implant in one eye for a combination of patients with unilateral and bilateral uveitis compared with limited current practice, as per the HURON trial, to be £19,509 per quality-adjusted life-year (QALY) gained. The ICER of ADA (systemic, therefore treatment for both eyes) for patients with mainly bilateral uveitis compared with limited current practice, as per the VISUAL trials, was estimated to be £94,523 and £317,547 per QALY gained in active and inactive uveitis respectively.

Exploratory analyses suggested that the two factors that have the largest impact on the ICERs, both highly uncertain, are the rate of blindness in the comparator group and the relative risk of blindness for ADA or DEX compared with the comparator. The ICER for DEX compared with (limited) current practice varied from dominating to £56,329 per QALY gained when varying these parameters. When the rate of legal blindness was set to zero to explore the cost-effectiveness of DEX for unilateral uveitis, the estimated ICER was £50,627 per QALY gained. Under all assumptions tested for these parameters, the ICER for ADA compared with (limited) current practice, based on the VISUAL trials, remained above £30,000 and £82,000 per QALY for active and inactive uveitis respectively. The factor that had the largest impact on the ICER for ADA was the proportion of patients who were assumed to stop ADA treatment following remission and maintain the

same quality of life; assuming that all patients go into remission after 2 years on ADA, the ICER was reduced to £35,299 and £84,132 per QALY for active and inactive uveitis respectively.

Discussion

The results of the economic model are highly uncertain because of the limited evidence base. In addition to the issues explored within the sensitivity analyses, several further differences between evidence and practice were not possible to quantify. First, clinical advisors to the AG (three of the authors, AD, IP and FQ, who provided clinical advice throughout) suggested that the proportion of patients remaining on ADA may be underestimated within the VISUAL trials because of strict criteria for treatment failure. If more people remained on treatment, the additional patients would incur the same costs but experience reduced effectiveness of ADA and hence the ICERs for ADA would increase. Second, clinical advisors suggested that ADA use in 'inactive' patients would be restricted to patients discontinuing immunosuppressants because they are ineffective or not tolerated; however, there are no data for this group. Third, the model assumed the use of only one DEX implant per patient. There is no RCT evidence assessing more than one implant, either in both eyes or consecutively. Although the AG explored the impact of consecutive implants, there were insufficient data to consider the cost-effectiveness of DEX implants in both eyes. However, because costs would essentially be doubled and the HRQoL increase would probably be lower for the second eye, implants in both eyes are expected to be less cost-effective than treatment in one eye only. Fourth, clinical advisors suggested that ADA and DEX are likely to be provided alongside other treatments. In the trials, around one-third of patients in both arms received other treatments. However, it is unclear whether or not the relative effectiveness of ADA and DEX predicted within the trials would remain if the use of alternative treatments in both the intervention group and the comparator group was increased. Finally, because of a lack of evidence for a comparator representing current practice, it is unclear how ADA and DEX may affect the use of other treatments. The model incorporated the impact of DEX on use of rescue therapy, but this was based on the analysis using a sham comparator. If treatment with DEX or ADA led to a reduction in use of immunosuppressants and/or corticosteroids without having an impact on efficacy, then they would be more cost-effective than currently predicted.

The population considered in the model was heterogeneous and the interventions may be more cost-effective in some groups than others. However, there was no trial evidence to facilitate subgroup analyses. Patients with more severe uveitis, such as those with macular oedema, may benefit more from ADA or DEX; hence, the treatments may be more cost-effective as baseline disease worsens. In addition, ADA used to concurrently treat uveitis and systemic symptoms may be more cost-effective than ADA used to treat uveitis alone. The analysis in which the rate of blindness was set to zero, which could be used to explore the cost-effectiveness of DEX for patients with unilateral uveitis, suggested that the ICER compared with (limited) current practice increases substantially.

The analysis presented here takes a NHS and PSS perspective. Non-infectious uveitis affects a working-age population and can affect workplace productivity and leisure time. Therefore, there are likely to be additional non-NHS and non-PSS costs and benefits associated with the treatments that are not captured within our analyses.

Conclusions

Two RCTs of systemic ADA and one RCT of a unilateral single DEX implant showed significant benefits of the treatments compared with placebo or a sham procedure for outcomes including visual acuity, inflammation, macular oedema, VFQ-25 score and time to treatment failure. Use of one DEX implant in a mixed group of unilateral and bilateral patients had an estimated ICER of £19,509 per QALY gained compared with (limited) current practice. The ICER associated with ADA compared with (limited) current practice did not fall below £30,000 per QALY gained in any of the analyses carried out.

There is substantial uncertainty around the evidence, in particular with regard to the comparative effectiveness and cost-effectiveness of DEX and ADA and their effectiveness and cost-effectiveness compared with those of systemic immunosuppressants and corticosteroids and how short-term improvements in visual acuity and inflammation relate to long-term effects on vision loss and blindness. The impact of differences between clinical practice and trial evidence is uncertain. Finally, there is insufficient evidence from patient subgroups in which the interventions may be more or less effective and cost-effective.

Study registration

This study is registered as PROSPERO CRD42016041799.

Funding

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Chapter 1 Background

Description of the health problem

Uveitis is a heterogeneous group of ocular disorders involving inflammation of the uveal tract of the eye, which consists of the iris, the ciliary body and the choroid,[1–5] or surrounding tissues (e.g. sclera, retina and optic nerve).[6]

Criteria for the classification of uveitis according to anatomical site of inflammation were formally developed by the International Uveitis Study Group in 1987.[7] These were later revised in 2004 following the Standardization of Uveitis Nomenclature (SUN) Workshop.[8] The SUN criteria included onset, duration and course of uveitis in the classification of the condition. There are currently no agreed guidelines for describing uveitis-related systemic conditions.[9] A summary of uveitis classification according to the SUN criteria[8] is presented in *Table 1*.

Anterior uveitis is inflammation of the anterior chamber (AC) involving the iris and the anterior aspect of the ciliary body; this is outside the scope of this assessment. Intermediate uveitis affects the posterior part of the ciliary body and the vitreous humour. Posterior uveitis affects the back of the eye, including the retina or the choroid. Intermediate and posterior uveitis may be referred to collectively as posterior segment-involving uveitis. Panuveitis is inflammation of the whole of the uveal tract (front and back of the eye), extending from the AC to the choroid or retina.[3] A diagram of the eye and the parts affected in anterior, intermediate and posterior uveitis is shown in *Figure 1*.

Intermediate uveitis, posterior uveitis and panuveitis account for around 10% of uveitis cases in the UK[10] but are more severe and more likely to cause vision loss.[11]

TABLE 1 Classification of uveitis: SUN[8]

Type of uveitis	Primary site of inflammation
Anterior uveitis	Anterior chamber
Intermediate uveitis	Vitreous
Posterior uveitis	Retina and choroid
Panuveitis	Anterior chamber, vitreous, retina or choroid
Criteria	**Description**
Onset	
Sudden	(No detail provided)
Insidious	(No detail provided)
Duration	
Limited	< 3 months' duration
Persistent	> 3 months' duration
Course	
Acute	Episode characterised by sudden onset and limited duration
Recurrent	Repeated episodes with intermittent periods of inactivity not requiring treatment for > 3 months
Chronic	Persistent episodes with relapse in < 3 months of treatment discontinuation

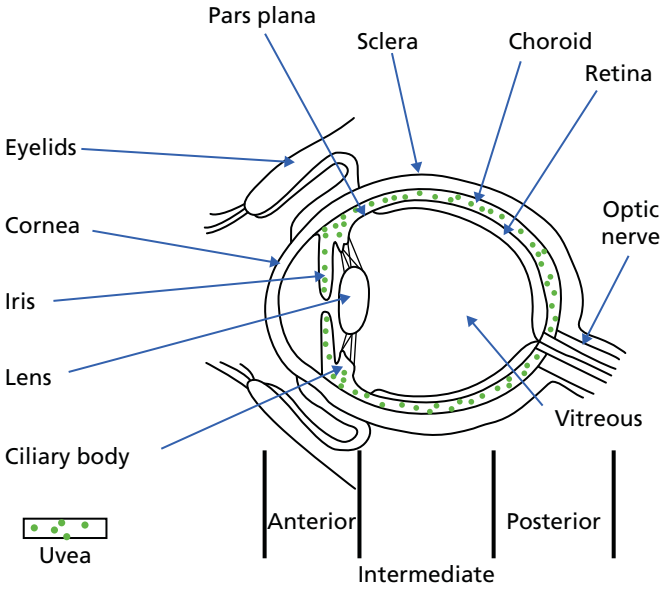

FIGURE 1 Types of uveitis based on parts of the eye affected. Reproduced with permission from Phil Hibbert, Uveitis Information Group (Scotland).[12]

Aetiology, pathology and prognosis

Uveitis may have an infectious or a non-infectious cause; this appraisal is restricted to non-infectious uveitis. Non-infectious uveitis may occur as an ocular manifestation of a systemic autoimmune condition such as Behçet's disease, sarcoidosis, multiple sclerosis or Vogt–Koyanagi–Harada disease (VKH).[13,14] A study from the Netherlands including almost 400 patients with posterior uveitis, intermediate uveitis or panuveitis reported that around half of all cases were likely to be related to systemic disease.[15] In the remaining cases, no systemic association could be found; these cases are known as idiopathic uveitis, although it is presumed that the disease is still likely to be autoimmune in nature.[14] Specific forms of uveitis include birdshot chorioretinopathy (also referred to as birdshot uveitis).

One or both eyes may be affected in uveitis. Estimates of the proportion of bilateral cases from studies of uveitis patients in tertiary centres in the UK and Europe range from 41% to 67%.[11,16–18] Each of these centres included patients with both anterior and posterior segment-involving uveitis. Three of the authors (AD, IP and FQ) provided clinical advice throughout, hereafter referred to as clinical advisors to the Assessment Group (AG). They suggested that the proportion of bilateral cases is higher for posterior segment-involving uveitis patients only, with the proportion of bilateral cases in this group estimated to be 70–80%. Many patients have asymmetric disease, with some inflammation in both eyes but more severe disease in one eye (these patients may or may not be included in the above estimates for bilateral uveitis).

Symptoms of uveitis depend on the parts of the eye affected. The main symptoms of the forms of uveitis considered in this study include blurred vision and floaters in the eye. However, pain and redness in the eye, sensitivity to light, loss of peripheral vision and headaches may also be reported.[13] In general, clinical manifestations of uveitis of different aetiologies may be similar but treatment strategies are predominantly determined by the underlying pathophysiology[3] and may often require a multidisciplinary approach.

The consequences of uveitis that may lead to loss of vision include early complications, such as cystoid macular oedema (swelling of the retina) and vitreous haze (VH) (inflammatory cell debris in the vitreous), and late complications, such as cataracts (cloudiness of the lens), glaucoma (optic nerve damage associated with increased pressure inside the eye) and irreversible damage to the retina.[14] Many patients with posterior segment-involving uveitis require cataract surgery at a relatively early age; however, as cataract surgery is relatively efficacious and safe, clinicians may be less concerned about cataract formation than other complications of uveitis (clinical advisors to the AG, personal communication).

Dick *et al.*[19] conducted a retrospective analysis of insurance claim data from 1998 to 2012 for patients with a diagnosis of non-infectious intermediate uveitis, posterior uveitis or panuveitis in the USA. In total, 1769 patients with uveitis were followed up for a mean period of 5.6 years. The reported 5-year risks for patients with non-infectious intermediate uveitis, posterior uveitis or panuveitis were as follows: glaucoma 20%, cataracts 35%, visual disturbance 29%, blindness or low vision 4.5%, retinal detachment 11% and retinal disorder 28%. The supplemental material included a Kaplan–Meier curve of time to blindness, which showed a 10-year risk of blindness or low vision of 6.6%.

Tomkins-Netzer *et al.*[18] conducted a cross-sectional study of all patients ($n = 1076$) who attended the uveitis clinic of a single consultant at Moorfields Eye Hospital in London. The mean follow-up duration was 7.97 years and vision loss [best corrected visual acuity (BCVA) $\leq$ 20/50] was reported in 19.2% of eyes. Macular scarring (4%), retinal detachment (1.33%) and chronic macular oedema (1.16%) were the most common causes of irreversible severe vision loss (BCVA $\leq$ 20/200). Twenty patients had bilateral severe vision loss and were registered as legally blind.

Another retrospective review of records of 315 patients with uveitis in the UK from January 1998 to December 2000 described visual impairment (BCVA $\leq$ 6/18 in at least one eye) in 220 out of 315 uveitis patients (70%) overall and in 149 of 192 patients with intermediate uveitis, posterior uveitis or panuveitis (78%) after a mean follow-up duration of 36.7 months.[11] Severe visual impairment (BCVA $\leq$ 6/60) occurred in 38% ($n = 120/315$) of patients. Permanent visual impairment was present in 17% ($n = 54/315$) of patients, with 15% ($n = 46/315$) of patients experiencing bilateral impairment. The World Health Organization (WHO)'s criteria for blindness (BCVA in better eye of $<$ 3/60 or a visual field of $\leq 10°$)[20] were met in 36 out of 315 patients (11.4%). Cystoid macular oedema, cataract and the coexistence of both conditions were the predominant causes of visual loss in 26.8% ($n = 59/220$), 17.7% ($n = 39/220$) and 20% ($n = 44/220$) of uveitic patients respectively. Reported predictors of poor visual outcome were older age ($p = 0.02$ via logistic regression), bilateral inflammation ($p = 0.0005$ via *t*-test), panuveitis ($p = 0.0005$ via logistic regression) and increasing duration of reduced vision ($p = 0.0005$ via *t*-test).[11] Overall, around 10% of cases of blindness in the developed world are caused by uveitis.[18,21]

Epidemiology and prevalence

Uveitis affects people of any age but generally presents in people of working age, aged 20–50 years.[3,14] The mean age at presentation for patients with all types of uveitis attending tertiary centres has been reported to range from 35 to 48 years across studies in the UK,[11,18] the Netherlands[15] and France.[16]

There is extensive variation in the causes of uveitis worldwide, genetic factors and environmental features contributing significantly to its pathology.[14] Whereas infectious uveitis is frequently seen in developing countries, idiopathic non-infectious uveitis is more common in most of the developed world, including England.[3]

Earlier epidemiological studies in Europe and the USA have estimated annual incidence rates of uveitis ranging from 14 to 22.5 per 100,000 people and prevalence rates of between 38 and 380 per 100,000 people.[11] Wide variations in epidemiological statistics have been explained by differences in the classification of uveitis, aetiological causes and demographic risk factors.[14] There are limited data on the prevalence of non-infectious posterior segment-involving uveitis in England. The Scottish Uveitis Network reported prevalence rates for patients with uveitis treated with immunosuppression (systemic corticosteroids, second-line immunosuppressants or a combined treatment of the two agents) collected prospectively over a 4-month period between August and November 2005; estimates ranged from 2 to 59 per 100,000 people.[22] A claims-based analysis conducted in the USA based on 2012 data from the OptumHealth Reporting and Insights claims database reported an overall prevalence of adult non-infectious uveitis ($n = 4827$ cases; 2086 men and 2741 women) of 121 cases per 100,000 people [95% confidence interval (CI) 117.5 to 124.3 cases per 100,000 people].[23] The observed prevalence rates of non-infectious intermediate uveitis, posterior uveitis and panuveitis in adults were 1 case (95% CI 0.8 to 1.5 cases), 10 cases (95% CI 9.4 to 11.5 cases) and 12 cases (95% CI 10.6 to 12.7 cases) per 100,000 people respectively.[23] Earlier studies have generally

provided no or limited data for patients with non-infectious uveitis[24,25] or have had issues (e.g. missing data, use of administrative data, variations in referral patterns), making estimates less generalisable.[22,26] Between 3 and 16 out of 100,000 people are estimated to have non-infectious posterior segment-involving uveitis (see *Chapter 5*).

Impact of the health problem

Uveitis is the fifth leading cause of visual impairment in developed countries and accounts for 10% of cases of legal blindness.[23,27] Patients may experience sudden and temporary or progressive and permanent visual impairment.[11]

With regard to anatomical classification of uveitis, patients with posterior segment-involving uveitis and panuveitis tend to suffer more severe visual impairment than those with anterior uveitis.[27] Compared with uveitis affecting only the posterior segment, patients with panuveitis (both posterior and anterior) tend to have a poorer prognosis.[11] Additionally, the underlying cause of uveitis may also significantly influence the prognosis of intraocular inflammation.[11] For example, patients with uveitis as a result of Behçet's disease have poorer visual outcomes than patients with non-infectious uveitis without an associated systemic condition, even when intense treatment is initiated at early stages of the disease.[11] Complications of uveitis, namely cystoid macular oedema, cataract, glaucoma or a combination of any of these, significantly influence the visual morbidity.

A post hoc analysis of health-related quality of life (HRQoL) in patients with non-infectious intermediate or posterior uveitis participating in the HURON trial compared with that in a matched set of the general US population found that the uveitis group had lower mean scores on the following subscales of the National Eye Institute (NEI) 25-item Visual Function Questionnaire (VFQ-25):[28] role emotional ($p < 0.001$), mental health ($p < 0.001$), role physical ($p < 0.001$), vitality ($p < 0.001$), general health ($p = 0.01$) and mental component summary ($p < 0.001$).[29] No statistically significant differences between the groups were found for the physical component summary, physical functioning, bodily pain and social functioning subscales of the VFQ-25 or for EuroQol-5 Dimensions (EQ-5D)[30] scores.

Loss of visual function can lead to an inability to work and drive. It can also affect the ability to take part in leisure activities. In addition, the currently available treatments, including corticosteroids and immunosuppressants, are associated with substantial adverse events (AEs). The most common AEs associated with long-term use of corticosteroids include osteoporosis and fractures, gastric conditions, psychiatric conditions, skin conditions, hyperglycaemia, weight gain, ocular conditions (including cataract) and cerebrovascular disease.[31] The most common AEs associated with immunosuppressants include cataracts, ocular hypertension, headache, fever, nausea, diarrhoea, fatigue, paraesthesia, tremors and systemic infection.[32,33] These can lead to substantial reductions in HRQoL for the patient and may also have an impact on the patient's family.

Significance for the NHS

Patients with uveitis often require referral to secondary care to confirm the diagnosis and for the provision of treatment. Patients require regular monitoring. There are substantial costs to the NHS and Personal Social Services (PSS) associated with treatment of the complications of uveitis and blindness, as well as treatment for the AEs associated with current practice. As the cause and presentation of uveitis varies between individuals, it is important for clinicians to have a range of treatment options available. In practice, a range of unlicensed immunosuppressants and corticosteroids are used to treat patients with uveitis. Clinical advisors to the AG suggest that dexamethasone (DEX) implants and adalimumab (ADA) are both used variably in current practice depending on funding availability. The number of patients who would be eligible for these treatments annually is uncertain, but Allergan and AbbVie, the manufacturers of DEX and ADA, respectively, estimate that it would be 589 and 175 patients respectively (see *Chapter 5*).

Measurement of disease

Outcome measures in uveitis may be grouped according to the different aspects that they measure: (1) disease activity or inflammation in the eye (e.g. VH, which is the degree of cloudiness in the vitreous humour, and acute cystoid macular oedema); (2) disease-associated tissue damage or complications (e.g. cataract, glaucoma, chronic cystoid macular oedema); (3) visual loss (e.g. visual acuity, visual field loss); and (4) patient-reported visual function (e.g. via the VFQ-25).[34]

There are some issues worth highlighting about outcome measurements in patients with uveitis. Vision loss has a complex interaction with visual acuity [which is a measure of central vision according to a validated measure such as the Early Treatment Diabetic Retinopathy Study (ETDRS) chart, Snellen chart or another similar tool[35]], visual field contrast sensitivity and colour vision. Visual acuity in patients with uveitis may reflect both the degree of intraocular inflammation and the extent of damage in the eye; whereas inflammation may vary over short time periods (days or weeks), damage may accrue slowly (months or years) and, with the important exception of cataract and acute cystoid macular oedema, is usually irreversible. It will be immediately evident that, whereas short-term effects on vision (related to inflammation) may be captured within a clinical trial, the commonly used time frames in studies are too short to capture important long-term consequences for vision of damage to the eye caused by inadequately controlled uveitis. This may lead to systematic underestimates of the effects of interventions for treating uveitis in clinical trials.

Markers of structural damage to the eye, such as macular oedema (swelling of the retina), cataract and glaucoma, are important outcomes because they are the mechanisms by which uveitis patients lose vision and they are objective measures. However, they may not be good markers of whether or not a treatment reduces inflammation because they indicate structural damage to the eye, which might not resolve when the inflammation is treated.

In clinical practice, a combination of several outcomes is used to assess the response of uveitic activity to treatment. Generally, outcomes related to uveitis are assessed by clinical examination (visual acuity, slit-lamp examination of AC cells, VH grading) and by imaging (e.g. optical coherence tomography).

The NEI system for VH grading and AC cell grading proposed by the SUN Working Group[8] is the 'current gold standard' for assessing intraocular inflammation (i.e. AC cell grade and VH grade).[36] The SUN system was a formalisation and adoption of the Nussenblatt scale.[8,37] Grading requires the examination of a patient's eye by an indirect ophthalmoscope followed by a comparison of the appearance with a series of photographs of varying grades of fundus VH.[37] Although the grading system is accepted by the US Food and Drug Administration and has been used in a number of recent studies of uveitis,[36] it is a subjective grading of cloudiness in the vitreous humour caused by inflammatory cells and cell debris on a non-continuous scale (0, 0.5+, 1, 2, 3 and 4+).[7,8,34,37] Its poor discriminatory property for detecting changes in the lower VH grades and extensive inter-rater variations have been reported to be limitations of this system.[29,36,38]

Inflammation in the AC is assessed on the basis of the number of cells per one field on standard slit-lamp examination or by high-speed optical coherence tomography.[8]

Complications of structural changes in the eye as a result of uveitis are typically reported according to the type of complication. For example, the SUN Working Group suggests that macular oedema could be determined by clinical examination and additional tests, for example optical coherence tomography or fluorescein angiography.[8] A patient is considered to have an increased or elevated intraocular pressure (IOP) if the pressure rises above a specified limit or increases from a baseline value in a study in which patients are followed over time (i.e. longitudinal data).[8] Although no consensus has been reached on the threshold for considering elevated IOP, an increase of $\geq$ 10 mmHg is considered to be important.[8] However, the SUN Working Group recommends the reporting of IOPs above the following thresholds: 21 mmHg (above the accepted upper limit of normal), 24 mmHg (associated with a significant risk of glaucoma) and 30 mmHg (when treatment for raised IOP is often started).[8]

Other outcomes reported in studies of patients with uveitis include generic utility measures such as the EQ-5D and vision-specific measures such as the VFQ-25.[39] These outcome measures capture broader considerations and hence may overcome some of the issues associated with the alternative outcome measures. The EQ-5D also allows treatments to be compared with treatments for other diseases and patient populations, although it may not be as sensitive as the VFQ-25.[40]

Current service provision

Non-infectious intermediate uveitis, posterior uveitis and panuveitis are initially treated with corticosteroids. Corticosteroids may be administered systemically (oral or parenteral) or locally via periocular or intravitreal injections or intravitreal implants. Additionally, if the front of the eye is also affected, topical corticosteroids and dilating eye drops may be offered. Systemic corticosteroids carry significant morbidity (e.g. cataract, glaucoma, diabetes, osteoporosis, weight gain, raised blood pressure) and long-term use above 7.5 mg per day is not recommended.[41,42]

In terms of second-line treatment, people with severe or chronic non-infectious uveitis whose disease has not adequately responded to corticosteroid treatment, for whom corticosteroids are not appropriate or whose uveitis recurs after tapering the corticosteroid dose may be given immunosuppressive drugs (such as methotrexate, mycophenolate mofetil, ciclosporin, tacrolimus and azathioprine). Immunosuppressive drugs can allow a reduction in the corticosteroid dose and associated complications. If the disease does not respond to these treatments or if they are not tolerated, especially in patients at high risk of losing their vision or those with systemic disease related to uveitis, biological tumour necrosis factor (TNF)-alpha inhibitors may be used. The majority of these treatments are not currently licensed.

There are currently no national guidelines on treating non-infectious uveitis; however, all three clinical advisors to the AG, who practise within different regions of the UK (Birmingham, Liverpool and Sheffield), were in agreement that the above description represents the general treatment pathway. This description is also consistent with three local treatment pathways, two referenced in the DEX submission from Allergan[43] (North East Retinal Group[4] and NHS Southern Derbyshire Clinical Commissioning Group[5]) and one obtained by personal communication from Alastair Denniston (West Midlands Regional Uveitis Service, August 2016). The general treatment pathway does not differ according to whether a patient has intermediate uveitis, posterior uveitis or panuveitis. However, specific treatment is individualised based on a broad range of factors. In particular, treatment depends on whether or not systemic disease is known to be present, whether or not any systemic disease is controlled (i.e. whether or not current inflammation is restricted to the eye) and whether the disease affects one or both eyes. *Figure 2* shows the general treatment pathway developed based on the three local treatment pathways and input from the clinical advisors to the AG.

For the purposes of this report, the following terminology is used:

- *Systemic disease*. Known underlying systemic disease related to the uveitis.
- *Active systemic disease*. Systemic disease that is currently requiring symptomatic treatment (in these patients, systemic treatment may be more appropriate to treat both the uveitis and the underlying disease).
- *No active systemic disease*. Either no systemic disease related to uveitis or systemic disease that is currently controlled (in these patients, treatment local to the eye may be more appropriate).
- *Local treatment/local pathway*. Treatments that are local to the eye (may be given to one or both eyes; little effect on systemic disease).
- *Systemic treatment/systemic pathway*. Treatments that are given systemically (and by their nature treat both eyes and may also treat systemic disease).
- *Unilateral*. Uveitis affecting one eye. This does not relate to treatment for one eye.

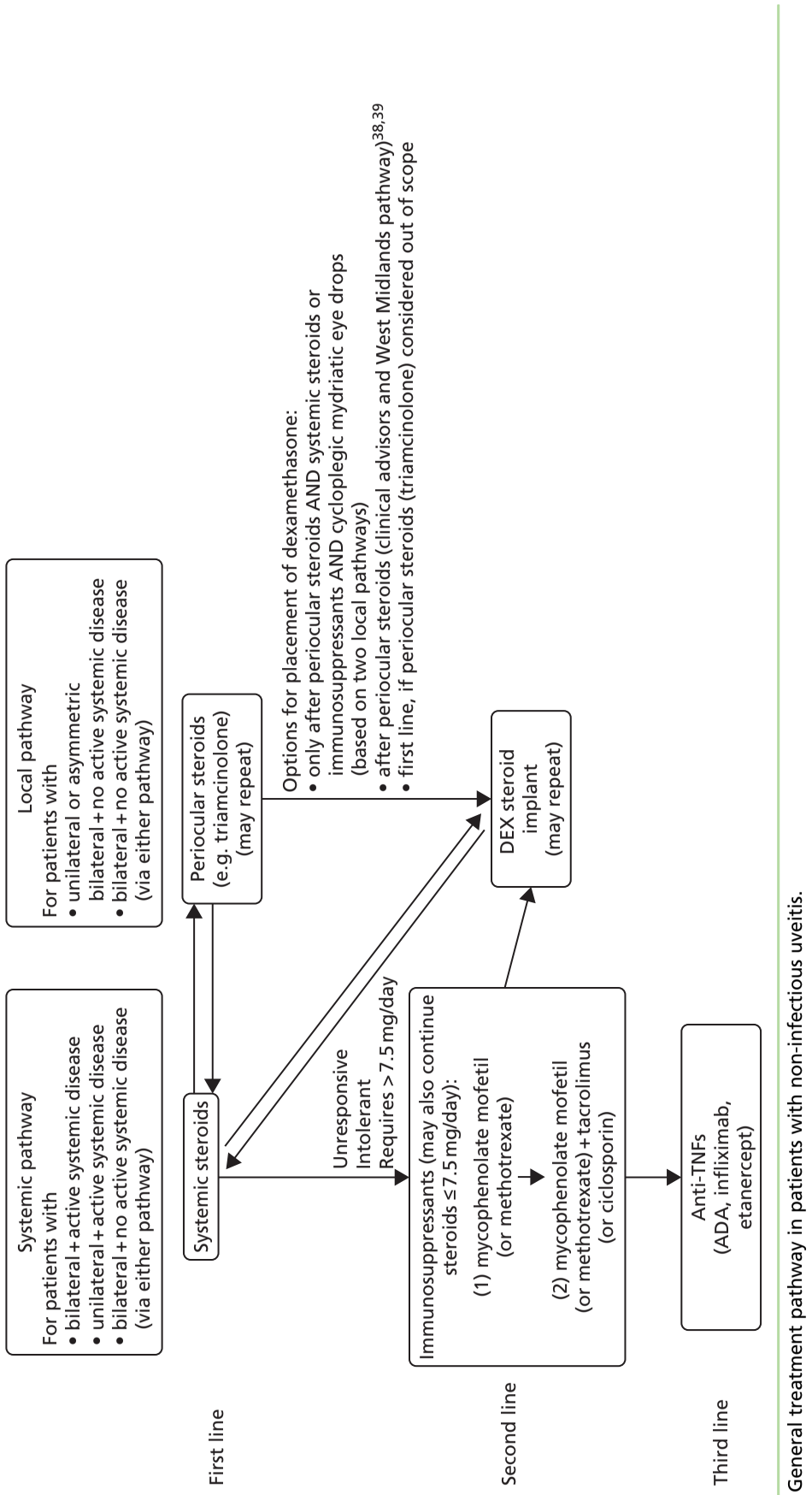

FIGURE 2 General treatment pathway in patients with non-infectious uveitis.

- *Bilateral*. Uveitis affecting both eyes. This does not relate to treatment for both eyes. In the case of local treatment, it may be for one or both eyes and will be referred to as such.
- *Legal blindness*. BCVA of ≤ 20/200 in the better-seeing eye and/or a visual field of ≤ 20°.

Description of the technologies under assessment

Adalimumab (Humira®; AbbVie Ltd, Maidenhead, UK) is a monoclonal antibody that inhibits the proinflammatory cytokine, TNF-alpha. ADA has a marketing authorisation from the European Medicines Agency (EMA) for the treatment of non-infectious intermediate uveitis, posterior uveitis and panuveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid sparing or in patients for whom corticosteroid treatment is inappropriate.[44] ADA is administered as a subcutaneous injection containing a 40-mg preparation of the active drug.

Dexamethasone intravitreal implant (Ozurdex®; Allergan Ltd, Marlow, UK) is a corticosteroid that suppresses inflammation by inhibiting the expression of proinflammatory mediators. The implant has a marketing authorisation from the EMA for treating adults with inflammation of the posterior segment of the eye presenting as non-infectious uveitis (i.e. intermediate uveitis, posterior uveitis and panuveitis). DEX intravitreal implant is a biodegradable ophthalmic implant that contains 0.7 mg of the active drug. Each implant is intravitreally administered using a single-use solid polymer drug delivery system or applicator.[45] The Summary of Product Characteristics (SmPC) for DEX notes that administration to both eyes concurrently is not recommended because of a lack of data.[45]

Place of the interventions in the treatment pathway

Clinical advisors to the AG and three local treatment pathways from the North East Retinal Group[4] and the NHS Southern Derbyshire Clinical Commissioning Group[5] (as referenced in the DEX submission[43]) and the West Midlands Regional Uveitis Service (Alastair Denniston, personal communication) were consulted to determine the place of the interventions in the treatment pathway. A general view was that DEX and ADA would generally not be used for the same patients or at the same point in the pathway. Treatments local to the eye (including the DEX implant) are considered to be appropriate for unilateral uveitis or asymmetric bilateral uveitis (when disease is more severe in one eye) when systemic disease is not present or is well controlled. Systemic treatments (including ADA) are considered to be appropriate to treat patients with bilateral uveitis (i.e. affecting both eyes) and/or active systemic disease. According to clinical advice provided to the AG, systemic treatments would generally not be given to a patient with unilateral uveitis and no active systemic disease because of the adverse effects associated with them. Patients with bilateral uveitis but no active systemic disease could be treated using either a local or a systemic approach. Although the inclusion criteria for the clinical trials of these drugs[46–48] were not limited by these factors, our clinical experts suggest that clinicians may have selected patients for the trials accordingly.

In addition, the licensing of ADA and DEX differ in that, to be eligible for ADA, patients must have had an inadequate response to corticosteroids or require steroid-sparing treatment or corticosteroid treatment must be inappropriate, whereas DEX implants can used as first-line treatment. Clinical advisors to the AG suggest that in practice it is likely that DEX would be used as second-line treatment following local or systemic treatment with corticosteroids, whereas ADA would be used as a third-line option for patients with insufficient control with, or intolerance to, systemic corticosteroids and immunosuppressants; however, for some patients this may be as a result of current funding availability rather than clinical need. *Figure 2* shows the general treatment pathway, indicating the most likely place of DEX and ADA (based on the opinion of the clinical advisors to the AG).

Although for most patients there is a clear clinical rationale for providing DEX and ADA at different points in the treatment pathway, the licensing allows both treatments to be given at overlapping points in the pathway (i.e. for patients with an inadequate response to corticosteroids, in need of corticosteroid sparing or in whom corticosteroid treatment is inappropriate),[44] although the DEX implant is also licensed in a less

restricted group.[45] This overlap is reflected somewhat by their use in clinical trials (see *Chapter 3*). *Table 2* presents the situations in which ADA and DEX may be used according to both licensing and clinical appropriateness. The most likely places in the pathway where these treatments would be used according to clinicians are shown in bold.

In addition to the issues described above, because uveitis covers a heterogeneous group of diseases, clinical advice suggests that maintaining a range of options is important depending on a patient's requirements.

Identification of important subgroups

The following have been identified as important subgroups that might affect the treatment offered:

- unilateral or bilateral uveitis
- the presence or absence of underlying autoimmune or inflammatory disease
- whether any underlying systemic disease is active or controlled
- existing treatment with long-term systemic immunosuppressants
- baseline visual acuity
- patients for whom systemic or local corticosteroid treatments are not appropriate.

Current usage in the NHS

Dexamethasone implants and subcutaneous ADA injections are both used variably in current practice, which may partly depend on funding availability and/or clinician and patient preference.

Anticipated costs associated with the interventions

Table 3 shows the 6-monthly costs of DEX and ADA. One DEX implant is expected to last around 6 months, based on observational trial data[18,50,51] and clinical advice. It should be noted that patients could receive

TABLE 2 Situations in which ADA and DEX may be used

Line of therapy (see *Figure 2*)	Unilateral (or temporary flare in one eye), no active systemic disease, local treatment appropriate	Bilateral, no active systemic disease, systemic or local treatment appropriate	Unilateral (or temporary flare in one eye), active systemic disease, systemic or local treatment appropriate	Bilateral, active systemic disease, systemic treatment appropriate
First line	DEX or ADA licensed if corticosteroid treatment is inappropriate			ADA licensed if corticosteroid treatment is inappropriate
Second line (after systemic corticosteroids)	**DEX** or ADA[a]	**DEX** or ADA[a]	**DEX** or ADA[a]	ADA
Third line (after systemic corticosteroids and immunosuppressants)	DEX or ADA[a]	DEX or **ADA**	DEX or **ADA**	**ADA**

a In practice ADA would be used only if there was a specific contraindication to DEX.

TABLE 3 Costs of ADA and the DEX vitreal implant

Drug	Licensed dose	Company	Cost (£)	Six-monthly cost (£)
ADA	40 mg once every 2 weeks	AbbVie	352.14	4578
DEX	One 0.70-mg implant	Allergan	870	870

Data from *British National Formulary*.[49]

more than one implant, either in succession or in the other eye, with staggered implementation; however, these options have not been assessed within a randomised controlled trial (RCT). ADA is administered every 2 weeks until treatment failure. In the VISUAL I trial of ADA in active patients, 50% of patients had failed on treatment by 6 months and 66% had failed by 1 year.[52] Clinical advisors to the AG suggest that some patients may remain on ADA treatment for many years.

Chapter 2 Definition of the decision problem

This study assessed the clinical effectiveness and cost-effectiveness of ADA (via subcutaneous injections) and a DEX intravitreal implant for treating inflammation of the posterior segment of the eye presenting as non-infectious uveitis. ADA is licensed for the treatment of non-infectious intermediate uveitis, posterior uveitis and panuveitis in adult patients who have had an inadequate response to corticosteroids or who are in need of corticosteroid-sparing therapy or for whom corticosteroid treatment is inappropriate, whereas DEX intravitreal implant is licensed for the treatment of adults with inflammation of the posterior segment of the eye presenting as non-infectious uveitis.

Decision problem

The decision problem was specified as in the following sections.

Population

- Adults (aged ≥ 18 years) with non-infectious intermediate uveitis, posterior uveitis or panuveitis.

Interventions

- Adalimumab (via subcutaneous injections).
- Dexamethasone intravitreal implant.

Relevant comparators

Relevant comparators included:

- periocular or intravitreal corticosteroid injections
- intravitreal corticosteroid implants
- systemic corticosteroids
- systemic immunosuppressive therapies including azathioprine, methotrexate, cyclophosphamide, ciclosporin, chlorambucil, tacrolimus, mycophenolate mofetil and TNF-alpha inhibitors
- intravitreal methotrexate
- best supportive care (when all other treatment options have been tried)
- placebo or a sham procedure.

Combinations of the above treatments were also considered as relevant comparators.

Outcomes

The following outcomes were considered relevant for this assessment:

- visual acuity (the affected eye)
- visual acuity (both eyes)
    - measured as the mean difference (MD) in BCVA according to a validated measure such as the ETDRS chart, Snellen chart or a similar tool
    - other measures of visual acuity would be considered if outcomes could be justified and validated in relation to accepted relevant standard measures
- improvement in disease activity (e.g. VH grade, AC cell grade)
- uveitis-related tissue damage or complications (e.g. cataract, macular oedema, retinal vascular occlusion)
- reduction in systemic steroid use

- mortality
- adverse effects of treatment
- HRQoL, including generic measures such as the EQ-5D and functional measures such as the VFQ-25
- composite end points incorporating more than one of the above.

Overall aims and objectives of the study

The aims of the study were to:

1. evaluate the clinical effectiveness and safety of ADA subcutaneous injection and DEX intravitreal implant within their marketing authorisations for treating non-infectious intermediate uveitis, posterior uveitis or panuveitis in adults
2. estimate the incremental cost-effectiveness of ADA subcutaneous injection and DEX intravitreal implant within their marketing authorisations for treating non-infectious intermediate uveitis, posterior uveitis or panuveitis compared with each other and with current treatment
3. estimate the expected overall costs of ADA and DEX in England
4. identify key areas for primary research.

Chapter 3 Assessment of clinical effectiveness

A systematic review was undertaken to assess the clinical effectiveness and safety of ADA subcutaneous injection and DEX intravitreal implant within their marketing authorisations in adults with non-infectious intermediate uveitis, posterior uveitis or panuveitis. The review of the evidence of clinical effectiveness was carried out in accordance with the principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[53] First, the methods used in the systematic review of the clinical effectiveness evidence are presented. The results of the review are then reported followed by a summary of the results.

Methods for reviewing effectiveness

A registered protocol of this systematic review (CRD42016041799) is available on the PROSPERO website at www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016041799 (accessed 1 September 2016).

Identification of studies

The scope of the searches took into account the potential need to make simultaneous comparisons between all interventions, including, when appropriate, a network meta-analysis (NMA). The search strategy was designed to identify RCTs and systematic reviews of the relevant interventions, ADA and DEX intravitreal implant, as well as studies reporting on any comparators relevant to the scope, in patients with non-infectious intermediate uveitis, posterior uveitis and/or panuveitis. Given the broad range of possible comparators, the searches consisted only of terms for 'uveitis' combined with search filters for relevant study types and did not include terms for the interventions.

The search strategy consisted of medical subject headings (MeSH) or EMTREE Thesauri terms and free-text synonyms for 'uveitis'. Searches were translated across databases and were not limited by language or publication date. Search strategies are presented in *Appendix 1*. Search filters designed to retrieve clinical trials, systematic reviews and economic evaluations were used in MEDLINE and other databases when appropriate.

Electronic database searches

The search approach involved the following:

- searching of electronic databases and clinical trials registries
- contact with experts in the field
- examination of bibliographies of retrieved papers.

The following electronic databases and clinical trials registries were searched from inception for RCTs and systematic reviews:

- MEDLINE (via Ovid) (1946 to 2016)
- MEDLINE Epub Ahead of Print, MEDLINE In-Process & Other Non-Indexed Citations (via Ovid) (1946 to 2016)
- EMBASE (via Ovid) (1974 to 2016)
- Cochrane Database of Systematic Reviews (CDSR) (via Wiley Online Library) (1996 to 2016)
- Database of Abstracts of Reviews of Effects (DARE) (via Wiley Online Library) (1995–2015)
- Cochrane Central Register of Controlled Trials (CENTRAL) (via Wiley Online Library) (1995 to 2016)
- Health Technology Assessment (HTA) database (via Wiley Online Library) (1995 to 2016)
- NHS Economic Evaluation Database (NHS EED) (via Wiley Online Library) (1995–2015)
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) (via EBSCO*host*) (1982 to 2016)

- Conference Proceedings Citation Index (CPCI) (Thomson Reuters) (1990 to June 2016)
- the WHO's International Clinical Trials Registry Platform [see http://apps.who.int/trialsearch/ (accessed 15 June 2016)].

Literature searching was undertaken in June 2016. Further searches were conducted in MEDLINE and CINAHL in October 2016.

Supplementary searches

References of relevant systematic reviews, primary studies and company submissions were checked to identify additional studies. Citation searching using Web of Science Citation Index (Thomson Reuters, 1899 to June 2016) was also undertaken. Searches were also conducted in Toxicology Literature Online (TOXLINE) in October 2016 to identify records reporting AEs for the technologies of interest.

Inclusion and exclusion criteria

The inclusion and exclusion criteria for selecting studies with relevant clinical effectiveness and safety data for ADA subcutaneous injection, DEX intravitreal implant or clinically relevant comparators in adults with non-infectious intermediate uveitis, posterior uveitis or panuveitis were consistent with the decision problem outlined in the National Institute for Health and Care Excellence (NICE) scope.[54]

Population

The population of interest was adults with non-infectious intermediate uveitis, posterior uveitis or panuveitis. Eligible participants were considered for inclusion regardless of type of non-infectious posterior segment-involving uveitis (i.e. active or inactive uveitis; unilateral or bilateral uveitis; presence or absence of uveitis-related systemic disease or previous treatments for uveitis). Patients with infectious uveitis or uveitis as part of a masquerade syndrome were excluded from this review. In terms of patient age, studies were eligible if the enrolled patients were aged $\geq$ 18 years, or if separate data were provided for adults, or if at $\geq$ 80% of patients were adults. Studies conducted in paediatric populations were excluded.

Intervention

Interventions of interest were subcutaneous injection of ADA (40 mg) and DEX intravitreal implant (0.7 mg).

Comparators

Relevant comparators considered were as outlined in the NICE scope.[54] Studies reporting a comparison between subcutaneous injection of ADA and DEX intravitreal implant or between one of these interventions and any of the following comparator treatments were considered for inclusion:

- periocular or intravitreal corticosteroid injections
- intravitreal corticosteroid implants
- systemic corticosteroids
- systemic immunosuppressive therapies including azathioprine, methotrexate, cyclophosphamide, ciclosporin, chlorambucil, tacrolimus, mycophenolate mofetil and TNF-alpha inhibitors
- intravitreal methotrexate
- best supportive care (when all other treatment options have been tried)
- placebo or a sham procedure.

In addition, studies reporting on any of the comparator treatments were considered for inclusion in a potential NMA.

Combinations of the above-mentioned interventions were also considered as relevant comparators.

Comparative studies in uveitis including interventions not specifically covered in the scope, or not considered to be clinically relevant comparators following consultation with clinical advisors to the AG, were excluded from the review. Excluded interventions included sirolimus, secukinumab, bevacizumab, acetazolamide, diclofenac, lisinopril, vitamin E, retinal antigens, echinacea and vitrectomy.

Outcomes

Outcomes of interest were:

- visual acuity (the affected eye)
- visual acuity (both eyes)
    - measured as the MD in BCVA according to a validated measure such as the ETDRS chart, Snellen chart or a similar tool
    - other measures of visual acuity would be considered if outcomes could be justified and validated in relation to accepted relevant standard measures
- improvement in disease activity (e.g. VH grade, AC cell grade)
- uveitis-related tissue damage or complications (e.g. cataract, macular oedema, retinal vascular occlusion)
- reduction in systemic steroid use
- mortality
- adverse effects of treatment
- HRQoL, including generic measures such as the EQ-5D and functional measures such as the VFQ-25
- composite end points incorporating more than one of the above.

Study design

Data from RCTs were considered to be the most relevant for inclusion in the systematic review of the clinical effectiveness and safety of ADA subcutaneous injection and DEX intravitreal implant.

In addition, the DEX company submission[43] included efficacy and safety data from non-randomised retrospective studies of 0.7 mg of dexamethasone (DEX 700) for non-infectious posterior segment-involving uveitis, reported in English, which included at least 10 patients. These data are summarised here for information, as some non-RCTs assessed DEX repeat implants (in the same eye) or implants in both eyes, whereas the RCT of DEX assessed only one implant in one eye per patient. It was beyond the scope of this assessment to undertake further searches or check the study selection and data extraction process undertaken within the DEX company submission. Non-randomised studies of ADA are not included here as they were not provided in the company submission[55] and it was beyond the scope of this assessment to undertake a de novo review of non-randomised studies of ADA.

The following publication types were excluded from the review: narrative reviews, systematic reviews, clinical guidelines, editorials, letters, opinion pieces, abstracts with insufficient detail to assess study quality or results and non-English-language articles. Studies of animal models and preclinical and biological studies were not included.

Study selection process

Study selection was undertaken using a two-stage process guided by prespecified inclusion and exclusion criteria, as presented in the previous section.

All retrieved records were exported into a reference management database (EndNote version X7; Thomson Reuters, CA, USA). After deduplication, records were assessed for relevance by initially examining titles/abstracts, followed by a detailed scrutiny of the related full-text versions of potentially includable studies. At each step, studies that did not satisfy the eligibility criteria were excluded. One reviewer (EP or KC) checked a set of records; this was followed by a 10% check of selected studies by a second reviewer (KC or EP). Disagreements were resolved by discussion and involvement of a third researcher (HS) if needed.

Data extraction

Data were extracted by one reviewer (EP or KC) using a standardised piloted data extraction form and checked by a second reviewer (KC or EP). Disagreements were resolved by discussion. Data relevant to the decision problem were extracted, with no blinding to authors or journal. In relation to the interventions of

interest, namely ADA and DEX, data extraction was limited to patients randomised to treatment arms with doses consistent with their licensed indications. Extracted information for each study included the study name (when reported), first author with publication year, characteristics of the study population, interventions, comparators and outcomes. When multiple publications of the same study were identified, data were extracted and reported as a single study.

Quality assessment

The methodological quality of each included study was assessed using an adapted Cochrane risk-of-bias tool.[56] Quality assessment was undertaken by one reviewer (EP or KC) and checked by a second reviewer (KC or EP).

Data synthesis

It was initially anticipated that, to compare the interventions of interest with each other and with current standard care, pairwise meta-analyses and/or NMAs may be undertaken, depending on the availability of relevant RCTs with common comparators reporting consistent outcomes. However, conducting pairwise meta-analyses or NMAs was not possible for the reasons presented in *Indirect comparison of treatments: rationale for not undertaking*. Data from studies contributing to the review were therefore summarised and presented using tabular and narrative syntheses. Summary statistics, for example MDs between treatments for continuous outcomes and relative risks (RRs) for binary outcomes, were calculated if not provided in the study reports.

Results of the clinical effectiveness review

Quantity and quality of research available

Literature searches retrieved 10,585 records (10,582 from the database searches and three from searching reference lists). A total of 10,451 records were excluded at title and abstract stage. Of the 134 full-text articles obtained for detailed examination, 117 were excluded because they did not meet the eligibility criteria for the review. Details of the excluded full-text articles with reasons for exclusion are presented in *Appendix 2*. Seventeen potentially relevant articles (relating to 16 studies) were retained for potential inclusion in meta-analyses; 13 studies[32,33,57–67] were related to comparators within the scope of the review and three studies (four articles[46–48,68]) evaluated ADA or DEX 700. It was not possible to include any of the 13 studies of comparators within a NMA (the reasons why this was not possible, and a summary of the 13 studies, are provided in *Indirect comparison of treatments: rationale for not undertaking* and *Table 24*). This section therefore focuses specifically on studies of DEX 700 and ADA. The selection of studies informing the clinical effectiveness review is summarised in *Figure 3*. An example data extraction form is provided in *Appendix 3* and the criteria for the assessment of methodological quality are provided in *Appendix 4*.

Assessment of effectiveness

Study characteristics

The characteristics of the two included studies of ADA and the one included study of DEX 700 in patients with non-infectious uveitis are summarised in *Table 4*.

All three included studies were international, multicentre RCTs conducted in regions including Europe, North America and Australia.

Two trials, VISUAL I[46] ($n = 223$ patients) and VISUAL II[47] ($n = 229$ patients), compared ADA administered subcutaneously as an 80-mg loading dose followed by 40 mg every other week with a corresponding placebo treatment in patients with active (VISUAL I)[46] or inactive (VISUAL II)[47] non-infectious intermediate uveitis, posterior uveitis or panuveitis. The treatment and follow-up period had a duration of up to 80 weeks (18 months) or until treatment failure. Main study data were available for 223 patients with active uveitis (67 study sites)[46,52,55] and 229 patients with inactive uveitis (62 study sites).[47,55,72] The VISUAL I and VISUAL II

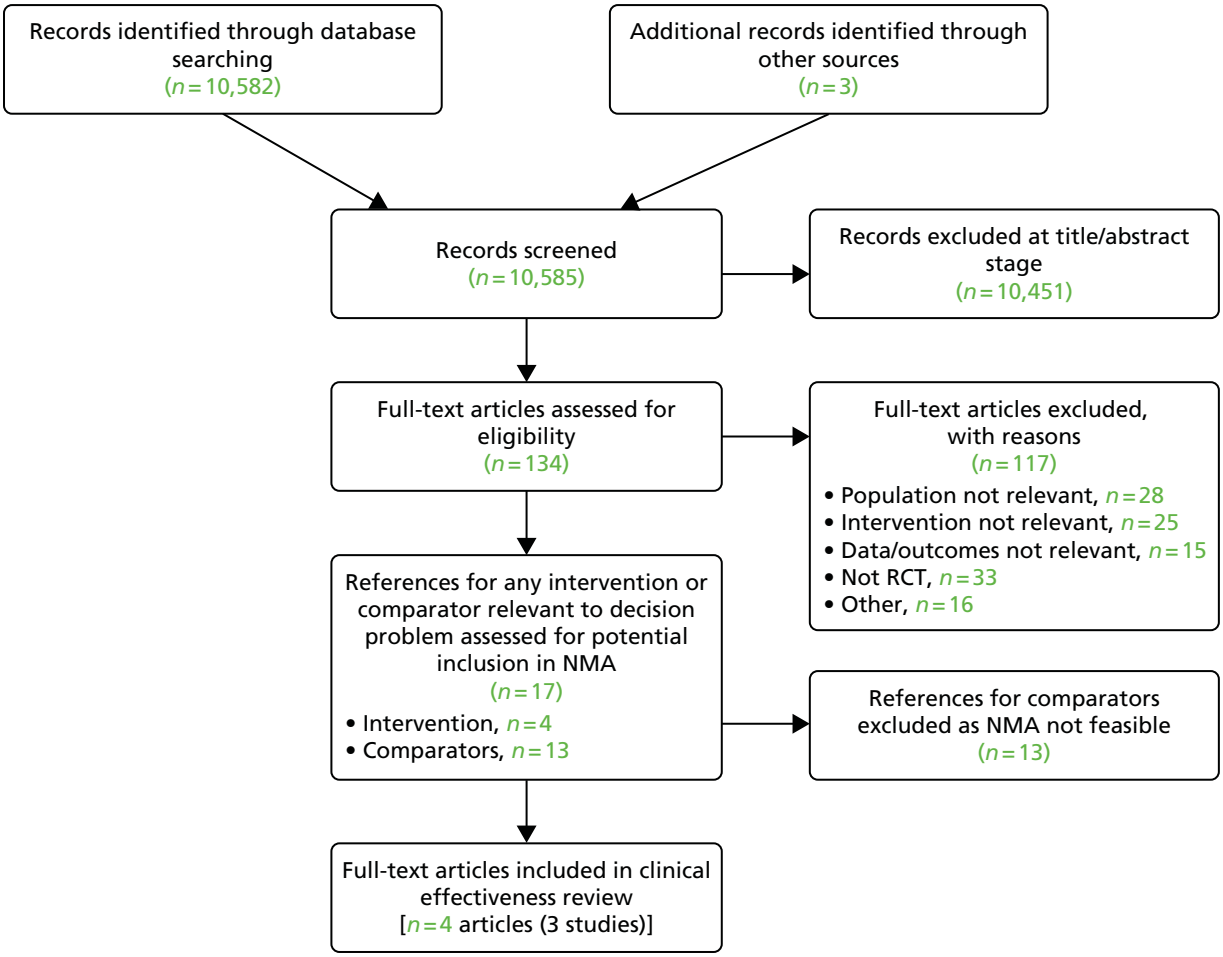

FIGURE 3 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart.

trials also included a subpopulation of patients from Japan ($n = 16$ and $n = 32$ patients respectively).[55] Data for this subgroup were not included in related publications[46,47] or the company submission.[55]

One study, HURON[48] (46 study sites; $n = 229$ patients), a 26-week Phase III trial, evaluated the effectiveness of two different dosages of DEX intravitreal implants, DEX 700 and DEX 350 (0.35 mg), compared with a sham procedure in patients with active, chronic non-infectious intermediate and posterior uveitis. Only data relating to the licensed DEX 700 arm are included in this review.

Patient characteristics

Patients included in the HURON trial[48] (mean age 44.8 years) were slightly older than those included in the VISUAL I[46] and VISUAL II[47] trials (mean age 42.7 and 42.5 years respectively). The proportion of women varied from 57%[46] to 63%.[48]

Inclusion criteria for patients with active uveitis in the VISUAL I trial[46] were based on the manifestation of one or more of the following: VH score of ≥ 2; AC cell grade of ≥ 2 and/or active inflammatory chorioretinal or retinal vascular lesions while on high-dose oral corticosteroids (10–60 mg/day) for ≥ 2 weeks. Inactive uveitis in patients included in the VISUAL II trial[47] was characterised by a VH score of ≤ 0.5 and an AC cell grade of ≤ 0.5, with no active inflammatory chorioretinal or retinal vascular lesions (i.e. uveitis inactivity), while receiving 10–35 mg/day of oral prednisone or its equivalent to maintain an inactive state of inflammation ≥ 28 days before study entry. Patients were considered for inclusion if control of their disease was corticosteroid dependent, that is, they had had more than one uveitic flare in the past 18 months occurring within 1 month of tapering steroids. In the HURON trial,[48] active intraocular inflammation was based on the presence of a VH score of $\geq 1.5+$ and patients unresponsive to previous treatment with corticosteroids were excluded.[48]

TABLE 4 Summary of the study characteristics of the included studies

Study, company, study dates, setting	Population: sample size, mean age, % of females, type of uveitis	Population: diagnosis	Intervention and comparator	Previous treatments	Concomitant treatments	Outcomes
• VISUAL I (NCT01138657)[46,55,69] • AbbVie • August 2010–August 2014 • 67 sites, 18 countries[a]	• $n = 223$,[b] age 42.7 years, 57% female ($n = 217$ analysed) • Active uveitis[c] • Intermediate 22%, posterior 33%, pan 45% • Bilateral 91%, unilateral 9% • Duration (months), mean (SD): intervention 40.2 (51.3), comparator 51.0 (72.2)	Idiopathic 37% ($n = 81/217$), sarcoidosis 8% ($n = 18/217$), Behçet's disease 7% ($n = 16/217$), VKH 12% ($n = 25/217$), birdshot chorioretinopathy 20% ($n = 44/217$), multifocal choroiditis and panuveitis 5% ($n = 11/217$), other 10% ($n = 22/217$)	• Intervention: ADA subcutaneous injection, 80-mg loading dose followed by 40-mg dose every other week • Comparator: placebo	All patients: high-dose oral corticosteroids	• All patients: oral prednisone 60 mg/day tapered to 0 mg by week 15 • PRN: topical corticosteroids, discontinued by week 9; immunosuppressants (maximum one): azathioprine 4% ($n = 8/217$), ciclosporin 6% ($n = 13/217$), mycophenolate mofetil or similar 12% ($n = 25/217$), methotrexate 10% ($n = 21/217$)	• Primary outcome: TTF (worsening of one or more of AC grade, VH grade, BCVA or inflammatory retinal or chorioretinal vascular lesions) at/after week 6, one or more eyes • Secondary outcomes: BCVA (logMAR), change in VH or AC grade, % change in CRT, time to MO, change in VFQ-25 score, AEs
• VISUAL II (NCT01124838)[47,55,70] • AbbVie • August 2010–May 2015 • 72 sites, 22 countries[d]	• $n = 229$,[e] age 42.5 years, 61% female ($n = 226$ analysed), 18 patients from the UK • Inactive uveitis[f] • Intermediate 21%, posterior 33%; pan 46% • Bilateral 96%, unilateral 4% • Duration (months), mean (SD): intervention 59.5 (64.5), comparator 62.9 (67.7)	Idiopathic 31% ($n = 69/226$), sarcoidosis 14% ($n = 32/226$), Behçet's disease 7% ($n = 16/226$), VKH 23% ($n = 51/226$), birdshot chorioretinopathy 13% ($n = 30/226$), multifocal choroiditis and panuveitis 3% ($n = 7/226$), other 9% ($n = 21/226$)	• Intervention: ADA subcutaneous injection, 80-mg loading dose followed by 40-mg dose every other week • Comparator: placebo	All patients: high-dose oral corticosteroids	• All patients: oral prednisone 10–35 mg/day tapered to 0 mg by week 19 or earlier • PRN: topical corticosteroids, discontinued by week 9; immunosuppressants (maximum one): azathioprine 6% ($n = 14/226$), ciclosporin 12% ($n = 26/226$), mycophenolate mofetil or similar 15% ($n = 34/226$), methotrexate 15% ($n = 33/226$)	• Primary outcome: TTF (worsening of one or more of AC grade, VH grade, BCVA or inflammatory retinal or chorioretinal vascular lesions) at after week 2, one or more eyes • Secondary outcomes: BCVA (logMAR), change in VH or AC grade, % change in CRT, time to MO, change in VFQ-25 score, AEs

Study, company, study dates, setting	Population: sample size, mean age, % of females, type of uveitis	Population: diagnosis	Intervention and comparator	Previous treatments	Concomitant treatments	Outcomes
• HURON (NCT003338)[48,68,71] • Allergan • May 2006–October 2008 • 46 sites, 18 countries	• $n = 229$,[g] age 44.8 years, 63.3% female (153 of analysed sample included) • Active uveitis • Intermediate 81%, posterior 19% • Bilateral NR, unilateral NR • Duration (months), mean (SD): intervention[h] 50.5 (54.2), comparator 61.2 (62.5)	None specified (no patients had uncontrolled systemic conditions)	• Intervention: single-dose, DEX intravitreal implant, 0.7 mg or 0.35 mg • Comparator: sham injection	• All patients: none specified • Systemic immunosuppressant or anti-inflammatory treatment at baseline 25% ($n = 38/153$)	• PRN (stable dose): corticosteroids (topical or systemic); immunosuppressants; topical NSAIDs • Rescue medication:[i] intravitreal/periocular steroids or systemic medication for uveitis (new or increased)	• Primary outcome: % of patients with VH = 0 at week 8 • Secondary outcomes: % of patients with a ≥ 15-letter improvement in BCVA, % of patients with a ≥ 10-point improvement in VFQ-25 score, change in CRT

CRT, central retinal thickness; logMAR, logarithm of the minimum angle of resolution; MO, macular oedema; NR, not reported; NSAID, non-steroidal anti-inflammatory drug; pan, panuveitis; PRN, pro re nata; SD, standard deviation; TTF, time to treatment failure.

a Patients included in a substudy in Japan ($n = 16$, seven sites) were excluded from the analyses of outcomes in this study because of regional heterogeneity.
b 217 patients analysed as an intention-to-treat population.
c Active uveitis was characterised by the presence of a VH score of ≥ 2 and/or an AC cell grade of ≥ 2 and/or active inflammatory chorioretinal or retinal vascular lesions while on oral corticosteroids (10–60 mg/day) for ≥ 2 weeks.
d Patients included in a substudy in Japan ($n = 32$, 10 sites) were excluded from the analyses of outcomes in this study.
e 226 patients reported in the AbbVie submission.
f Inactive uveitis was defined as an AC cell or a VH grade of ≤ 0.5+ without evidence of active inflammatory chorioretinal or retinal vascular lesions and receiving 10–35 mg/day of oral prednisone to maintain inactivity, ≥ 28 days before study entry.
g 153 patients in relevant groups, patients randomised to DEX 700 and sham procedure.
h Treatment received by patients in this study arm was DEX 700.
i Rescue medications were permitted if VH increased by ≥ 1 between week 3 and week 8 or VH was ≥ 1.5 between week 8 and week 26.

The mean duration of uveitis was shorter in the active treatment arms than in the comparator arms across all three studies (40.2 vs. 51.0 months for VISUAL I,[46] 59.5 vs. 62.9 months for VISUAL II[46] and 50.5 vs. 61.2 months for HURON[48]). Intermediate uveitis was the most common site of inflammation in patients (81% of patients) in the HURON trial,[48] whereas panuveitis was seen more frequently in patients in the VISUAL trials[46,47] (approximately 46% panuveitis vs. 22% intermediate uveitis vs. 33% posterior uveitis). Uveitis-related systemic conditions reported for patients in the VISUAL trials[46,47] included Behçet's disease, sarcoidosis and VKH. More patients with active uveitis had no diagnosed systemic condition (73%) than those with inactive uveitis (56%) in the VISUAL trials.[46,47] Limited information about relevant coexisting systemic conditions was provided for the HURON trial in the journal article,[48] company submission[43] or clinical study report,[71] only that no patients had uncontrolled systemic conditions. Over 90% of patients in the VISUAL trials[46,47] presented with bilateral uveitis; outcomes in the left and right eyes were considered separately and were then averaged across eyes in the analysis of the study findings. Conversely, in the HURON trial,[48] the proportion of patients with bilateral uveitis was not reported (the AG queried this and was informed by the company that these data were not collected). In patients with bilateral uveitis, the right eye was selected for treatment; only the study eye was analysed for relevant outcomes. Overall, 84% of patients received treatment in the worse-seeing eye.

Study treatment and follow-up

The active treatment in the HURON trial[48] was a single DEX intravitreal implant. The study compared the licensed dose of 0.7 mg (DEX 700, $n = 77$ patients, reported here) and a dose of 0.35 mg (DEX 350, $n = 76$ patients, not reported here) with a sham procedure ($n = 76$ patients). One implant was received per patient; no repeat implants were given during the 26-week follow-up period and patients had an implant in only one eye.

The active treatment evaluated in the VISUAL trials[46,47] was ADA. Patients randomised to the study arms ($n = 111$[46] and 115[47] patients) received a loading dose of 80 mg by subcutaneous injection and then a 40-mg dose, repeated every other week.[46] A corresponding placebo was administered to patients in the comparator arms ($n = 112$[46] and 114[47] patients). For patients with active uveitis,[46] visits during the study were scheduled at baseline and weeks 1, 4, 6 and 8. Subsequently, further visits occurred every 4 weeks until the primary end point (treatment failure) was achieved or until completion of 80 weeks of treatment. The treatment and follow-up duration was therefore up to 80 weeks (18 months) or until treatment failure. The median duration of treatment and follow-up in the VISUAL I trial[46] was 19 weeks for ADA and 13 weeks for placebo. In the VISUAL II trial,[47] the median duration of treatment and follow-up was 35 weeks for ADA and 22 weeks for placebo. There was a longer duration of ADA treatment in both studies because patients in the placebo groups met the treatment failure end points earlier than patients in the ADA groups and were taken off treatment.

Previous treatments and concomitant treatments

All patients in the VISUAL trials[46,47] had previously received high-dose oral corticosteroids (> 10 mg/day of prednisone or its equivalent) prior to study entry. Within the VISUAL I trial,[46] all patients received standardised oral prednisone (60 mg/day; hereafter referred to as a steroid burst) from randomisation, which was gradually tapered to 0 mg by week 15 of the study. Furthermore, topical corticosteroids were permitted but were tapered and discontinued by week 9. In the VISUAL II trial,[47] all patients were already receiving oral prednisone (10–35 mg/day); this was tapered to 0 mg by week 19 or earlier depending on the steroid dose at baseline. During the study, patients were eligible to receive at least one immunosuppressant including azathioprine, ciclosporin, mycophenolate mofetil or methotrexate, at the discretion of the study investigator(s).

Limited information on prior and concomitant treatments for uveitis was reported in the HURON trial,[48] although one-quarter of patients in the relevant population (DEX 700 and sham groups) for this review had received or were using systemic immunosuppressants or anti-inflammatory treatment at baseline ($n = 38/153$, 25%). The company did, however, provide patient-level data, which showed that treatment received was generally similar across arms but that more patients received immunosuppressant rescue therapy in the sham arm (10.5%) than in the DEX 700 arm (1.3%).

In the HURON trial,[48] patients were permitted to receive different treatments at the discretion of the investigator(s) if they were indicated. Permitted treatments before the study and at baseline as well as during the study included the following:[71]

- perioperative prophylactic antibiotics (at the visit prior to implantation and 3 days postoperatively)
- IOP-lowering treatments (if IOP was > 30 mmHg in the study eye)
- topical corticosteroids or non-steroidal anti-inflammatory drugs (NSAIDs) in the study eye (if doses remained stable for ≥ 2 weeks before screening, were stable throughout the study visits and were anticipated to remain stable up to week 8)
- intravitreal, topical or periocular corticosteroids in the non-study eye (if inflammation occurred in the non-study eye)
- cycloplegics (indication not specified)
- cataract surgery (if reduced visual acuity had a limiting impact on the patient, the cataract interfered with uveitis management and/or the cataract resulted in local inflammation or glaucoma; the decision to operate was at the discretion of the investigator and patient and a delay to surgery until after week 26 was encouraged)
- systemic immunosuppressants, for example methotrexate or ciclosporin (if doses remained stable for ≥ 3 months before screening, were unchanged throughout study visits and were anticipated to remain stable up to week 8)
- systemic corticosteroids, for example oral prednisone or equivalent (if doses remained stable and were ≤ 20 mg/day at ≥ 1 month before screening, were stable throughout study visits and were anticipated to remain stable up to week 8)
- oral NSAIDs (indication not specified).

Within the HURON trial,[48] new treatment or previous management requiring dose escalation with systemic corticosteroids or immunosuppressants or local (intravitreal, periocular and topical) corticosteroids was permitted only if any of these interventions was administered as rescue treatment. In general, rescue anti-inflammatory treatments were permissible if the VH score increased by ≥ 1 unit from week 3 to the start of week 8 and if VH = 1.5+ was recorded from week 8 to week 26.[48] Other rescue medications included anticoagulants and surgical procedures on the study eye.[48,71]

Study outcomes

The primary study end point varied across the studies:

- In the VISUAL I[46] trial of ADA for active uveitis, the primary end point was time to treatment failure, a composite outcome including worsening of at least one of the following in one or more eyes (from best state achieved following the steroid burst, on or after week 6): AC cell grade, VH grade, BCVA or new active inflammatory retinal or chorioretinal vascular lesions.
- In the VISUAL II[47] trial of ADA for inactive uveitis, the primary end point was time to treatment failure, a composite outcome including worsening of at least one of the following in one or more eyes (from baseline, on or after week 2): AC cell grade, VH grade, BCVA or new active inflammatory retinal or chorioretinal vascular lesions.
- In the HURON[48] trial of DEX, the primary outcome was the proportion of patients with a VH score of zero at week 8 in the study eye (outcomes were also measured up to week 26).

Outcomes reported in the included studies and grading criteria for intraocular inflammation are presented in *Tables 5* and *6* respectively.

Secondary outcomes for the VISUAL I trial[46] (see *Table 5*) were measured from the best state prior to week 6 (following the steroid burst), whereas secondary outcomes for the VISUAL II trial[47] were measured from baseline. Secondary outcomes in the VISUAL trials were measured only up to treatment failure or the study end and, as treatment failure occurred in more patients in the placebo arms than in the ADA arms, the

TABLE 5 Reported efficacy outcomes in the included studies

Outcome	Assessment method
***VISUAL I*[46]**	
Primary outcome (composite end point): time to treatment failure at or after 6 weeks – evidence of one or more of the following in one or more eyes	
AC cell grade: ≥ 0.5+ (at 6 weeks); two-step or greater increase in AC cell grade relative to best state achieved (after 6 weeks)	DIO, graded by SUN criteria
VH grade: ≥ 0.5+ (at 6 weeks); two-step or greater increase in VH grade relative to best state achieved (after 6 weeks)	DIO, graded by NEI/SUN criteria
New active, inflammatory chorioretinal or retinal lesions compared with baseline	DIO
Worsening of BCVA by ≥ 15 letters compared with best score previously observed	LogMAR units using ETDRS chart
***VISUAL II*[47]**	
Primary outcome (composite end point): time to treatment failure on or after 2 weeks – evidence of one or more of the following in one or more eyes	
New active, inflammatory chorioretinal or retinal lesions compared with baseline	DIO
AC cell grade: two-step or greater increase relative to baseline	DIO, graded by SUN criteria
VH grade: two-step or greater increase relative to baseline	DIO, graded by NEI/SUN criteria
Worsening of BCVA by ≥ 15 letters relative to baseline	LogMAR units using ETDRS chart
***VISUAL I and VISUAL II*[46,47,73]**	
Secondary outcomes: VISUAL I from best state achieved prior to week 6 to final or early termination visit; VISUAL II – from baseline to final or early termination (all measured for left and right eyes separately and then treatment effects averaged across eyes)	
Change in AC cell grade in each eye	DIO, graded by SUN criteria
Change in VH score in each eye	DIO, graded by NEI/SUN criteria
Change in BCVA in each eye	LogMAR units using ETDRS chart
Time to develop MO in at least one eye	Assessed in patients without MO at baseline
% change in CRT in each eye	Stratus OCT (Carl Zeiss Meditec, Inc., Dublin, CA, USA); Cirrus HD-OCT (Carl Zeiss Meditec, Inc., Dublin, CA, USA) or Spectralis (Heidelberg Engineering, Franklin, MA, USA)
Change in generic and vision-specific quality of life in each eye	EQ-5D score; VFQ-25 composite score, near vision subscore, distance vision subscore, ocular pain subscore
Disease quiescence	Absence of new active inflammatory lesions with AC cell and VH grade of ≤ 0.5+
***HURON*[43,48,71]**	
Primary outcome (all in study eye only)	
VH score = 0 at week 8	Scores consistent with published colour photographic scale
Secondary outcomes (all in study eye only)	
BCVA	AREDS-adapted ETDRS chart
Central macular thickness	OCT (at least six scans required at selected sites)
Early treatment failure	VH increase of ≥ 1 unit from baseline at week 3
Late treatment failure	VH ≥ 1.5+ at week 8 or after week 8

TABLE 5 Reported efficacy outcomes in the included studies (*continued*)

Outcome	Assessment method
Use of escape medications	Medications administered to patients with early or late treatment failure
Patient-reported outcomes	VFQ-25 composite score and subscores

AREDS, Age Related Eye Disease Study Research Group; CRT, central retinal thickness; DIO, dilated indirect ophthalmoscopy; HADS, Hospital Anxiety and Depression Scale; logMAR, logarithm of the minimum angle of resolution; OCT, optical coherence tomography; MO, macular oedema.

TABLE 6 Grading criteria for intraocular inflammation in the included studies

AC cell score		VH grade			
VISUAL I and II[46,47]		VISUAL I and II[46,47]		HURON[48]	
Grade	Criteria (number of cells)[a]	Grade	Criteria	Grade[b]	Criteria
0	< 1	0	No evident VH	0	No inflammation
0.5+	1–5	0.5+	Slight blurring of the optic disc margin because of the haze; normal striations and reflex of the nerve fibre layer cannot be visualised	+0.5	Trace inflammation (slight blurring of the optic disc margins and/or loss of the nerve fibre layer reflex)
1+	6–15	1+	Permits a better definition of both the optic nerve head and the retinal vessels (compared with higher grades)	+1	Mild blurring of retinal vessels and the optic nerve
2+	16–25	2+	Permits better visualisation of the retinal vessels (compared with higher grades)	+2	Moderate blurring of the optic nerve head
3+	26–50	3+	Permits the observer to see the optic nerve head, but the borders are quite blurry	+3	Marked blurring of the optic nerve head
4+	> 50	4+	Optic nerve head is obscured	+4	Optic nerve head not visible

a Assessed according to field size of 1 mm^2 of slit beam.[8]
b In the HURON trial, a modified grade of 1.5+ was introduced, which was assessed on the basis of optic nerve head and posterior retina view obstruction of > +1 but < +2.

results may have been worse in the placebo arms at the point of outcome measurement. The last observation carried forward (LOCF) method was used for dealing with missing data.

Assessment of the methodological quality of the included studies

An overview of the methodological quality of the included studies is presented in *Figure 4* and *Table 7*. Generally, all three studies performed well against all of the main quality items in the Cochrane risk-of-bias tool.[56] Suitable methods for random sequence generation were reported across all studies. In the VISUAL trials,[46,47] the randomisation list was remotely generated by the statistics department of the manufacturer (AbbVie). Patients were subsequently allocated to study arms by means of a voice-response or web-response system. Similar methods were used in the HURON trial,[48] with the manufacturer (Allergan) providing a centrally generated randomisation schedule, which was followed by an interactive allocation procedure for study participants that was remotely managed. In the VISUAL trials,[46,47] randomisation to study arms was stratified according to prior immunosuppressant treatment; conversely, randomisation was stratified according to baseline VH in the HURON trial.[48] Blinding of participants and investigators was assessed as

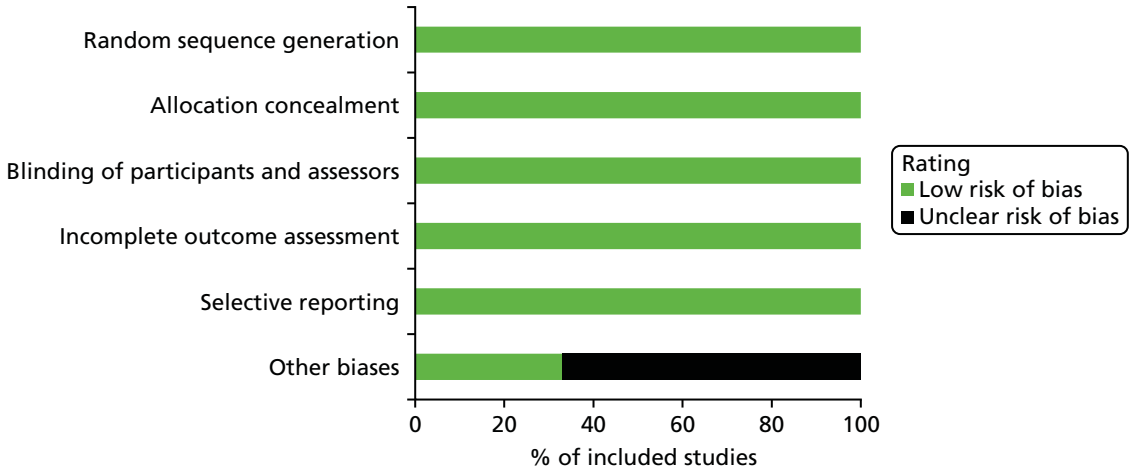

FIGURE 4 Summary of the methodological quality of the included studies: review authors' judgement about each quality item across the included studies.

TABLE 7 Summary of methodological quality assessment: review authors' judgement about each methodological quality item for each study

	Quality assessment item[a]								
Study	1	2	3	4	5	6	7	8	9
VISUAL I[46]	Y	Y	Y	N	Y	Y	Y	Y	Y
VISUAL II[47]	Y	Y	Y	Y	Y	Y	Y	Y	Y
HURON[48]	Y	Y	Y	Y	Y	Y	Y	Y	Y

N, no (high risk of bias); U, unclear (insufficient details to assess the quality item); Y, yes (low risk of bias).

a (1) Were participants assigned to study groups using an acceptable random method?; (2) Was allocation concealment adequately conducted?; (3) Were eligibility criteria specified for selecting participants?; (4) Was the study adequately powered?; (5) Were study groups comparable for most prognostic indicators at baseline?; (6) Were patients and investigators/outcome assessors blinded to treatment allocation?; (7) Was follow-up adequate (≥ 70% randomised patients analysed)?; (8) Were reasons for attrition/exclusions stated?; and (9) Was an intention-to-treat analysis included?

satisfactory across studies. In the VISUAL trials,[46,47] unmasking of treatment allocation was permitted only in the event of a medical emergency. In the HURON trial,[48] treatment investigators were responsible for the implantation procedure; however, outcome assessors were masked to the treatment received by patients. In terms of selective reporting, all studies reported prespecified primary outcomes. However, specific clinical outcomes (e.g. visual acuity or macular oedema) were assessed and reported differently across studies. This highlights the lack of standardisation in ophthalmic outcome reporting and makes it difficult to assess whether or not selective reporting occurred.

In terms of other biases, as noted in *Study characteristics*, secondary outcomes for the VISUAL I trial[46] (see *Table 5*) were measured from the best state prior to week 6 (following the steroid burst); this use of a postrandomisation baseline may introduce bias. Conversely, secondary outcomes for the VISUAL II trial[47] were measured from baseline. A further potential source of bias is that secondary outcomes in the VISUAL trials were measured only up to treatment failure or the study end and, as treatment failure occurred in more patients in the placebo arms than the ADA arms, the results may have been worse in the placebo arms at the point of outcome measurement. The LOCF method used for dealing with missing data may have introduced systematic bias as it assumes that data are missing at random, which is not the case here.

In terms of additional considerations for methodological and reporting quality, all studies reported prespecified inclusion and exclusion criteria. A priori sample size calculations for detecting between-group differences for the specified primary outcomes at a significance level of 5% indicated that 234 patients

were needed to achieve a power of 90% in the VISUAL I trial[46] (outcome time to treatment failure at or after 6 weeks); 220 patients were needed to achieve 80% power in the VISUAL II trial[47] (outcome time to treatment failure at or after 2 weeks) and 73 patients were needed per study arm to achieve a power of 93% in the HURON trial[48] (outcome proportion of patients with a VH score of 0). In the VISUAL I trial[46] 223 patients were randomised, slightly fewer than the 234 suggested by the power calculation; however, given that the study showed a significant between-group difference for the primary outcome (time to treatment failure), this was not an issue. Demographic and baseline characteristics between study arms were comparable for all studies with the exception of the duration of uveitis, which was slightly longer in the non-active comparator arms, as noted earlier. The impact of the non-study treatment options that were available throughout the duration of the studies is unclear, in particular in the HURON trial,[48] in which patients with worsening of intraocular inflammation following the implantation procedure could receive rescue (escape) medication consisting of systemic corticosteroids or immunosuppressants or topical steroids. Indications for escape medication were early treatment failure (i.e. patients with a VH increase of ≥ 1 unit from baseline at week 3) or late treatment failure (i.e. patients with a VH grade of ≥ 1.5+ at week 8 or after week 8).

In the VISUAL I[46] and II[47] trials data for patients in the Japanese substudies were not included in the analyses. In the HURON trial,[48] 100% of the patients were included in the intention-to-treat (ITT) analyses, whereas in the VISUAL trials the analyses described as 'ITT' excluded 6 of 223 patients (3%)[46] and 3 of 229 patients (1%)[47] because of incomplete efficacy data and compliance issues at these sites.

Feasibility of meta-analysis

It was not considered appropriate to meta-analyse the findings of the VISUAL I[46] and VISUAL II[47] trials because the VISUAL I trial[46] enrolled patients with active uveitis and the VISUAL II trial[47] enrolled patients with inactive uveitis. Active uveitis refers to current inflammation in the eye whereas patients with inactive uveitis have limited inflammation, usually because of treatment with corticosteroids or immunosuppressants. In addition, the magnitude of the treatment effect is likely to be associated with the degree of disease activity and inflammation at baseline, with patients with little inflammation or vision loss at baseline less likely to show an improvement in outcomes. NMA was also not considered feasible or appropriate for the reasons discussed in *Indirect comparison of treatments: rationale for not undertaking*.

Effectiveness results from the included studies

Treatment failure

Treatment failure: VISUAL trials The primary outcome for the VISUAL trials[46,47] of ADA was a composite treatment failure outcome, defined as worsening of at least one of the following in one or more eyes: AC cell grade, VH grade, BCVA or new active inflammatory retinal or chorioretinal vascular lesions (see *Table 5*). In the VISUAL I trial,[46] outcomes were measured relative to the best state achieved following the initial steroid burst and treatment failure was assessed from week 6. In the VISUAL II trial,[47] outcomes were measured relative to baseline and treatment failure was assessed from week 2.

In the VISUAL I trial[46] (active uveitis), treatment failure was experienced by 54.5% of patients in the ADA arm and 78.5% of patients in the placebo arm (*Table 8*). The median time to treatment failure was 5.6 months for ADA and 3 months for placebo, giving a hazard ratio (HR) of 0.50 (95% CI 0.36 to 0.70; $p < 0.001$). Treatment failure related to each of the four individual criteria (worsening of AC cell grade, VH grade or BCVA or new lesions) was also significantly greater in the placebo arm than in the ADA arm ($p = 0.04$ to $p < 0.001$).

In the VISUAL II trial[47] (inactive uveitis), treatment failure was experienced by 39% of patients in the ADA arm and 55% of patients in the placebo arm (see *Table 8*). The median time to treatment failure was not estimable for the ADA arm (> 18 months), because fewer than half of the patients had experienced treatment failure, and was 8.3 months for the placebo arm (HR 0.57, 95% CI 0.39 to 0.84; $p = 0.004$).

TABLE 8 Summary of treatment failure outcomes reported in the VISUAL I, VISUAL II and HURON studies

	Study					
	VISUAL I[46,55] (active uveitis)		VISUAL II[47,55] (inactive uveitis)		HURON[48,71] (active uveitis)	
Outcome	ADA	Placebo	ADA	Placebo	DEX 700	Sham
TF, *n/N* (%)	60/110 (54.5)[a]	84/107 (78.5)[a]	45/115 (39)[b]	61/111 (55)[b]	NR[c]	NR[c]
Comparison between groups	NR		NR		$p < 0.001$[d]	
Time to TF in one or more eyes (months), median (IQR)	5.6 (3.0 to not estimable)	3.0 (1.5–5.6)	Not estimable (4.7 to not estimable)	8.3 (3.0 to not estimable)	NR	NR
Comparison between groups, HR (95% CI)	0.50 (0.36 to 0.70); $p < 0.001$		0.57 (0.39 to 0.84); $p = 0.004$		NR	
TF because of new lesions, *n/N* (%)	17/110 (15.5)	29/107 (27.1)	NR	NR	NR	NR
Comparison between groups, HR (95% CI)	0.38 (0.21 to 0.69); $p = 0.001$		0.55 (0.26 to 1.15); $p = 0.105$		NR	
TF because of AC cell grade, *n/N* (%)	24/110 (21.8)	34/107 (31.8)	NR	NR	NR	NR
Comparison between groups, HR (95% CI)	0.51 (0.30 to 0.86); $p = 0.01$		0.70 (0.42 to 1.18); $p = 0.180$		NR	
TF because of VH grade, *n/N* (%)	16/110 (14.5)	39/107 (36.4)	NR	NR	NR	NR
Comparison between groups, HR (95% CI)	0.32 (0.18 to 0.58); $p < 0.001$		0.79 (0.34 to 1.81); $p = 0.589$		NR	
TF because of reduction in BCVA, *n/N* (%)	23/110 (20.9)	27/107 (25.2)	10/115 (9)	23/111 (21)	NR	NR
Comparison between groups, HR (95% CI)	0.56 (0.32 to 0.98); $p = 0.04$		0.33 (0.16 to 0.70); $p = 0.002$		NR	

IQR, interquartile range; NR, not reported; TF, treatment failure.

a Treatment failure = at least one of AC cell grade of ≥ 0.5+ (at week 6) or increase of ≥ 2 (after week 6), VH grade of ≥ 0.5+ (at week 6) or increase of ≥ 2 (after week 6), BCVA worsening by ≥ 15 letters and new active inflammatory retinal or chorioretinal vascular lesions. Outcomes were measured relative to the best state achieved following the initial steroid burst.[46]

b Treatment failure = uveitis recurrence, defined as at least one of AC cell grade increase of ≥ 2, VH grade increase of ≥ 2, BCVA worsening of ≥ 15 letters and new active inflammatory retinal or chorioretinal vascular lesions on or after week 2 (relative to baseline).[47]

c Treatment failure = VH increase of ≥ 1 unit at weeks 3–8 or VH of ≥ +1.5 at weeks 8–26.[71]

d From Kaplan–Meier curve.

Note

In the VISUAL I[46] and II[47] trials, dropouts for reasons other than treatment failure were censored at the time of dropping out. Within the analyses of cause-specific treatment failure, failures from other causes were censored at the time of failure.

Treatment failure because of a reduction in BCVA was significantly greater in the placebo arm than in the ADA arm ($p = 0.002$), although failure related to the other three criteria (worsening of AC cell grade or VH grade or new lesions) was not statistically significant ($p = 0.105$ to $p = 0.589$).

Treatment failure: HURON trial Treatment failure in the HURON trial[48] was defined as a VH grade increase of ≥ 1 unit at weeks 3–8 or a VH of ≥ +1.5 at weeks 8–26. No data were reported in the journal article,[48] company submission[43] or clinical study report,[71] but a statistically significant difference between the DEX 700 arm and the sham arm ($p < 0.001$) was noted.

Best corrected visual acuity

Best corrected visual acuity: VISUAL trials The studies of ADA reported change in BCVA in units of logMAR (logarithm of the minimum angle of resolution) (*Table 9*). In the VISUAL I trial,[46,52] change was measured from the best state reached prior to week 6 after the initial steroid burst rather than from baseline to the final value (week 80 or at the time of treatment failure). BCVA improved in both the ADA arm and the placebo arm following the initial steroid burst but worsened as time progressed, with greater worsening in the placebo arm. The change in BCVA (logMAR) from the best state prior to week 6 to final or early termination was 0.07 and 0.04 in the left and right eyes, respectively, in the ADA arm and 0.12 and 0.13 in the left and right eyes, respectively, in the placebo arm. The MD between groups in BCVA change, pooled across left and right eyes, was –0.07 (95% CI –0.11 to –0.02; $p = 0.003$).

In the VISUAL II trial,[47,72] change was measured from baseline to the final value (week 80 or at the time of treatment failure). BCVA stayed fairly constant from baseline to the final value in the ADA arm and worsened in the placebo arm (see *Table 9*). The change in BCVA (logMAR) from baseline to final or early termination was 0.01 and –0.01 in left and right eyes, respectively, in the ADA arm and 0.06 and 0.02 in left and right eyes, respectively, in the placebo arm. The MD between groups in BCVA change, pooled across left and right eyes, was reported as –0.04 (95% CI –0.08 to 0.01; $p = 0.096$).

Best corrected visual acuity: HURON trial In the HURON trial,[43,48] BCVA was measured as the proportion of patients with a change of two or more or three or more ETDRS lines over the 26 weeks (*Table 10*). The proportion with an improvement of three or more lines was 43% in the DEX 700 arm and 7% in the sham arm at week 8 ($p < 0.001$) and 38% in the DEX 700 arm and 13% in the sham arm at week 26 ($p < 0.001$). Improvement of two or more lines followed a similar pattern (see *Table 10*). In the DEX 700 arm, there was a significant improvement in mean BCVA over weeks 3–26 (no values reported, $p \leq 0.002$).[71]

Patient-reported outcome measures

Data on patient-reported outcome measures (PROMs) derived from the publications and submissions related to the VISUAL and HURON studies are reported here. These data are presented in this report before additional clinical outcomes because of their importance for the cost-effectiveness modelling.

Patient-reported outcome measures: VISUAL trials The main PROM reported in the journal articles for the VISUAL trials[46,47] was the VFQ-25. Additional PROMS reported in the company's submission[55] and clinical study reports[52,72] for the VISUAL trials included the EQ-5D, Hospital Anxiety and Depression Scale (HADS),[74] Work Productivity and Activity Impairment (WPAI) questionnaire[75] and Healthcare Resource Utilisation questionnaire.[76]

Visual Function Questionnaire scores: VISUAL trials The VFQ-25 is made up of 25 questions that cover 11 vision-specific quality-of-life subscales and one general health item.[28] Condition-specific subscales in the tool include those for general vision, ocular pain, distance activities, near activities, vision-specific dependency, vision-specific role difficulties, vision-specific social functioning, vision-specific mental health, driving, peripheral vision and colour vision. Responses to items in each subscale are coded and scored from 0 to 100. Summary scores for each subscale are derived from an average of scores for items within the subscale. A composite score is obtained by calculating the average of all of the scores from the 11 vision-specific subscales. The general health item score and blank items within the instrument are excluded when calculating the composite score. Higher scores indicate better visual functioning.

In the VISUAL I trial,[46] ADA produced a statistically significant and clinically meaningful improvement in the VFQ-25 composite score for patients with active uveitis relative to patients in the placebo arm (MD 4.20, 95% CI 1.02 to 7.38; $p = 0.01$), from the best state achieved following the initial steroid burst to time of treatment failure (early termination) or study end (80 weeks), as shown in *Table 11*. Of the three subscales predefined as secondary outcomes in the VISUAL trials, statistically significant and clinically meaningful

TABLE 9 Visual acuity outcomes [logMAR (SD)] reported in the VISUAL I and VISUAL II studies: LOCF analysis

Outcome	Study							
	VISUAL I[46,52] (active uveitis)				VISUAL II[47,72] (inactive uveitis)			
	ADA		Placebo		ADA		Placebo	
	Left eye ($n = 101$)	Right eye ($n = 101$)	Left eye ($n = 103$)	Right eye ($n = 103$)	Left eye ($n = 115$)	Right eye ($n = 115$)	Left eye ($n = 110$)	Right eye ($n = 110$)
Mean VA, baseline (for VA change in VISUAL II[47] only)	0.22 (0.344)	0.23 (0.277)	0.24 (0.291)	0.25 (0.307)	0.14 (0.255)	0.12 (0.222)	0.16 (0.287)	0.15 (0.274)
Mean VA, best value prior to week 6 following steroid burst (used as 'baseline' for changes in VISUAL I[46])	0.13 (0.290)	0.14 (0.243)	0.12 (0.262)	0.14 (0.271)	NA	NA	NA	NA
Mean VA, final (week 80 or early termination)	0.20 (0.370)	0.18 (0.294)	0.24 (0.319)	0.27 (0.442)	0.15 (0.338)	0.11 (0.282)	0.22 (0.388)	0.16 (0.293)
Mean change in VA								
VISUAL I:[46] from best state reached prior to 6 weeks to final or early termination	0.07 (0.160)	0.04 (0.143)	0.12 (0.169)	0.13 (0.320)	NA	NA	NA	NA
VISUAL II:[47] from baseline to final or early termination	NA	NA	NA	NA	0.01 (0.251)	–0.01 (0.165)	0.06 (0.239)	0.02 (0.198)
Difference in mean VA change between groups (pooled across left and right eyes), mean (95% CI)	–0.07 (–0.11 to –0.02); $p = 0.003$				–0.04 (–0.08 to 0.01); $p = 0.096$			

NA, not applicable; SD, standard deviation; VA, visual acuity.

TABLE 10 Visual acuity outcomes reported in the HURON trial: percentage of patients with BCVA improvement according to ETDRS lines

Outcome	Treatment, *n*/*N* (%)		MD (95% CI) (%); *p*-value	RR (95% CI); *p*-value
	DEX 700	Sham		
Patients with BCVA improvement of three or more ETDRS lines (≥ 15 letters)				
Week 8	33/77 (43)	5/76 (7)	36.3 (24 to 49); $p < 0.001$	6.5 (2.7 to 15.8); $p < 0.001$
Week 26	29/77 (38)	10/76 (13)	24.5 (11 to 38); $p < 0.001$	2.9 (1.5 to 5.5); $p < 0.001$
Patients with BCVA improvement of two or more ETDRS lines (≥ 10 letters)				
Week 8	46/77 (60)[a]	13/76 (17)[a]	43 (29 to 56); $p < 0.001$	3.5 (2.1 to 5.9); $p < 0.001$
Week 26	42/77 (55)[a]	19/76 (25)[a]	30 (15 to 44); $p < 0.001$	2.2 (1.4 to 3.4); $p < 0.001$

a Read off Figure 4 in the company's submission.[43]

TABLE 11 Changes in VFQ-25 scores in the VISUAL I and VISUAL II studies

Outcome	Study					
	VISUAL I[46] (active uveitis)			VISUAL II[47] (inactive uveitis)		
	Treatment, mean (SD)			Treatment, mean (SD)		
	Placebo ($n = 102$)	ADA ($n = 101$)	MD (95% CI), *p*-value	Placebo ($n = 109$)	ADA ($n = 115$)	MD (95% CI), *p*-value
Composite score	–5.50 (11.97)	–1.30 (10.98)	4.20 (1.02 to 7.38), $p = 0.010$	1.24 (10.7)	3.36 (11.7)	2.12 (–0.84 to 5.08), $p = 0.16$
Distance vision subscale	–5.64 (14.65)	–3.77 (13.41)	1.86 (–2.03 to 5.75), $p = 0.346$	0.76 (16.3)	2.64 (17.2)	1.88 (–2.53 to 6.29), $p = 0.40$
Near vision subscale	–8.09 (17.75)	–2.97 (16.78)	5.12 (0.34 to 9.90), $p = 0.036$	3.98 (17.4)	3.88 (18.3)	–0.10 (–4.81 to 4.61), $p = 0.97$
Ocular pain subscale	–12.62 (21.44)	–2.6 (15.34)	10.02 (4.86 to 15.19), $p < 0.001$	2.87 (17.2)	3.42 (21.3)	0.56 (–4.56 to 5.68), $p = 0.83$

SD, standard deviation.

differences favouring ADA over placebo were observed for changes in the near vision subscale (MD 5.12, 95% CI 0.34 to 9.90; $p = 0.036$) and the ocular pain subscale (MD 10.02, 95% CI 4.86 to 15.19; $p < 0.001$); differences in the distance vision subscale were not statistically significant (MD 1.86, 95% CI –2.03 to 5.75; $p = 0.346$).

In the VISUAL II trial,[47] differences between the ADA arm and the placebo arm were not statistically significant for change in VFQ-25 composite score (MD 2.12, 95% CI –0.84 to 5.08; $p = 0.16$) or for the distance vision, near vision or ocular pain subscales ($p = 0.40$ to $p = 0.97$; see *Table 11*).

Other patient-reported outcome measures: VISUAL trials In the VISUAL I trial, EQ-5D estimates were higher in ADA-treated patients than in the placebo group (*Table 12*). Reported EQ-5D predicted values, assessed from change from the best state achieved before week 6 to the final visit or early termination, demonstrated statistical significance, favouring ADA over placebo (MD 0.04, 95% CI 0.00 to 0.07; $p = 0.044$).[52,55] According to estimates based on the WPAI, compared with patients treated with placebo, those receiving ADA had less time off work (MD –10.61 days, $p = 0.011$). There were no significant differences between treatment groups for the remaining outcomes.[52,55]

There was no significant improvement in patients' EQ-5D scores in the VISUAL II trial (MD 0.00, 95% CI –0.03 to 0.04; $p = 0.836$).[72] No other significant differences were reported for the other outcomes.

TABLE 12 EuroQol-5 Dimensions outcomes reported in the VISUAL I and VISUAL II studies

	Study, mean (SD)			
	VISUAL I[52,55] (active uveitis)		VISUAL II[72] (inactive uveitis)	
Outcome	ADA ($n = 101$)	Placebo ($n = 100$)	ADA ($n = 115$)	Placebo ($n = 108$)
EQ-5D score, baseline	0.83 (0.15)	0.82 (0.164)	0.86 (0.160)	0.85 (0.138)
EQ-5D score, best value prior to week 6	0.89 (0.128)	0.88 (0.142)	NA	NA
EQ-5D score, final or early termination	0.86 (0.153)	0.80 (0.187)	0.85 (0.165)	0.84 (0.177)
Mean change in EQ-5D score				
VISUAL I:[46] from best state prior to week 6 to final or early termination	–0.04 (0.129)	–0.07 (0.135)	NA	NA
VISUAL II:[47] from baseline to final or early termination	NA	NA	–0.01 (0.134)	–0.01 (0.161)
MD (95% CI)	0.04 (0.00 to 0.07); $p = 0.044$		0.00 (–0.03 to 0.04); $p = 0.836$	

NA, not applicable; SD, standard deviation.
Predicted values based on LOCF in the ITT population.

Visual Function Questionnaire scores: HURON trial

Change from baseline in Visual Function Questionnaire score *Table 13* provides a summary of the VFQ-25 composite scores at baseline and weeks 8 and 26 in the HURON trial.[43,68,71] At baseline, the mean composite VFQ-25 score was 63.7 in the DEX 700 group and 71.3 in the sham group.[43]

By week 8 (based on analyses using raw scores for patients available at each time point), the change from baseline in composite VFQ-25 score in the DEX 700 group was 11.6 points and in the sham group was 3.4 points ($p < 0.001$).[71] Change at week 8 using LOCF analyses was 9.6 for the DEX 700 group and 4.2 for the sham group ($p = 0.007$).[68] Change at week 26 using LOCF analyses was 10.1 and 2.8 for patients in the DEX 700 and sham groups respectively ($p = 0.001$).

TABLE 13 Change in VFQ-25 composite scores in the HURON trial: LOCF and PP populations

	Absolute values				Change from baseline				
	DEX 700		Sham		DEX 700		Sham		MD (95% CI); *p*-value
Time point	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	
Baseline[a]	73	63.7 (20.74)	73	71.3 (19.0)	NR	NA	NR	NA	
Week 8 LOCF[a]	73	75.1 (NR)	74	74.2 (NR)	73	9.6 (NR)	74	4.2 (NR)	5.4 (NR); $p = 0.007$
Week 8 PP	69	74.4 (17.3)	70	74.5 (18.1)	69	11.6 (14.7)	69	3.4 (11.2)	8.2 (NR); $p < 0.001$
Week 16 LOCF[a]	73	75.9 (NR)	74	75.3 (NR)	NR	NR	NR	NR	NR
Week 16 PP	69	75.3 (18.12)	70	75.6 (19.1)	69	10.5 (14.3)	69	4.5 (12.7)	6.0 (NR); $p =$ NR
Week 26 LOCF[a]	73	76.2 (NR)	74	73.2 (NR)	73	10.1 (NR)	74	2.8 (NR)	7.3 (NR); $p = 0.001$
Week 26 or early exit (CSR[71])	72	74.6 (19.32)	73	74.3 (20.4)	72	10.3 (16.7)	72	2.8 (13.9)	7.5 (NR); $p =$ NR

CSR, clinical study report; NA, not applicable; NR, not reported; PP, per protocol; SD, standard deviation.
a Estimated from graph for absolute values.[68]

Statistically significant differences between the DEX 700 group and the sham group for changes in distance vision ($p = 0.023$), near vision ($p = 0.031$), peripheral vision ($p = 0.045$) and vision-specific social functioning ($p = 0.019$) were reported at the primary time point (week 8).[46,71]

Percentage of patients with a ≥ 5-point or ≥ 10-point improvement in Visual Function Questionnaire composite score More patients in the DEX 700 group than the sham group had a ≥ 5-point improvement in VFQ-25 composite score (week 8: 54.8% vs. 27.0%, $p < 0.001$; week 26: 57.5% vs. 32.4%, $p < 0.05$; *Table 14*). More patients in the DEX 700 group than the sham group also had a ≥ 10-point improvement in VFQ-25 composite score (week 8: 45.2% vs. 14.9%, $p < 0.001$; week 26: *p*-value reported as significant but no value given; see *Table 14*).[43,71] Additionally, statistically significant differences between the groups were reported for the percentage of patients with ≥ 5-point and ≥ 10-point improvements in distance vision, general vision, peripheral vision, colour vision, ocular pain, vision-specific social functioning and vision-specific mental health (all $p < 0.05$).

Other patient-reported outcome measures: HURON trial EuroQol-5 Dimensions (US tariff), Short Form questionnaire-6 Dimensions (SF-6D)[77] and Short Form questionnaire-36 items (SF-36)[78] estimates were presented at baseline in the HURON trial but not beyond this and no other outcomes were reported.[43,71]

Vitreous haze grade

Vitreous haze was measured by dilated indirect ophthalmoscopy in the VISUAL[46,47] and HURON[48] studies. In both cases grading was based on the original scale proposed by Nussenblatt *et al.*[37] and later adopted by SUN[8] (with the minor modification of 'trace' being replaced by 0.5+ in the ordinal scale). An important difference between the VISUAL trials and the HURON trial, however, was that the HURON trial[48] proposed an additional 1.5+ grade for cases that were deemed to lie between the 1+ and 2+ grades (see *Table 6*). Vitreous grade scores are presented in *Study outcomes*.

Vitreous haze grade: VISUAL trials In the VISUAL trials,[46,47] VH outcomes were considered as criteria contributing to the primary composite end points of treatment failure. In the VISUAL I trial,[46] VH was assessed as the change from the best achieved score following a mandatory steroid burst until the final or early termination visit. In the VISUAL II trial,[47] VH was assessed as the change from baseline to the final or early termination visit. Higher scores are correlated with increased severity of uveitis.

A statistically significant difference in change in VH score was reported for patients in the ADA group compared with patients in the placebo group in the VISUAL I trial[46] (–0.27, 95% CI –0.43 to –0.11; $p < 0.001$; *Table 15*). Lower mean VH scores were also noted for the ADA group compared with the

TABLE 14 Visual Function Questionnaire composite scores in the HURON trial: percentage of patients with a ≥ 5-point or ≥ 10-point improvement

VFQ-25 scores	DEX 700, *n*/*N* (%)	Sham, *n*/*N* (%)	MD (95% CI) (%); *p*-value
Patients with a ≥ 5-point improvement			
Week 8	40/73 (54.8)	20/74 (27.0)	27.8 (13 to 43); $p < 0.001$
Week 16	NR	NR	NR (NR); p = significant (NR)
Week 26	42/73 (57.5)	24/74 (32.4)	25.1 (10 to 41); $p < 0.05$
Patients with a ≥ 10-point improvement			
Week 8	33/73 (45.2)	11/74 (14.9)	30.3 (16 to 44); $p < 0.001$
Week 16	NR	NR	NR (NR); p = significant (NR)
Week 26	NR	NR	NR (NR); p = significant (NR)

NR, not reported.

TABLE 15 Vitreous haze in the VISUAL trials

Outcome	Study							
	VISUAL I[46] (active uveitis)				VISUAL II[47] (inactive uveitis)			
	ADA		Placebo		ADA		Placebo	
	Left eye ($n = 101$)	Right eye ($n = 101$)	Left eye ($n = 103$)	Right eye ($n = 103$)	Left eye ($n = 115$)	Right eye ($n = 115$)	Left eye ($n = 110$)	Right eye ($n = 110$)
Mean (SD) VH score, final (week 80 or early termination)	0.44 (0.736)	0.47 (0.636)	0.73 (0.795)	0.78 (0.865)	0.32 (0.594)	0.32 (0.601)	0.48 (0.728)	0.42 (0.630)
Mean (SD) change in VH score								
VISUAL I:[46] from best state reached prior to week 6 to final or early termination	0.11 (0.559)	0.13 (0.648)	0.33 (0.666)	0.45 (0.781)	NA	NA	NA	NA
VISUAL II:[47] from baseline to final or early termination	NA	NA	NA	NA	0.16 (0.601)	0.18 (0.604)	0.33 (0.733)	0.27 (0.605)
Difference in mean change in VH score between groups (pooled across left and right eyes) (95% CI)	–0.27 (–0.43 to –0.11); $p < 0.001$				–0.13 (–0.28 to 0.01); $p = 0.070$			

SD, standard deviation.

placebo group in the VISUAL II trial,[47] but the difference between the groups was not statistically significant (–0.13, 95% CI –0.28 to 0.01; $p = 0.070$). In the VISUAL I trial,[46] VH worsening was the least common cause of treatment failure in the ADA group (15% of events) and the most common reason for treatment failure in the placebo group (36% of events; HR 0.32, 95% CI 0.18 to 0.58; $p < 0.001$). Conversely, increases in VH grade in the VISUAL II trial[47] were not significantly different between the treatment groups and did not affect the time to treatment failure (HR 0.79, 95% CI 0.34 to 1.81; $p = 0.569$).

Vitreous haze grade: HURON trial Study entry eligibility criteria included, among others, a VH score of $\geq +1.5$.[48] At baseline, more patients had a VH score of +1.5 to +2 (DEX 700: 84%, $n = 65/77$; sham: 87%, $n = 66/76$) than a score of +3 to +4 (DEX 700: 16%, $n = 12/77$; sham: 13%, $n = 10/76$). Patients were stratified using these two VH cut-off points. The primary efficacy outcome was the proportion of patients with a VH score of zero. The analysis was based on an ITT population and the primary time point was week 8 following implantation; outcomes were also measured up to week 26.

Proportion of eyes achieving a vitreous haze score of zero: HURON trial Compared with patients receiving a sham procedure, a statistically significantly higher proportion of patients in the DEX 700 arm achieved a VH score of zero at week 8 (MD 34.9%, 95% CI 22% to 48%; $p < 0.001$) and week 26 (MD 16.7%, 95% CI 4% to 30%; $p = 0.014$)[48] (*Table 16*). Subgroup analyses by baseline VH score and previous systemic therapy are also shown in *Table 16*.

Time to vitreous haze score of zero: HURON trial Time to a VH score of zero was measured from day 0 (day of implantation) to the first event of VH of zero. Time points considered included weeks 3, 6 and 8 and any unplanned visit or early exit from study before week 8. A decrease in VH score to zero occurred earlier and was of a greater magnitude in effect in patients in the DEX 700 group than in those in the sham arm ($p < 0.001$; see *Table 16*).[48]

TABLE 16 Vitreous haze outcomes in the HURON trial: ITT population

Outcome	DEX 700	Sham	MD (95% CI) (%); *p*-value	RR (95% CI); *p*-value
VH score = 0, % (n)				
Week 8: all patients	46.8 (36/77)	11.8 (9/76)	34.9 (22 to 48); $p < 0.001$	4.0 (2.0 to 7.6); $p < 0.001$
Week 26: all patients	31.2 (24/77)	14.5 (11/76)	16.7 (4 to 30); $p = 0.014$	2.2 (1.1 to 4.1); $p = 0.02$
Week 8[a]				
Baseline VH +1.5 or +2	48.4 (31/64)	12.1 (8/66)	36 (22 to 51); $p < 0.001$	4.0 (2.0 to 8.0); $p < 0.001$
Baseline VH +3 or +4	41.7 (5/12)	10.0 (1/10)	32 (–2 to 65); $p = 0.06$	4.2 (0.6 to 30.1); $p = 0.16$
Week 26[a]				
Previous systemic therapy	28.6 (4/14)	7.1 (1/14)	21 (–6 to 49); $p = 0.12$	4.0 (0.5 to 31.5); $p = 0.19$
No previous systemic therapy	31.7 (20/63)	16.1 (10/62)	16 (1 to 30); $p = 0.04$	2.0 (1.0 to 3.9); $p = 0.05$
Improvement of ≥ 1 in VH score, % (n)				
Week 8	94.8 (73/77)	44.7 (34/76)	50.1 (38 to 62); $p < 0.001$	2.1 (1.6 to 2.7); $p < 0.001$
Week 26	81.8 (63/77)	51.3 (39/76)	30.5 (16 to 45); $p < 0.001$	1.6 (1.3 to 2.0); $p < 0.001$
Improvement of ≥ 2 in VH score, % (n)				
Week 8	44.2 (34/77)	13[b] (10/76)	Approximately 31; $p < 0.001$	Approximately 3.4; $p < 0.001$
Week 26	33.8 (26/77)	14[b] (11/76)	Approximately 19; $p = 0.001$	Approximately 2.3; $p = 0.008$
Mean (SD) VH score				
Week 8	0.47 (NR)	1.44 (NR)	–0.97; $p < 0.001$	
Week 26	0.72 (NR)	1.30 (NR)	–0.58; $p < 0.001$	
Time to VH score = 0				
Cumulative response rate	NR	NR	NR; $p < 0.001$	

NR, not reported; SD, standard deviation.
a Reported according to subgroup.
b Estimated from a graph in the study by Lowder *et al.*[48]

Mean vitreous haze score and change in vitreous haze score: HURON trial The VH score for each study eye was assessed at each study visit.[48] Mean VH scores were significantly lower in the DEX 700 group than in the sham group at week 8 (–0.97; $p < 0.001$) and week 26 (–0.58; $p < 0.001$). The proportion of patients with an improvement in VH score of ≥ 1 unit was significantly greater in the DEX 700 group than in the sham group ($p < 0.001$ throughout the study), as was the proportion with an improvement of ≥ 2 units (DEX 700 vs. sham: week 3, $p = 0.023$; weeks 6–26, $p \leq 0.002$).

Anterior chamber cell grade

Anterior chamber cell grade: VISUAL trials In the VISUAL I trial,[46,52,55] AC cell grade (see *Table 6* for criteria) worsened to a greater extent in the placebo group than in the ADA group (MD –0.29; 95% CI –0.51 to –0.07; $p = 0.011$). In the VISUAL II trial,[47,55,72] no significant difference in worsening of AC cell grade was noted between patients in the ADA group and patients in the placebo arm (MD –0.14; 95% CI –0.37 to 0.08; $p = 0.218$; *Table 17*).

TABLE 17 Anterior chamber cell grade in the VISUAL trials

Outcome	Study							
	VISUAL I[46,52,55] (active uveitis)				VISUAL II[47,55,72] (inactive uveitis)			
	ADA		Placebo		ADA		Placebo	
	Left eye ($n = 101$)	Right eye ($n = 101$)	Left eye ($n = 102$)	Right eye ($n = 102$)	Left eye ($n = 115$)	Right eye ($n = 115$)	Left eye ($n = 110$)	Right eye ($n = 110$)
Mean (SD) change in AC cell grade								
VISUAL I: from best state reached prior to week 6 to final or early termination	0.35 (NR)	0.36 (NR)	0.59 (NR)	0.69 (NR)	NA	NA	NA	NA
VISUAL II: from baseline to final or early termination	NA	NA	NA	NA	0.41 (NR)	0.40 (NR)	0.57 (NR)	0.53 (NR)
MD (95% CI) in change in AC cell grade between groups (pooled across left and right eyes)	–0.29 (–0.51 to –0.07); $p = 0.011$				–0.14 (–0.37 to 0.08); $p = 0.218$			

NA, not applicable; NR, not reported; SD, standard deviation.

Anterior chamber cell grade: HURON trial In the HURON trial,[48] the difference in the percentage of patients with ≥ 1 cell in the AC was statistically significant between the DEX 700 group and the sham group (14.5% vs. 38.7%; $p = 0.002$ between all three groups).

Disease quiescence: VISUAL trials In the VISUAL trials,[46,47] intraocular inflammation (assessed by VH grade and AC cell grade) was used to define disease quiescence and steroid-free quiescence as follows:[73]

- disease quiescence:
  - no new active inflammatory lesions
  - AC cell grade of ≤ 0.5
  - VH grade of ≤ 0.5+
- steroid-free quiescence (when not receiving steroid therapy):
  - no active inflammatory lesions
  - AC cell grade of zero
  - VH grade of zero.

In both studies, a statistically significant higher proportion (*p*-values not available) of patients in the ADA group were reported to have experienced disease quiescence and steroid-free quiescence at all assessment time points except for weeks 6 and 12 in the VISUAL I trial[46] and week 16 in the VISUAL II trial.[47]

Macular oedema

Measures of macular oedema were reported in terms of change in central macular thickness for patients with macular oedema at baseline and time to optical coherence tomography evidence of macular oedema for patients who developed the condition during the studies.

Macular oedema: VISUAL trials In the VISUAL trials,[46,47] ADA did not significantly reduce the time to optical coherence tomography evidence of macular oedema in patients with active uveitis (HR 0.70, 95% CI 0.39 to 1.26; $p = 0.231$) or in patients with inactive uveitis (HR 0.75, 95% CI 0.34 to 1.69; $p = 0.491$). Additional post hoc analyses presented by the company for patients without a macular hole and/or retinal detachment in the VISUAL I trial showed that ADA resulted in statistically significant reductions in time to optical coherence tomography evidence of macular oedema in at least one eye at or after week 6 (HR 0.33, 95% CI 0.12 to 0.90; $p = 0.023$).

There was a significant difference between the groups in the percentage change in central macular thickness for patients with active uveitis (MD –11.4%, 95% CI –20.9% to –1.8%; $p = 0.020$)[46] but not for those with inactive uveitis (MD –2.3%, 95% CI –8.5% to 3.8%; $p = 0.451$)[47] (*Table 18*).

Macular oedema: HURON trial Central macular thickness was assessed by optical coherence tomography at a number of study sites in the HURON trial.[48] The MD in decrease in central macular thickness between patients in the DEX 700 group and patients in the sham group was statistically significant at week 8 (MD –87.0 µm, 95% CI –147 to –27 µm; $p = 0.004$) but not at week 26 (MD –14.7 µm, 95% CI –66 to 37 µm; $p = 0.58$) (see *Table 18*).

The incidence of macular oedema is discussed further in *Safety of the included interventions*.

TABLE 18 Macular oedema outcomes in the VISUAL I, VISUAL II and HURON studies

	Study							
	VISUAL I[46] (active uveitis)[a]				VISUAL II[47] (inactive uveitis)			
	ADA ($n = 101$)		Placebo ($n = 102$)		ADA ($n = 114$)		Placebo ($n = 107$)	
Outcome	Left eye	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye	Right eye
Percentage change in macular thickness, mean (SD)	9.6 (29.8)	8.2 (25.8)	20.2 (52.0)	22.0 (62.5)	4.5 (29.8)	5.4 (34.8)	6.4 (20.7)	7.7 (28.9)
MD (95% CI) (pooled across left and right eyes)	–11.4 (–20.9 to –1.8); $p = 0.02$				–2.3 (–8.5 to 3.8); $p = 0.451$			
Outcome	**ADA ($n = 55$)**		**Placebo ($n = 45$)**		**ADA ($n = 90$)**		**Placebo ($n = 95$)**	
Median time to macular oedema in one or more eyes, months (IQR)								
Time frame: at or after week 6	11.1 (2.6–15.9)		6.2 (1.4 to not estimable)		NA		NA	
Time frame: at or after week 2	NA		NA		Not estimable[b]		Not estimable[b]	
MD (95% CI)	0.70 (0.39 to 1.26); $p = 0.23$				0.75 (0.34 to 1.69); $p = 0.49$			
	HURON[48]							
Outcome	**DEX 700 ($n = 39$)**				**Sham ($n = 43$)**			
Decrease in macular thickness (µm), mean (SD)								
Week 8	–99.4 (151.8)				–12.4 (123.7)			
Week 26	–50.2 (102.9)				–35.5 (134.9)			
Week 8: MD (95% CI) (µm)	–87.0 (–147 to –27); $p = 0.004$							
Week 26: MD (95% CI) (µm)	–14.7 (–66 to 37); $p = 0.58$							

IQR, interquartile range; MD, mean difference; NA, not applicable; SD, standard deviation.
a Comparison: change from best state reached prior to week 6 to final or early termination.[55]
b Not estimable because of the low number of events.

Effectiveness data from non-randomised studies of dexamethasone and adalimumab

Dexamethasone studies

A summary of effectiveness data from 11 non-randomised, non-comparative studies of the DEX 700 implant is shown in *Appendix 5*.[18,50,51,79–86] This is based on data from the company submission for DEX;[43] the original study publications have not been examined because of time constraints. These data are included here as they provide some data on repeat implants, implants in both eyes and corticosteroid reduction, which were not assessed in the HURON trial.[48] Non-randomised study data for ADA are not included here as they were not provided in the company submission and it was beyond the scope of this assessment to undertake a de novo review of such data.

Following a single implant, two studies reported significant improvements in BCVA at 2–3 months, with a return to baseline values by 6 months,[18,82] and significant improvements in VH up to 6 months,[18,82] with a return to baseline by 12 months in the study with a longer follow-up.[18] Significant improvements in central retinal thickness were reported in one study up to 6 months after a single implant[82] and in another study up to 3 months, with a return to baseline by 6 months.[83]

Studies in which patients received between one and four implants reported improvements in BCVA at 12 months,[50,83,86] with the improvements reported to be significant in one study.[50] Among studies with patients having a mix of single or multiple implants and macular oedema, significant improvements in central retinal thickness were reported up to 12 months in one study,[50] with another study reporting significant improvements at 3 months but not at 6 months.[85]

In terms of repeat implants, one study reported that after the second implant BCVA improved significantly by 1 month but then decreased, with a similar trend following up to six implants (not significant but small patient numbers).[18] Central retinal thickness and VH also showed a significant temporary improvement after the second implant, with similar (non-significant) improvements after the third and fourth implants.[18] Another study reported that the improvements in BCVA and central retinal thickness at 1 month were similar (not significantly different) following the first and second implants.[84]

In a study of uveitis patients the median time from first to second implant was 10 months[50] whereas in four studies of uveitic macular oedema the mean/median time from first to second implant was 4.7,[81] 5.0,[51] 7.1[83] and 10[86] months. The mean time from second to third implant was 3.4 months in one study of uveitic macular oedema.[81]

Implants in both eyes were assessed in one study, with 3 out of 11 patients (27%) receiving implants in both eyes having a response (reduced central retinal thickness and improved BCVA) in the second eye.[18]

In terms of reduction in other therapies following a single implant, one study reported that 21 out of 27 patients (78%) reduced or stopped systemic or local treatment,[18] whereas in another study 3 out of 12 patients (25%) reduced their corticosteroid dose[79] and in another study systemic corticosteroids were reduced or discontinued in 14 out of 32 patients (44%) and discontinued in 8 out of 32 patients (25%) at 6 months.[82] Among studies using a mix of single or multiple implants, in one study systemic corticosteroids or immunosuppressants were reduced in 62% of patients and steroids were discontinued in 36% of patients at 12 months[50] and in another study systemic corticosteroids were reduced or discontinued in 78% of patients and discontinued in 32% of patients at 12 months.[51]

Adalimumab studies

Non-RCT data were presented in the company submission[72] and these were based on a retrospective audit presented in the Clinical Commissioning Policy for anti-TNF treatment options for adult patients with severe refractory uveitis.[87] The study evaluated data for patients aged > 18 years with different clinical

forms of uveitis receiving ADA (40 mg every other week) or infliximab (3–5 mg/kg every other week). The main findings of the audit were as follows:

- Clinical remission of uveitis was observed in all patients ($n = 41$) on biologics [mean ± standard deviation (SD) follow-up of 1.36 ± 0.88 person-years].
- In total, 48.78% of patients experienced visual acuity improvement (mean ± SD follow-up of 2.51 ± 2.01 person-years).
- Fewer patients (17.07%) had worsening of visual acuity (mean ± SD follow-up of 4.38 ± 3.50 person-years).
- Patients receiving biologics, in due course, required fewer or reduced concomitant treatments:
  - 88.89% of patients showed a reduction in steroid dose to ≤ 10 mg (mean ± SD follow-up of 3.06 ± 2.32 person-years)
  - 75.85% of patients showed a reduction in steroid dose to ≤ 5 mg (mean ± SD follow-up of 3.15 ± 1.76 person-years)
  - 45.16% of patients discontinued steroid treatment (mean ± SD follow-up of 3.49 ± 1.59 person-years)
  - 83.33% of patients showed a reduction in the number and/or frequency of immunomodulatory therapy (mean ± SD follow-up of 1.54 ± 0.99 person-years).
- Patient-reported outcomes reported in the audit[87] are summarised as follows:
  - A significant decrease in vision-related quality of life [Vision Core Measure (VCM) scale[88]] was directly associated with a decrease in visual acuity in the worse eye within 1 year of starting biologics ($p = 0.0064$).
  - Median vision-related VCM scores decreased with increasing follow-up time from the time of starting treatment with biologics.
  - Mean SF-36 physical component summary scores (< 47) were lower than estimates for the general population. However, the SF-36 mental component summary scores (> 47) were higher than estimates for the general population, with the exception of scores obtained at year 3 (duration of audit period not reported).

Safety of the included interventions

Safety information from Summaries of Product Characteristics

The SmPC for the DEX implant[45] states that the most commonly reported AEs are those frequently observed with ophthalmic steroid treatment or intravitreal injections, including elevated IOP, cataract and conjunctival or vitreal haemorrhage. Less frequently reported but more serious adverse reactions include endophthalmitis (severe eye infection), necrotising retinitis (viral infection of the retina), retinal detachment and retinal tear.[45]

The SmPC for ADA[44] summarises AEs from studies of 9506 patients across a range of conditions. The SmPC states that the most commonly reported AEs are infections (such as nasopharyngitis, upper respiratory tract infection and sinusitis), injection site reactions (erythema, itching, haemorrhage, pain or swelling), headache and musculoskeletal pain. TNF antagonists such as ADA affect the immune system and their use may affect the body's defence against infection and cancer. Fatal and life-threatening infections (including sepsis, opportunistic infections and tuberculosis), hepatitis B virus reactivation and various malignancies (including leukaemia, lymphoma and hepatosplenic T-cell lymphoma) have also been reported with use of ADA. Serious haematological, neurological and autoimmune reactions have also been reported, including rare reports of pancytopenia, aplastic anaemia, central and peripheral demyelinating events and lupus, lupus-related conditions and Stevens–Johnson syndrome.[44]

Safety data from pivotal randomised controlled trials

Safety data from the RCTs are based on the published journal articles for the HURON trial[48] and VISUAL I[46] and II[47] trials, the company submissions[43,55] and the clinical study reports.[52,71,72] In the case of the HURON

trial the safety data are based on all patients who were randomised to a group and received treatment [$n = 76/77$ (99%) for the DEX 700 group and $n = 75/76$ (99%) for the sham group]. Within the 26-week trial, the mean exposure to the intervention was 25.9 weeks in both groups. For the two RCTs of ADA compared with placebo, safety data are based on all randomised patients in both trials [$n = 111$ (100%, ADA) and 112 (100%, placebo) in VISUAL I and $n = 115$ (100%, ADA) and 114 (100%, placebo) in VISUAL II]. It should be noted that, in these trials, exposure to ADA was longer than exposure to placebo because treatment failure (and cessation of study treatment) occurred earlier in the placebo groups (median exposure: VISUAL I – 19 weeks ADA vs. 13 weeks placebo; VISUAL II – 35 weeks ADA vs. 22 weeks placebo). Therefore, one might expect more events in the ADA groups than in the placebo groups.

A summary of AEs is provided in *Table 19*. An AE of any type occurred in 80% of patients in the DEX 700 group compared with 68% in the sham group in the HURON trial[48] and in 85–91% of patients in the ADA group compared with 79–84% of patients in the placebo group in the two VISUAL trials.[46,47] Serious AEs (SAEs) occurred in 9% of patients in the DEX 700 group compared with 6.7% of the sham group in the HURON trial[48] and in 6–14% of patients in the ADA group compared with 5–8% of patients in the placebo group in the VISUAL trials.[46,70] There were no deaths in the HURON trial[48] and one death in the ADA arm in each of the VISUAL trials;[46,70] neither death was considered to be treatment related.

Systemic adverse events

Serious systemic AEs are shown in *Table 20*. *Table 21* lists other systemic AEs that (1) occurred in ≥ 5% of patients in any treatment group in the HURON trial,[48] (2) occurred in ≥ 5% of patients in the ADA groups in the VISUAL trials[46,89] and (3) were noted as potentially important within uveitis treatments by clinical advisors to the AG. No reported systemic AEs (serious or non-serious) had a substantially higher rate in the DEX 700 arm than in the sham arm. The rate of serious infections was higher in the ADA group than the placebo group in the VISUAL I trial[46] (4.5% vs. 1.8%) but not the VISUAL II trial[47] (1.7% vs. 1.8%). Malignancies and chronic renal failure each occurred in a total of three patients across the ADA arms of both VISUAL trials but in no patients in the placebo arms. The majority of the listed systemic AEs had a somewhat higher rate in the ADA arms than the placebo arms.

TABLE 19 Summary of AEs in the included RCTs

	Study					
	HURON[48] (active uveitis)		VISUAL I[46] (active uveitis)		VISUAL II[47] (inactive uveitis)	
AE summary	DEX 700	Sham	ADA	Placebo	ADA	Placebo
Time over which AEs were measured (weeks)	26 (mean 25.9)	26 (mean 25.9)	≤ 80 (median 19)	≤ 80 (median 13)	≤ 80 (median 35)	≤ 80 (median 22)
AEs (all), *n/N* (%)	61/76 (80.3)	51/75 (68.0)	94/111 (84.7)	88/112 (78.6)	105/115 (91.3)	96/114 (84.2)
AEs considered possibly treatment related, *n/N* (%)	46/76 (60.5)	21/75 (28.0)	ADA related: 45/111 (40.5)	ADA related: 35/112 (31.3)	ADA related: 64/115 (55.7)	ADA related: 52/114 (45.6)
			Steroid related: 57/111 (51.4)	Steroid related: 53/112 (47.3)	Steroid related: 50/115 (43.5)	Steroid related: 48/114 (42.1)
SAEs, *n/N* (%)	7/76 (9.2)	6/75 (8.0)	15/111 (13.5)	5/112 (4.5)	7/115 (6.1)	9/114 (7.9)
SAEs considered possibly treatment related, *n/N* (%)	NR	NR	ADA related: 6/111 (5.4)	ADA related: 2/112 (1.8)	ADA related: 2/115 (1.7)	ADA related: 2/114 (1.8)
			Steroid related: 2/111 (1.8)	Steroid related: 2/112 (1.8)	Steroid related: 0/115 (0)	Steroid related: 3/114 (2.6)
Discontinuation because of AEs, *n/N* (%)	2/76 (2.6)	0/75 (0)	11/111 (9.9)	4/112 (3.6)	10/115 (8.7)	7/114 (6.1)

TABLE 20 Serious systemic AEs (all those reported in RCTs)

	Study, *n*/*N* (%)					
	HURON[48] (active uveitis)		VISUAL I[46] (active uveitis)		VISUAL II[47] (inactive uveitis)	
AE	DEX 700	Sham	ADA	Placebo	ADA	Placebo
Deaths	0/76 (0)	0/75 (0)	1/111 (0.9) (not treatment related)	0/112 (0)	1/115 (0.9) (not treatment related)	0/114 (0)
Hospitalisation	NR	NR	NR	NR	NR	NR
Infections (serious)	NR	NR	5/111 (4.5)	2/112 (1.8)	2/115 (1.7)	2/114 (1.8)
Tumours/malignancy	NR	NR	2/111 (1.8)	0/112 (0)	1/115 (0.9)	0/114 (0)
Anaphylactic reaction	NR	NR	1/111 (0.9)	0/112 (0)	NR	NR
Demyelinating disease	NR	NR	1/111 (0.9)	0/112 (0)	0/115 (0)	0/114 (0)
Renal failure, chronic	NR	NR	1/111 (0.9)	0/112 (0)	2/115 (1.7)	0/114 (0)
Accidental overdose	NR	NR	1/111 (0.9)	0/112 (0)	NR	NR
Ligament/tendon rupture	NR	NR	1/111 (0.9)	0/112 (0)	NR	NR
Fracture	NR	NR	0/111 (0)	1/112 (0.9)	1/115 (0.9)	1/114 (0.9)
Hepatitis, acute	NR	NR	0/111 (0)	1/112 (0.9)	NR	NR
Abortion, induced	NR	NR	0/111 (0)	1/112 (0.9)	NR	NR
Neutropenia	NR	NR	NR	NR	1/115 (0.9)	0/114 (0)
Dysphagia (difficulty swallowing)	NR	NR	NR	NR	1/115 (0.9)	0/114 (0)
Dysarthria (unclear speech)	NR	NR	NR	NR	1/115 (0.9)	0/114 (0)
Status migrainosus	NR	NR	NR	NR	1/115 (0.9)	0/114 (0)
Epistaxis (nosebleed)	NR	NR	NR	NR	1/115 (0.9)	0/114 (0)
Pleurisy	NR	NR	NR	NR	1/115 (0.9)	0/114 (0)
Cardiac tamponade	NR	NR	NR	NR	1/115 (0.9)	0/114 (0)
Aortic dissection	NR	NR	NR	NR	1/115 (0.9)	0/114 (0)
Deep-vein thrombosis	NR	NR	NR	NR	0/115 (0)	2/114 (1.8)
Hypertensive crisis	NR	NR	NR	NR	0/115 (0)	1/114 (0.9)
Arthritis	NR	NR	NR	NR	0/115 (0)	1/114 (0.9)
Cerebrovascular accident	1/76 (1.3)	0/75 (0)	NR	NR	NR	NR
Pelvic inflammatory disease	1/76 (1.3)	0/75 (0)	NR	NR	NR	NR
Cerebellar infarction	1/76 (1.3)	0/75 (0)	NR	NR	NR	NR
Pyelonephritis	0/76 (0)	1/75 (1.3)	NR	NR	NR	NR
Ankylosing spondylitis	0/76 (0)	1/75 (1.3)	NR	NR	NR	NR

NR, not reported.

TABLE 21 Other systemic AEs in RCTs

AE	Study, *n*/*N* (%)					
	HURON[48] (active uveitis)		VISUAL I[46] (active uveitis)		VISUAL II[47] (inactive uveitis)	
	DEX 700	Sham	ADA	Placebo	ADA	Placebo
Systemic AEs (≥ 5% in any group for the HURON trial or ≥ 5% in the treatment group in the VISUAL trials)						
Nasopharyngitis	NR	NR	21/111 (18.9)	8/112 (7.1)	18/115 (15.7)	19/114 (16.7)
Headache	5/76 (6.6)	5/75 (6.7)	12/111 (10.8)	15/112 (13.4)	17/115 (14.8)	17/114 (14.9)
Fatigue	0/76 (0)	2/75 (2.7)	12/111 (10.8)	7/112 (6.3)	14/115 (12.2)	9/114 (7.9)
Arthralgia (joint pain)	0/76 (0)	2/75 (2.7)	10/111 (9.0)	11/112 (9.8)	27/115 (23.5)	12/114 (10.5)
Back pain	NR	NR	9/111 (8.1)	2/112 (1.8)	9/115 (7.8)	7/114 (6.1)
Injection site reactions	NR	NR	7/111 (6.3)	7/112 (6.3)	23/115 (20.0)	15/114 (13.2)
Urinary tract infection	NR	NR	7/111 (6.3)	0/112 (0)	13/115 (11.3)	10/114 (8.8)
Cough	NR	NR	7/111 (6.3)	4/112 (3.6)	11/115 (9.6)	6/114 (5.3)
Bronchitis	NR	NR	7/111 (6.3)	4/112 (3.6)	NR	NR
Hyperhidrosis (increased sweating)	NR	NR	7/111 (6.3)	3/112 (2.7)	NR	NR
Muscle spasms	NR	NR	7/111 (6.3)	4/112 (3.6)	NR	NR
Nausea	0/76 (0)	4/75 (5.3)	6/111 (5.4)	7/112 (6.3)	2/115 (1.7)	3/114 (2.6)
Paraesthesia ('pins + needles')	NR	NR	6/111 (5.4)	0/112 (0)	NR	NR
Insomnia	NR	NR	5/111 (4.5)	8/112 (7.1)	8/115 (7.0)	3/114 (2.6)
Myalgia (muscle pain)	NR	NR	5/111 (4.5)	2/112 (1.8)	6/115 (5.2)	2/114 (1.8)
Hypertension	2/76 (2.6)	3/75 (4.0)	4/111 (3.6)	1/112 (0.9)	7/115 (6.1)	5/114 (4.4)
Liver changes: elevated alanine aminotransferase	NR	NR	1/111 (0.9)	2/112 (1.8)	8/115 (7.0)	1/114 (0.9)
Liver changes: elevated aspartate aminotransferase levels	NR	NR	1/111 (0.9)	1/112 (0.9)	6/115 (5.2)	1/114 (0.9)
Pain in extremity	NR	NR	NR	NR	10/115 (8.7)	3/114 (2.6)
Upper respiratory tract infection	NR	NR	NR	NR	10/115 (8.7)	3/114 (2.6)
Injection site pain	NR	NR	NR	NR	8/115 (7.0)	9/114 (7.9)
Sinusitis	NR	NR	NR	NR	8/115 (7.0)	4/114 (3.5)
Additional systemic AEs (noted as potentially important by clinical advisors)						
Anxiety	NR	NR	5/111 (4.5)	0/112 (0)	5/115 (4.3)	2/114 (1.8)
Renal: elevated creatinine	NR	NR	4/111 (3.6)	2/112 (1.8)	2/115 (1.7)	3/114 (2.6)
Weight gain	NR	NR	3/111 (2.7)	2/112 (1.8)	2/115 (1.7)	0/114 (0)
Anaemia	NR	NR	3/111 (2.7)	0/112 (0)	0/115 (0)	2/114 (1.8)
Muscle weakness (myasthenia)	NR	NR	3/111 (2.7)	0/112 (0)	NR	NR
Cushing syndrome	NR	NR	2/111 (1.8)	1/112 (0.9)	1/115 (0.9)	0/114 (0)
Depression	NR	NR	1/111 (0.9)	1/112 (0.9)	2/115 (1.7)	3/114 (2.6)
Diabetes	NR	NR	1/111 (0.9)	2/112 (1.8)	2/115 (1.7)	0/114 (0)
Osteoporosis	NR	NR	1/111 (0.9)	1/112 (0.9)	0/115 (0)	2/114 (1.8)

AE, adverse event; NR, not reported.

Immunogenicity

In the VISUAL I trial,[46] anti-ADA antibodies were detected in 3 out of 110 patients (2.7%) in the ADA group. These three patients had treatment failure at 16, 44 and 48 weeks (compared with a median time to treatment failure of 24 weeks among the remaining 107 patients). In the VISUAL II trial,[47] anti-ADA antibodies were detected in 6 out of 115 patients (5.2%) in the ADA group. Five of these six patients had treatment failure at weeks 13, 16, 16, 24 and 31 (not estimable for the remaining patient).

Ocular adverse events

Ocular AEs are shown in *Table 22*. In terms of serious ocular AEs, endophthalmitis (severe eye infection) and severe uveitis worsening occurred in one patient each in the DEX 700 group and in no patients in the sham group in the HURON trial.[48] Conjunctival haemorrhage occurred in 30% of patients in the DEX 700 group and 21% of patients in the sham group in the HURON trial,[48] whereas rates for this AE were low in the VISUAL trials.[46,47]

Raised IOP occurred in 25% of the DEX 700 group compared with 7% of the sham group in the HURON trial,[48] whereas there was little difference between the ADA group and the placebo group in the VISUAL trials.[46,47] In the DEX 700 group, IOP of $\geq$ 25 mmHg peaked at week 3 (7.1% vs. 1.4% in the sham group), whereas IOP of $\geq$ 35 mmHg peaked at week 12 (4.1% vs. 0% in the sham group). By week 26, no patients in the DEX 700 group had an IOP of $\geq$ 25 mmHg whereas 4.2% of patients in the sham group had an IOP of $\geq$ 25 mmHg.

Glaucoma rates showed little difference between the DEX 700 group (0%) and the sham group (2.7%) in the HURON trial[48] or between the ADA group (0.9%) and the placebo group (0%) in the VISUAL I trial.[46] In the HURON trial[48] no patients required incisional surgery for glaucoma, whereas two patients (2.6%) in the DEX 700 group required laser iridotomy in the study eye for iris bombe and raised IOP. At any single time point across the 26 weeks, up to 23% of patients in the DEX 700 group required IOP-lowering medication (the percentage requiring this at any point in the study is not reported).

In the HURON trial,[48] 9 out of 62 eyes (15%) in the DEX 700 group and 4 out of 55 eyes (7%) in the sham group had cataracts in eyes that were phakic (had a natural lens) at baseline. Among phakic eyes with no cataract at baseline, 9 out of 42 eyes (21%) in the DEX 700 group and 4 out of 28 eyes (14%) in the sham group had cataracts. For the ADA group, no data were reported on whether eyes were phakic or had cataract at baseline; among all patients there were more cataracts in the ADA group than in the placebo group in the VISUAL I trial[46] (3.6% vs. 1.8%) but more in the placebo group than in the ADA group in the VISUAL II trial[47] (1.7% vs. 5.3%). Cataract surgery among phakic eyes occurred in 1 out of 62 patients (1.6%) in the DEX 700 group and 2 out of 55 patients (3.6%) in the sham group; in the VISUAL II trial[47] cataract surgery occurred in one patient in the ADA group and two patients in the placebo group.

Safety data from non-randomised studies of dexamethasone

A summary of safety data from 11 non-randomised, non-comparative studies of the DEX implant is shown in *Appendix 6*.[18,50,51,79–86] This is based on data presented within the company submission for DEX.[43] The proportion of patients with an increased IOP is typically higher in real-world studies than in a RCT, which may reflect the inclusion of patients with a prior need for IOP-lowering medications, who were excluded from the HURON trial.[43] Implant migration to the AC has been reported in a few patients and occurred in eyes that were aphakic (no lens) or pseudophakic (artificial lens).[43] A few cases of endophthalmitis or retinal detachment were reported after administration of DEX 700.[43] Non-randomised studies of ADA are not included here as they were not included in the company submission and it was beyond the scope of this assessment to undertake a de novo review of these data.

Ongoing studies

Ongoing studies relevant to the decision problem are shown in *Table 23*. These were identified through a search of the ClinicalTrials.gov database (using terms for uveitis plus ADA or DEX) and from the DEX company submission.[43]

TABLE 22 Ocular AEs in RCTs

	Study, *n/N* (%)					
	HURON[48] (active uveitis)		VISUAL I[46] (active uveitis)		VISUAL II[47] (inactive uveitis)	
AE	DEX 700	Sham	ADA	Placebo	ADA	Placebo
Serious ocular AEs in the study eye[a] (all reported in trials)						
Retinal detachment	2/76 (2.6)	2/75 (2.7)	1/111 (0.9)	1/112 (0.9)	0/115 (0)	1/114 (0.9)
Endophthalmitis (severe eye infection)	1/76 (1.3)	0/75 (0)	NR	NR	NR	NR
Uveitis worsening (as SAE)	1/76 (1.3)	0/75 (0)	NR	NR	NR	NR
Cataract (as SAE)	0/76 (0)	1/75 (1.3)	NR	NR	NR	NR
Choroidal neovascularisation	NR	NR	1/111 (0.9)	0/112 (0)	0/115 (0)	1/114 (0.9)
Transient blindness	NR	NR	NR	NR	1/115 (0.9)	0/114 (0)
Subretinal fluid	NR	NR	NR	NR	0/115 (0)	1/114 (0.9)
Ocular AEs in the study eye[a] (≥ 5% in any group for the HURON trial and ≥ 5% in the treatment group for the VISUAL trials)						
Raised IOP	19/76 (25.0)	5/75 (6.7)	3/111 (2.7)	2/112 (1.8)	3/115 (2.6)	2/114 (1.8)
≥ 25 mmHg	Week 3: 5/70 (7.1) Week 8: 3/73 (4.1) Week 26: 0/74 (0)	Week 3: 1/70 (1.4) Week 8: 0/71 (0) Week 26: 3/72 (4.2)	NR	NR	NR	NR
≥ 35 mmHg	Week 3: 1/70 (1.4) Week 8: 2/73 (2.7) Week 26: 0/74 (0)	Week 3: 0/70 (0) Week 8: 0/71 (0) Week 26: 0/72 (0)	NR	NR	NR	NR
Conjunctival haemorrhage	23/76 (30.3)	16/75 (21.3)	0/111 (0)	1/112 (0.9)	3/115 (2.6)	2/114 (1.8)
Vitreous haemorrhage	NR	NR	Eye haemorrhage: 1/111 (0.9) Retinal haemorrhage: 1/111 (0.9)	Eye haemorrhage: 0/112 (0) Retinal haemorrhage: 2/112 (1.8)	1/115 (0.9)	0/114 (0)
Ocular discomfort	10/76 (13.2)	6/75 (8.0)	NR	NR	NR	NR
Eye pain	9/76 (11.8)	10/75 (13.3)	9/111 (8.1)	2/112 (1.8)	9/115 (7.8)	6/114 (5.3)
Cataract						
All patients	9/76 (11.8)	4/75 (5.3)	4/111 (3.6)	2/112 (1.8)	2/115 (1.7)	6/114 (5.3)
Phakic eyes at baseline	9/62 (14.5)	4/55 (7.3)	NR	NR	NR	NR
Phakic eyes with no cataract at baseline	9/42 (21.4)	4/28 (14.3)	NR	NR	NR	NR
Iridocyclitis	7/76 (9.2)	4/75 (5.3)	1/111 (0.9)	0/112 (0)	3/115 (2.6)	2/114 (1.8)
Ocular hypertension	6/76 (7.9)	0/75 (0)	3/111 (2.7)	1/112 (0.9)	0/115 (0)	2/114 (1.8)

TABLE 22 Ocular AEs in RCTs (*continued*)

	Study, *n*/*N* (%)					
	HURON[48] (active uveitis)		VISUAL I[46] (active uveitis)		VISUAL II[47] (inactive uveitis)	
AE	DEX 700	Sham	ADA	Placebo	ADA	Placebo
Myodesopsia (floaters or vitreal cells)	6/76 (7.9)	5/75 (6.7)	NR	NR	NR	NR
Uveitis/uveitis worsening	6/76 (7.9)	7/75 (9.3)	11/111 (9.9)	8/112 (7.1)	6/115 (5.2)	9/114 (7.9)
Conjunctival hyperaemia (red eye)	5/76 (6.6)	7/75 (9.3)	NR	NR	NR	NR
Vision blurred	5/76 (6.6)	3/75 (4.0)	8/111 (7.2)	2/112 (1.8)	NR	NR
Macular oedema	3/76 (3.9)	6/75 (8.0)	NR	NR	7/115 (6.1)	7/114 (6.1)
Eye pruritus (itching)	3/76 (3.9)	5/75 (6.7)	NR	NR	NR	NR
Visual acuity reduced	1/76 (1.3)	4/75 (5.3%)	NR	NR	6/115 (5.2)	10/114 (8.8)
Eye swelling	1/76 (1.3)	4/75 (5.3)	NR	NR	NR	NR
Conjunctivitis	0/76 (0)	4/75 (5.3)	NR	NR	NR	NR
Additional ocular AEs in the study eye[a] (noted as potentially important by clinical advisors)						
Cataract surgery						
All patients	1/76 (1.3)	2/75 (2.7)	NR	NR	1/115 (0.9)	2/114 (1.8)
Phakic eyes at baseline	1/62 (1.6)	2/55 (3.6)	NR	NR	NR	NR
Phakic eyes with no cataract at baseline	1/42 (2.4)	2/28 (7.1)	NR	NR	NR	NR
IOP-lowering medications	Up to 16/71 (23) at any single time point	NR, presumed 0%	NR	NR	NR	NR
IOP-lowering surgery						
Incisional surgery, laser trabeculoplasty, cryotherapy	0/76 (0)	0/75 (0)	NR	NR	NR	NR
Laser iridotomy	2/76 (2.6)	0/75 (0)	NR	NR	NR	NR
Glaucoma	0/76 (0)	2/75 (2.7)	1/111 (0.9)	0/112 (0)	NR	NR
Low IOP (hypotony)	1/76 (1.3)	0/75 (0)	NR	NR	NR	NR

NR, not reported.
a Study eye relates to the HURON trial,[48] in which one eye was designated the study eye.

Ongoing studies of dexamethasone

Two ongoing RCTs of DEX 700 were identified, both in patients with macular oedema as a result of uveitis. Both compared DEX 700 against other local treatments. The POINT trial [PeriOcular and INTravitreal Corticosteroids for Uveitic Macular Edema Trial (NCT02374060), due to complete in 2018] compares DEX 700 with intravitreal triamcinolone or periocular triamcinolone, whereas the MERIT trial [Macular Edema Ranibizumab v. Intravitreal Anti-inflammatory Therapy Trial (NCT02623426), due to complete in 2019] compares DEX 700 with intravitreal methotrexate or intravitreal ranibizumab. In addition, a long-term safety cohort study of DEX 700 (NCT01539577) in 875 patients with posterior segment-involving uveitis or central or branch retinal vein occlusion was due to complete in March 2016, but no published results were identified.

TABLE 23 Ongoing studies as of June 2016

Study name/company	Type and estimated number of participants	Population	Interventions	Key outcomes	Follow-up	Start and end dates	Reference
DEX 700							
PeriOcular and INTravitreal Corticosteroids for Uveitic Macular Edema Trial (POINT); Johns Hopkins Bloomberg School of Public Health (JHSPH) Center for Clinical Trials/NEI	RCT, $n = 267$	• Non-infectious anterior uveitis, intermediate uveitis posterior uveitis or panuveitis • Active or inactive • Macular oedema	• DEX 700 • 4 mg of intravitreal triamcinolone • 40 mg of periocular triamcinolone	• Change in CRT • IOP elevation • Change in BCVA	8 and 24 weeks	March 2015–July 2018	ClinicalTrials.gov (NCT02374060)
Macular Edema Ranibizumab v. Intravitreal Anti-inflammatory Therapy Trial (MERIT); JHSPH Center for Clinical Trials/NEI	RCT, $n = 240$	• Non-infectious anterior uveitis, intermediate uveitis, posterior uveitis or panuveitis • Inactive or minimally active • Macular oedema	• DEX 700 • 400 µg of intravitreal methotrexate • 0.5 mg of intravitreal ranibizumab	• Change in CRT	8 weeks and 6 months	November 2016–March 2019	ClinicalTrials.gov (NCT02623426)
A Long-Term Safety Study of Ozurdex in Clinical Practice; Allergan	Cohort, $n = 875$	• Central or branch retinal vein occlusion or non-infectious posterior segment-involving uveitis • Macular oedema	• DEX 700	• AEs	2 years	March 2012–March 2016 (CSR available September 2016[a])	ClinicalTrials.gov (NCT01539577)
ADA							
Adalimumab in Uveitis Refractory to Conventional Therapy (ADUR); Heidelberg University/Abbott	RCT, $n = 25$	• Non-infectious uveitis • Active despite ≥ 7.5 mg/day of corticosteroids	• 40 mg of ADA every other week + corticosteroids + immunosuppressants • Corticosteroids + immunosuppressants	• % BCVA improved by three or more lines on the ETDRS chart • Inflammatory activity • Cystoid macula oedema • Cumulative steroid dosage	Up to 24 weeks	August 2006–March 2013	ClinicalTrials.gov (NCT00348153); Mackensen 2012[90] (abstract)

Study name/company	Type and estimated number of participants	Population	Interventions	Key outcomes	Follow-up	Start and end dates	Reference
Randomized Trial Comparing Efficacy of Adalimumab, Anakinra and Tocilizumab in Non-infectious Refractory Uveitis (RUBI); Assistance Publique – Hôpitaux de Paris	RCT, $n = 120$	• Non-infectious intermediate uveitis, posterior uveitis or panuveitis • Active	• 40 mg of ADA every other week • 100 mg/day of anakinra • 162 mg/week of tocilizumab	• % with at least a two-step reduction in VH or AC score • Change in VH • Change in BCVA • Change in CRT • Change in steroid dose	16 weeks	October 2016–May 2019	ClinicalTrials.gov (NCT02929251)
Intravitreal Adalimumab Versus Subcutaneous Adalimumab in Non-infectious Uveitis (IVAS)	RCT, $n = 32$	• Non-infectious intermediate uveitis, posterior uveitis or panuveitis • Active	• 40 mg of ADA (subcutaneous) every other week • ADA (intravitreal) 1.5 mg/0.03 ml every 4 weeks	• Change in VH • Change in AC score • Change in BCVA (ETDRS, logMAR) • Change in CRT • Success in steroid tapering	26 weeks	February 2016–June 2019	ClinicalTrials.gov (NCT02706704)
A Study of the Long-term Safety and Efficacy of Adalimumab in Subjects with Intermediate-, Posterior-, or Panuveitis (VISUAL III); AbbVie (previously Abbott)	Non-RCT, $n = 400$	• Non-infectious intermediate uveitis, posterior uveitis or panuveitis • Active or inactive patients from the VISUAL I and VISUAL II studies (completed or experienced treatment failure)	• 40 mg of ADA every other week	• AEs • BCVA • New lesions • VH • AC cells • CRT • VFQ-25 • Reduction in immunosuppression (active and inactive patients separately)	Up to 330 weeks (6.3 years)	November 2010–March 2018	ClinicalTrials.gov (NCT01148225); Suhler 2016[91] (abstract)

CRT, central retinal thickness; CSR, clinical study report.
a Allergan submission.

Ongoing studies of adalimumab

Three ongoing RCTs of ADA were identified. One small RCT [Adalimumab in Uveitis Refractory to Conventional Therapy (ADUR) (NCT00348153)][90] compared ADA plus corticosteroids and immunosuppressants with corticosteroids in combination with immunosuppressants and was due to be completed in March 2013. This study is potentially of interest because of its active comparator arm. However, no published results were identified other than an abstract reporting intermediate results for 20 of 25 patients;[90] this was not included in the clinical effectiveness review because of the limited results presented. The two other RCTs of ADA are due to complete in 2019. The RUBI trial [Randomized Trial Comparing Efficacy of Adalimumab, Anakinra and Tocilizumab in Non-infectious Refractory Uveitis (NCT02929251)] aims to compare ADA against two further biological therapies: anakinra (an interleukin-1 receptor antagonist) and tocilizumab (an antibody against the interleukin-6 receptor). The IVAS trial [Intravitreal Adalimumab Versus Subcutaneous Adalimumab in Non-infectious Uveitis (NCT02706704)] aims to compare subcutaneous ADA against intravitreal ADA.

In addition, a non-randomised extension study of ADA [A Study of the Long-term Safety and Efficacy of Adalimumab in Subjects with Intermediate-, Posterior-, or Panuveitis (VISUAL III) (M11-327, NCT01148225)] enrolled patients from the VISUAL I and VISUAL II studies (ADA or placebo arms) who either completed these trials or experienced treatment failure. Patients who discontinued the VISUAL I or II study because of treatment failure were defined as having active disease on entry to the VISUAL III study, whereas patients who completed the VISUAL I or II study were defined as having inactive disease. Patients received open-label ADA (40 mg every other week) and were followed up for 78 weeks (active uveitis patients) or 54 weeks (inactive uveitis patients). The study is due to be completed in 2018. Preliminary data are available from a conference abstract.[91] This states that, of 243 patients with active uveitis after 78 weeks, 96.3% had no new inflammatory lesions relative to week 8, 91.0% had an AC cell grade of $\leq$ 0.5+ and 87.8% had a VH grade of $\leq$ 0.5+. Of 128 patients with inactive uveitis after 54 weeks, 98.5% had no new inflammatory lesions relative to baseline, 98.5% had an AC cell grade of $\leq$ 0.5+ and 92.6% had a VH grade of $\leq$ 0.5+. The mean systemic corticosteroid daily dose decreased from 12.7 to 3.68 prednisone equivalents by year 1 for patients with active uveitis and remained stable from 1.48 to 1.21 prednisone equivalents for inactive patients. AE rates were stated to be comparable to those in the VISUAL I and VISUAL II trials but no data were presented in terms of numbers of patients with events. No data were presented for visual acuity or the VFQ-25.

Indirect comparison of treatments: rationale for not undertaking

The decision problem states that relevant comparators include periocular or intravitreal corticosteroid injections, intravitreal corticosteroid implants, systemic corticosteroids, systemic immunosuppressants, TNF-alpha inhibitors and intravitreal methotrexate (see *Chapter 2*). The trials of DEX 700 and ADA compared these interventions only with placebo/sham procedure. In the absence of direct evidence comparing ADA and DEX 700 and the absence of direct evidence comparing either of these treatments with a comparator reflective of current UK practice, an indirect comparison using a NMA was considered. A NMA allows a simultaneous comparison between interventions based on a synthesis of any direct and indirect evidence about treatment effects across RCTs that share at least one treatment in common with at least one other study.

Consideration of indirect comparisons for all studies of clinically relevant comparators

Randomised controlled trials that included any of the treatments in the comparator decision set for posterior segment-involving uveitis were sought. In addition to the trials of DEX 700 (HURON[48]) and ADA (VISUAL I[46] and II[47]), 13 additional trials of relevant comparators were identified.[32,33,57–67]

Unfortunately, it was considered infeasible and inappropriate to conduct a NMA for the reasons outlined in *Table 24*. However, a brief summary of all identified trials of relevant comparators is provided in this section for information: study characteristics are provided in *Table 25* and a summary of reported outcomes is provided in *Table 26*. The reasons for not including the additional identified trials in a NMA were:

- No link to the network containing ADA and DEX 700, that is, no common comparator. This applied to studies of fluocinolone implant,[57,58] periocular steroids,[60] methotrexate[32,67] and mycophenolate mofetil.[32] The use of elicitation of experts' beliefs to inform the parameters required to link disconnected

TABLE 24 Studies considered for NMA: rationale for non-inclusion

Study	Intervention	Comparator	Reasons for non-inclusion in NMA
HURON[48,68]	DEX 700 implant (local steroid)	Placebo (sham)	• Outcomes measured from baseline (different from in the VISUAL trials)
VISUAL I[46]	ADA (anti-TNF)	Placebo	• Outcomes measured from peak after steroid burst to treatment failure (not from randomisation as in the HURON trial)
VISUAL II[47]	ADA (anti-TNF)	Placebo	• Inactive uveitis • Outcomes measured from baseline
Multicenter Uveitis Steroid Treatment Trial Research Group[57]	Fluocinolone implant (local steroid)	Steroids and immunosuppressants	• Not connected to network
Pavesio 2010[58]	Fluocinolone implant (local steroid)	Steroids and immunosuppressants	• Not connected to network
Shin 2015[59]	Triamcinolone intravitreal injection (local steroid)	Placebo (sham)	• 100% uveitic macular oedema • No data on VA, VH, VFQ-25
Ferrante 2000[60]	Triamcinolone periocular injection (local steroid)	Methylprednisolone periocular injection	• Not connected to network
Foster 2003[61]	Etanercept (anti-TNF)	Placebo	• Inactive uveitis • No comparable VA outcomes • No data on VH or VFQ-25
Yazici 1990[62]	Azathioprine (immunosuppressant)	Placebo	• 100% Behçet's disease • No clear data on VA, VH, VFQ-25
Murphy 2005[33]	Ciclosporin (immunosuppressant)	Tacrolimus	• Only connected via study of ciclosporin vs. sham,[63] which has no data on VA, VH, VFQ-25
de Vries 1990[63]	Ciclosporin (immunosuppressant)	Placebo	• No data on VA, VH, VFQ-25
Nussenblatt 1991[64]	Ciclosporin (immunosuppressant)	Prednisolone	• Only connected via study of ciclosporin vs. sham,[63] which has no data on VA, VH, VFQ-25
Bodaghi 2012 (active)[65,66]	Voclosporin (immunosuppressant)	Placebo	• No data on VA, VH, VFQ-25
Bodaghi 2012 (maintenance)[65,66]	Voclosporin (immunosuppressant)	Placebo	• Inactive uveitis • No data on VA, VH, VFQ
Mackensen 2013[67]	Methotrexate (immunosuppressant)	Interferon-beta	• Not connected to network
Rathinam 2004[32]	Methotrexate (immunosuppressant)	Mycophenolate mofetil	• Not connected to network

VA, visual acuity.

TABLE 25 Studies considered for NMA: study characteristics

Study	Intervention	Comparator	Patients randomised, *n*	Age (years); mean (range)	Location of uveitis	Duration of uveitis (months)	Bilateral uveitis (%)	% with MO	Systemic conditions
HURON[48,68]	DEX 700	Placebo (sham)	153 (DEX 700 + sham)	≥ 18; 45 (18–82)	Int/post	DEX 700 51, sham 61	NR	NR	No uncontrolled systemic condition
VISUAL I[46]	ADA (40 mg every 2 weeks)	Placebo	223	≥ 18; 43 (18–81)	Int/post/pan	ADA 40, placebo 51	91	Left 36, right 37	None 73%, sarcoid 8%, Behçet's disease 7%, VKH 12%
VISUAL II[47]	ADA (40 mg every 2 weeks)	Placebo	229	≥ 18; 43 (NR)	Int/post/pan	61	96	NR	None 56%, sarcoid 16%, Behçet's disease 6%, other 8%
Multicenter Uveitis Steroid Treatment Trial Research Group[57]	Fluocinolone implant (0.59 mg)	Systemic steroids and immunosuppressants	255	≥ 13; 46 (NR)	Int/post/pan	Fluocinolone 47, control 43	88	41	None 73%, systemic 27%; none requiring systemic therapy
Pavesio 2010[58]	Fluocinolone implant (0.59 mg)	Systemic steroids and immunosuppressants	140	≥ 6; 42 (12–75)	Int/post/pan	NR	NR	NR	None requiring systemic therapy
Shin 2015[59]	Triamcinolone intravitreal injection	Placebo (sham)	50	≥ 20; 52 (NR)	NR	NR	NR	100	None 48%, systemic 52% (sarcoid, Behçet's disease, VKH)
Ferrante 2000[60]	Triamcinolone periocular injection	Methylprednisolone periocular injection	36	NR; NR (NR)	Int/post	NR	NR	NR	NR
Foster 2003[61]	Etanercept (25 mg SC twice a week)	Placebo	20	≥ 18; 47 (NR)	NR	NR (6 months MTX)	NR	NR	None 60%, SLE 15%, HLA-B27 15%, arthritis 10%
Yazici 1990[62]	Azathioprine (2.5 mg/kg daily)	Placebo	48	Any age, 32 (NR)	NR	Azathioprine 103, placebo 83	71	NR	Behçet's disease 100%
Murphy 2005[33]	Ciclosporin (2.5–5.0 mg/kg/day)	Tacrolimus (0.03–0.08 mg/kg daily)	37	NR; median 43 (NR)	Int/post/pan	12–24	76	NR	None 70%, Behçet's disease 11%, sarcoidosis 8%
de Vries 1990[63]	Ciclosporin (10 mg/kg/day)	Placebo	27	≥ 18; 45 (22–75)	Int/post/pan	Ciclosporin 67, placebo 78	NR	NR	None 74%, Behçet's disease 15%, sarcoidosis 11%

Study	Current inflammation (active, non-active)	Inclusion criteria: VA and inflammation	% prior HD steroids/ immunosuppressants	Concomitant treatment	Eyes treated	Eyes analysed	Duration: treatment and follow-up
HURON[48,68]	Active	VH ≥ 1.5, BCVA 10–75 letters	26% steroids or immunosuppressants	26% stable dose steroids or immunosuppressants; rescue: local steroids, systemic medications (new or increased)	One (right if bilateral)	Study eye only	Single implant, follow-up 6 months (26 weeks)
VISUAL I[46]	Active	At least one of VH ≥ 2, AC cell grade ≥ 2, inflammatory lesions	100% HD steroids	All: prednisone 60 mg/day, tapered by week 15; some: immunosuppressants, maximum 1	NA (systemic)	Left and right separately	Up to 80 weeks (1.5 years); ADA 19 weeks (median), placebo 13 weeks (median)
VISUAL II[47]	Inactive (≥ 28 days)	VH ≤ 0.5, AC cell grade ≤ 0.5, no inflammatory lesions, steroid dependent	100% HD steroids, some immunosuppressants	All: prednisone 10–35 mg/day, tapered by week 19; some: immunosuppressants, maximum 1	NA (systemic)	Left and right separately	Up to 80 weeks (1.5 years); ADA 35 weeks (median), placebo 22 weeks (median)
Multicenter Uveitis Steroid Treatment Trial Research Group[57]	Active (or recently active)	No VH criteria (some had VH = 0), BCVA = hand motions or better	Some steroids, some immunosuppressants (% NR)	Fluocinolone arm: steroids and immunosuppressants discontinued; control arm: steroids (tapered), immunosuppressants (86%)	Both if bilateral	All uveitic eyes	Repeat if recurs, follow-up 2 years
Pavesio 2010[58]	Inactive ('clinically quiet')	VH ≤ 2, AC cells ≤ 10, visual acuity ≥ 1.4 logMAR (6/150)	100% HD steroids, some immunosuppressants	Fluocinolone arm: steroids and immunosuppressants discontinued; control arm: HD steroids ± immunosuppressants; rescue: steroids	One (worse if bilateral)	Study eye only	Single implant, follow-up 2 years
Shin 2015[59]	NR	UMO, BCVA 25–80 ETDRS letters	100% HD steroids, some immunosuppressants	All: systemic steroids or immunosuppressants and topical steroids	One (worse if bilateral)	Study eye only	Repeat if MO recurs, follow-up 6 months
Ferrante 2000[60]	Active (vitritis or UMO)	UMO or vitritis	NR	NR	NR (assume one)	NR	Repeat at 6 weeks if needed, follow up 3 months
Foster 2003[61]	Inactive, VH ≥ 1.5, BCVA 10–75 letters	NR	100% MTX (immunosuppressant)	All: MTX (tapered); steroid eye drops if needed	NA (systemic)	Both eyes, all patients	6 months (24 weeks)
Yazici 1990[62]	NR	NR	No steroids or immunosuppressants (past month)	Rescue: systemic steroids if required	NA (systemic)	Unclear	2 years
Murphy 2005[33]	NR	NR	100% HD steroids (or as required)	Some: oral steroids only	NA (systemic)	Per patient	3 months
de Vries 1990[63]	Active	BCVA ≤ 0.5 in best eye (or Behçet's or trauma)	100% HD steroids	All: oral steroids (tapered)	NA (systemic)	Unclear	Up to 1 year

TABLE 25 Studies considered for NMA: study characteristics (*continued*)

Study	Intervention	Comparator	Patients randomised, *n*	Age (years); mean (range)	Location of uveitis	Duration of uveitis (months)	Bilateral uveitis (%)	% with MO	Systemic conditions
Nussenblatt 1991[64]	Ciclosporin (10 mg/kg/day orally)	Prednisolone (42–64 mg/day orally)	56	≥ 10; 38 (10–61)	Int/post	NR	100	55	None 82%, sarcoidosis 13%, VKH 5%
Bodaghi 2012 (active)[65,66]	Voclosporin (0.2, 0.4, 0.6 mg/kg b.i.d.)	Placebo	218	≥ 13; median 42 (NR)	Int/post/pan	52	NR	NR	NR
Bodaghi 2012 (maintenance)[65,66]	Voclosporin (0.2, 0.4, 0.6 mg/kg b.i.d.)	Placebo	232	≥ 13; median 43 (NR)	Int/post/pan	52	NR	NR	NR
Mackensen 2013[67]	MTX (20 mg SC weekly)	Interferon-beta (44 µg SC three times weekly)	19	≥ 18; median 42 (NR)	Intermediate	≥ 1 year	NR	100	None 74%, multiple sclerosis 26%
Rathinam 2004[32]	MTX (25 mg orally weekly)	Mycophenolate mofetil (1 g twice/day)	80	≥ 16; 39 (NR)	Int/post/pan	NR	81	41	None 35.5%, VKH 54%, Behçet's disease 8%, sarcoidosis 2.5%

b.i.d., twice a day; HD, high-dose; HLA-B27, human leucocyte antigen B27; int, intermediate; MO, macular oedema; MTX, methotrexate; NA, not applicable; NR, not reported; pan, panuveitis; post, posterior; SC, subcutaneously; sep, separately; SLE, systemic lupus erythematosus; UMO, uveitic macular oedema; VA, visual acuity.

Study	Current inflammation (active, non-active)	Inclusion criteria: VA and inflammation	% prior HD steroids/ immunosuppressants	Concomitant treatment	Eyes treated	Eyes analysed	Duration: treatment and follow-up
Nussenblatt 1991[64]	Active	VA 20/40 or worse, both eyes; inflammation (VH, VA decrease, retinal lesions)	No steroids or immunosuppressants (past month)	No systemic treatments; topical medications permitted	NA (systemic)	Per patient	3 months
Bodaghi 2012 (active)[65,66]	Active	VH ≥ 2	100% HD steroids (or contraindicated refused)	Some: oral steroids	NA (systemic)	Study eye or either	6 months (24 weeks)
Bodaghi 2012 (maintenance)[65,66]	Inactive	NR	100% HD steroids	Some: oral steroids	NA (systemic)	Study eye or either	6 months (26 weeks)
Mackensen 2013[67]	Active	Uveitic macular oedema (≥ 250 um); visual acuity ≤ 20/30 (0.2 logMAR)	100% HD steroids and acetazolamide	NR	NA (systemic)	Study eye (worse)	3 months
Rathinam 2004[32]	Active	At least one of: VH ≥ 1, AC cell grade ≥ 1, Vitreous cells ≥ 1, Active lesions	100% HD steroids	All: oral steroids (tapered); some: topical steroid	NA (systemic)	All uveitic eyes	6 months

TABLE 26 Studies considered for NMA: outcomes reported

			VA		
Study	Intervention	Comparator	Final value	Change	% improved three or more lines
HURON[48,68]	DEX 700	Placebo (sham)		Y (ETDRS) (6 months)	Y (2, 6 months)
VISUAL I[46]	ADA	Placebo	Y (logMAR)	Y (logMAR)	
VISUAL II[47]	AD	Placebo	Y (logMAR)	Y (logMAR)	
Multicenter Uveitis Steroid Treatment Trial Research Group[57]	Fluocinolone implant	Systemic steroids and immunosuppressants	Y (ETDRS) (2, 6, 24 months)	Y (ETDRS) (6, 12, 24 months)	Y (24 months)
Pavesio 2010[58]	Fluocinolone implant	Systemic steroids and immunosuppressants			Y (24 months)
Shin 2015[59]	Triamcinolone intravitreal injection	Placebo (sham)	(No data just $p = NS$)		
Ferrante 2000[60]	Triamcinolone periocular injection	Methylprednisolone periocular injection			
Foster 2003[61]	Etanercept	Placebo			
Yazici 1990[62]	Azathioprine	Placebo		Unclear data	
Murphy 2005[33]	Ciclosporin	Tacrolimus			
de Vries 1990[63]	Ciclosporin	Placebo		Y (Landolt C, *p*-value only)	
Nussenblatt 1991[64]	Ciclosporin	Prednisolone			Y
Bodaghi 2012 (active)[65,66]	Voclosporin	Placebo			
Bodaghi 2012 (maintenance)[65,66]	Voclosporin	Placebo			
Mackensen 2013[67]	MTX	Interferon-beta	Y (Snellen, logMAR)	Y (ETDRS, logMAR)	
Rathinam 2004[32]	MTX	Mycophenolate mofetil		Y (logMAR)	

	Inflammatory activity					Complications	
% improved two or more lines	VH: final	% VH = 0	% VH improved ≥ 1	% VH improved ≥ 2	AC cell grade: change	Cataract: incidence	Cataract: % surgery
Y (2, 6 months)	Y (final, no SD)	Y	Y	Y		Y	Y
	Y (final and change)	Y			Y	Y	
	Y (change)				Y	Y	Y
		Y		HR only		Y	Y
						Y	Y
						Y	Y
Y							
Y							
Y							
				Y	Y		
	Unclear data						
Y	Y (final)				Y		
						Y	

Study	Complications						
	MO incidence	Time to MO	Macular thickness: change	% eyes MO improved	Steroid reduction	% reduced steroids	% rescue steroids
HURON[48,68]	Y		Y				Y (intravitreal/ systemic)
VISUAL I[46]	Y	Y	Y				
VISUAL II[47]		Y	Y				
Multicenter Uveitis Steroid Treatment Trial Research Group[57]	Y						
Pavesio 2010[58]				Y (improved)			
Shin 2015[59]			No data, *p*-value			Y (% reduced)	
Ferrante 2000[60]							Y (intravitreal)
Foster 2003[61]							
Yazici 1990[62]							Y (intravenous)
Murphy 2005[33]							
de Vries 1990[63]						Y (% stopped)	
Nussenblatt 1991[64]				Y (resolved)			
Bodaghi 2012 (active)[65,66]							
Bodaghi 2012 (maintenance)[65,66]							
Mackensen 2013[67]			Y	Y (improved/ resolved)			
Rathinam 2004[32]				Y (resolved)			

MO, macular oedema; MTX, methotrexate; NS, not significant; SE, standard error; SF-36, Short Form-36; VA, visual acuity; Y, yes (reported).
a Worsening of AC cell grade, VH grade or VA or new inflammatory lesions.

Composite outcomes			HRQoL			AEs	
Time to treatment failure (active uveitis)	Uveitis recurrence	Composite (positive)	Generic HRQoL	VFQ-25 composite: final	VFQ-25 composite: change	Systemic AEs	Ocular AEs
				Y (2, 4, 6 months)	Y (no SD/SE) (2, 6 months)	Y	Y
Y (worse AC cells, VH, VA, lesions)[a]			Y (EQ-5D, HADS, WPAI)	Y	Y	Y	Y
	Y (AC, VH, VA, lesions)				Y	Y	Y
			Y (EQ-5D, SF-36)	Y (6, 12, 24 months)	Y (6, 12, 24 months)	Y	Y
	Y (AC, VH, VA)					Y	Y
							Y
							Y
	Y (uveitis flare-ups)					Y	
						Y	
	Y (previous responders)	Y (VA two or more lines or ophthalmoscopy = 0)				Y	
		No data, *p*-values				Y	
		Y (VA three or more lines or VH improvement ≥ 2)				Y	
	Y (recurrence)						
			SF-36, no data	Y		Y	Y
		Y (% with minimal inflammation while on low or no steroid treatment)				Y	Y

networks was considered in depth but was not implemented for two reasons. It was deemed to be infeasible in the time frame and, moreover, would be of questionable benefit given the concerns related to the comparability of the two main trials (see *Consideration of indirect comparisons for trials of adalimumab and dexamethasone*) and hence the validity of the resulting connected network.

- Heterogeneity in patient populations in terms of active/inactive uveitis. It was not considered appropriate to pool studies of patients with active and inactive uveitis. Active uveitis refers to current inflammation in the eye, whereas patients with inactive uveitis have limited inflammation, usually because they have received treatment with corticosteroids or immunosuppressants. The treatment effect is likely to be related to the degree of activity/inflammation at baseline. The trial of etanercept,[61] one trial of ADA (VISUAL II)[47] and one trial of voclosporin[65,66] could not be analysed with the HURON[48] and VISUAL I[46] studies for this reason. In terms of trials in patients with inactive uveitis, the trials of etanercept[61] and voclosporin[65,66] had no comparable outcome data to enable a NMA to be conducted with the VISUAL II trial.[47]
- Heterogeneity in patient populations for other reasons. The trial of intravitreal triamcinolone[59] was carried out in patients who all had uveitic macular oedema, whereas in most trials only a subset of patients had uveitic macular oedema. The treatment effect is likely to be associated with the proportion of patients with uveitic macular oedema at baseline because this condition causes vision loss. Therefore, treating uveitic macular oedema is likely to lead to greater gains in vision than treating patients with uveitis but no uveitic macular oedema. The trial of azathioprine[62] was carried out in patients who all had Behçet's disease, whereas most trials were carried out in a mixed population with only a small percentage of patients having Behçet's disease and other systemic diseases; again, these are clinically very different populations. In addition, as noted in *Consideration of indirect comparisons for trials of adalimumab and dexamethasone*, there are many differences in the populations and the prior and concomitant treatments used between the DEX 700 (HURON[7]) and the ADA (VISUAL I[46]) studies for active uveitis.
- Lack of comparable outcomes. Within the trials that had a common comparator to DEX 700 or ADA (i.e. a placebo arm),[59,61–63,65,66] none reported outcomes that were consistent with those in the DEX 700 and ADA trials (see *Table 26*). Change in VFQ-25 score was reported for both the HURON trial[48] and the VISUAL I trial[46] but a NMA was not considered appropriate for the reasons listed in *Indirect comparison of treatments: rationale for not undertaking*.

Consideration of indirect comparisons for trials of adalimumab and dexamethasone

The outcomes reported for the ADA and DEX 700 trials varied from trial to trial (see *Study characteristics*) and so the potential networks of evidence were considered separately for each outcome of interest. Outcomes considered for the NMA were VFQ-25, visual acuity, VH and AEs. This was driven by the potential to undertake a NMA for these outcomes.

Two networks of evidence were considered. A diagram of network 1 is provided in *Figure 5*. Network 1 consists of two trials (HURON[48] and VISUAL I[46]) and allows pairwise comparisons to be made between ADA and DEX 700 and placebo/sham procedure (the common comparator of the two trials). The trials share common assessment time points of 8, 16 and 26/27 weeks (26 weeks for the HURON trial[48] and 27 weeks for the VISUAL I trial[46]). Given that the HURON trial[48] was a 26-week trial, comparison beyond this time point is not possible based on the observed data.

A diagram of network 2 is provided in *Figure 6*. Network 2 is an extension of network 1 including the Multicenter Uveitis Steroid Treatment (MUST) trial of fluocinolone corticosteroid implant compared with systemic corticosteroids and immunosuppressants,[57] under the assumption that the efficacy of the fluocinolone implant is the same as that of DEX 700. This allows an indirect comparison with treatment with systemic corticosteroids and immunosuppressants, which may be considered more reflective of current UK practice than treatment with placebo/sham procedure. An indirect comparison using this network is possible only at 26 weeks (the first follow-up time point in the MUST trial).

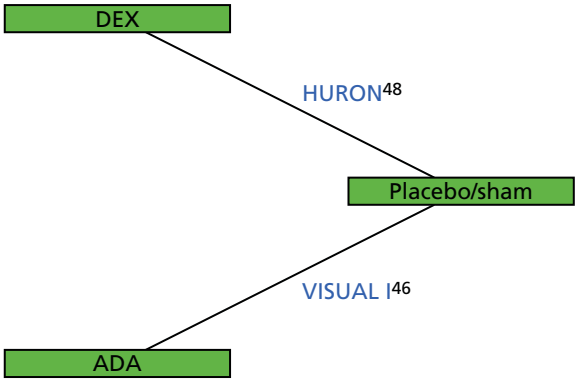

FIGURE 5 Network 1 for the VFQ-25 outcome: indirect comparison of ADA, DEX and placebo/sham.

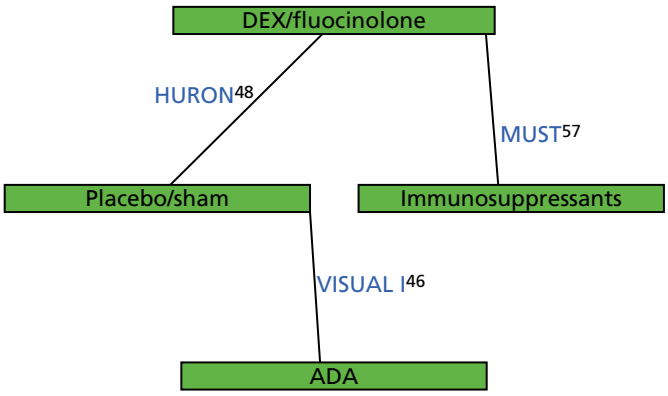

FIGURE 6 Network 2 for the VFQ-25 outcome: indirect comparison of ADA, DEX, placebo/sham and immunosuppressants.

The AG began with a question about the best way to compare the treatment options within a network, with the prior belief that such an analysis could be undertaken. However, after substantial deliberation between all members of the AG and discussion with the clinical advisors, it was reluctantly decided that a NMA was inappropriate and may provide misleading results. The main issues were as follows.

- Baseline systemic therapy: in the HURON trial[48] only 26% of patients were receiving systemic therapy at baseline, whereas in the VISUAL I trial[46] all patients were receiving systemic high-dose corticosteroids. Therefore, patients in these studies may have been on different 'lines' of treatment. In addition, in the VISUAL I trial[46] 91% of patients had bilateral uveitis, whereas the corresponding proportion was not reported in the HURON trial;[48] this may be a further difference between the patient populations in these studies.
- Rescue therapy: a greater proportion of patients in the sham arm than in the DEX 700 arm in the HURON trial[48] received rescue therapy (38.2% vs. 22.1%). In the VISUAL I trial[46] there was no reported difference in concomitant therapy between the two arms. It may be misleading to attribute an indirect effect of ADA compared with DEX 700 to these interventions alone.
- Comparability of the baseline treatments in the HURON[48] and VISUAL I[46] studies: the VISUAL I trial[46] included an initial steroid burst; this was not included in the HURON trial.[48] Thus, the baseline interventions were different and it would be meaningful to combine the treatment effects across studies only if the initial steroid burst did not affect the treatment effect. However, clinical advice suggests that the treatment effect will depend on the initial steroid burst. Patients experience an initial improvement from the steroid burst and there is less scope during this period for patients to demonstrate further improvement (i.e. the effect of ADA is not additive to the effect of the steroids). In the analyses undertaken by AbbVie this issue

was addressed by considering the change from the peak within the first 6 weeks to the final/termination visit for each individual. This approach was not considered appropriate for estimating the treatment effect because patients are comparable only at baseline and treatment effects should be estimated relative to baseline.

- Validity of the comparable efficacy assumption for dexamethasone and fluocinolone (network 2 only): although DEX 700 and fluocinolone are both corticosteroid intravitreal implants, they cannot be considered clinically equivalent because the fluocinolone implant has a higher potency (median duration of effect 30 months)[92] than the DEX 700 implant (median duration of effect 6 months).[43] There are no head-to-head trials comparing DEX 700 and fluocinolone implants.
- Issues with the reported data: patients in the VISUAL I trial[46] were followed up to the time of treatment failure only and missing data beyond this point were imputed using LOCF. No other methods for dealing with missing data were considered and it is possible that the use of LOCF may provide a biased estimate of the treatment effect as it assumes that the data are missing at random, which is not true in this case. Although LOCF was also used in the HURON trial[48] the issue is less problematic in this case because most patients were followed up for 26 weeks and treatment could not be discontinued (because the implants are not removed). Estimates of the treatment effect for secondary outcomes (including VFQ-25 score, EQ-5D score, visual acuity and VH) may be biased because data were collected only until treatment failure. Evidence about key outcome measures could be synthesised using either absolute values at each time point or change from baseline. The use of absolute values was ruled out because of differences in response at baseline between the sham arm and the treatment arm in the HURON trial[48] for the VFQ-25. The sham arm had a higher mean VFQ-25 score at baseline, whereas clinical advice suggests that the lower mean VFQ-25 score associated with the treatment arm is likely to be more representative of the population. It was not possible to account appropriately for baseline differences.
- Treatment with adalimumab and dexamethasone is generally appropriate for different patient groups: as discussed in *Description of the technologies under assessment*, there is only a small patient group in which it would be appropriate to compare DEX 700 and ADA, with the most likely group being patients with bilateral uveitis with a temporary flare-up. Consequently, an analysis that assumes that clinicians would be prepared to treat any patient in the population with any of the treatments is inappropriate.

Summary of clinical effectiveness and safety (randomised controlled trials)

Three RCTs were included in the review of clinical effectiveness; a summary of the results is provided in *Table 27*. Two RCTs compared ADA with placebo, for up to 80 weeks or until treatment failure, in patients with intermediate uveitis, posterior uveitis or panuveitis on high-dose oral corticosteroids: VISUAL I[46] (active uveitis) and VISUAL II[47] (inactive uveitis). Oral corticosteroids were tapered from baseline and patients could receive up to one systemic immunosuppressant. One RCT (HURON[48]) compared DEX 700 (a single 0.7-mg implant) with a sham procedure over 26 weeks' follow-up in patients with intermediate or posterior uveitis. At baseline, 25% of participants were on systemic therapies, which could be continued at a stable dose.[48] Thirteen additional studies of clinically relevant comparator treatments (vs. placebo or one another) were identified. However, because of clinical heterogeneity, differences in outcomes and a lack of common comparators, it was not feasible to undertake a NMA. Therefore, the summary of clinical efficacy evidence presented here is restricted to the VISUAL I,[46] VISUAL II[47] and HURON[48] studies.

Treatment failure in the VISUAL trials of ADA was defined as worsening of any of the following in either eye: AC cell grade, VH grade, BCVA or new inflammatory lesions. In the VISUAL I trial[46] (active uveitis), the median time to treatment failure was 5.6 months for ADA compared with 3 months for placebo (HR 0.50, 95% CI 0.36 to 0.70; $p < 0.001$). Treatment failure was experienced by 54.5% of participants on ADA compared with 78.5% of participants on placebo. In the VISUAL II trial[47] (inactive uveitis), the median time to treatment failure was not estimable for ADA and was 8.3 months for placebo (HR 0.57, 95% CI 0.39 to 0.84; $p = 0.004$). Treatment failure was experienced by 39% of participants on ADA compared with 55% of participants on placebo. In the VISUAL I trial[46,52] there were significant benefits of ADA compared with placebo for changes in the following (averaged across both eyes): visual acuity ($p = 0.003$), inflammation

TABLE 27 Summary of clinical effectiveness

Outcome	Difference between groups: treatment effect (95% CI), *p*-value			
	ADA: VISUAL I (active uveitis)	ADA: VISUAL II (inactive uveitis)	DEX 700: HURON – 8 weeks	DEX 700: HURON – 26 weeks
Time to treatment failure (worsening of AC, VH or BCVA or new lesions)	HR 0.50 (0.36 to 0.70), $p < 0.001$	HR 0.57 (0.39 to 0.84), $p = 0.004$	NR	NR
BCVA (change) (logMAR)	MD –0.07 (–0.11 to –0.02), $p = 0.003$	–0.04 (–0.08 to 0.01), $p = 0.096$	NR	MD NR, $p = 0.002$
BCVA improvement of three of more lines (15 letters)	NR	NR	MD 36.3% (24 to 49), $p < 0.001$; RR 6.5 (2.7 to 15.8), $p < 0.001$	MD 24.5 (11 to 38), $p < 0.001$; RR 2.9 (1.5 to 5.5), $p = 0.001$
BCVA improvement of two or more lines (10 letters)	NR	NR	MD 43 (29 to 56), $p < 0.001$; RR 3.5 (2.1 to 5.9), $p < 0.001$	MD 30 (15 to 44), $p < 0.001$; RR 2.2 (1.4 to 3.4), $p < 0.001$
VH grade (change)	MD –0.27 (–0.43 to –0.11), $p < 0.001$	MD –0.13 (–0.28 to 0.01), $p = 0.070$	NR	NR
VH grade (final)	NR	NR	MD –0.97 (NR), $p < 0.001$	MD –0.58 (NR), $p < 0.001$
% with VH = 0	NR	NR	MD 34.9 (22 to 48), $p < 0.001$; RR 4.0 (2.0 to 7.6), $p < 0.001$	MD 16.7 (4 to 30), $p = 0.014$; RR 2.2 (1.1 to 4.1), $p = 0.02$
% with VH improvement of ≥ 2	NR	NR	MD NR, $p < 0.001$	MD NR, $p = 0.001$
AC cell grade (change)	MD –0.29 (–0.51 to –0.07), $p = 0.011$	MD –0.14 (–0.37 to 0.08), $p = 0.218$	NR	NR
Macular oedema (change in macular thickness) (μm)	NR	NR	MD –87.0 (–147 to –27), $p = 0.004$	MD –14.7 (–66 to 37), $p = 0.58$
Macular oedema (change in macular thickness) (% change)	MD –11.4 (–20.9 to –1.8), $p = 0.020$)	MD –2.3 (–8.5 to 3.8), $p = 0.451$	NR	NR
VFQ-25 composite score (change)	MD 4.20 (1.02 to 7.38), $p = 0.010$	MD 2.12 (–0.84 to 5.08), $p = 0.160$	MD NR, $p = 0.007$	MD NR, $p = 0.001$
% with ≥ 5-point improvement in VFQ-25 score	NR	NR	MD NR, $p < 0.001$	MD NR, $p < 0.05$
EQ-5D score (change)	MD 0.04 (0.00 to 0.07), $p = 0.044$	MD 0.00 (–0.03 to 0.04), $p = 0.836$	NR	NR
% requiring rescue medication	NR	NR	NR	MD 16, $p = 0.030$

NR, not reported.

[VH ($p < 0.001$) and AC cell grade ($p = 0.011$)], macular oedema [change in central retinal thickness ($p = 0.020$)], VFQ-25 composite score ($p = 0.010$) and EQ-5D score ($p = 0.044$). In the VISUAL II trial,[47,72] differences were not significant for ADA compared with placebo for changes in any of the following (averaged across both eyes): visual acuity ($p = 0.096$), inflammation [VH ($p < 0.070$) and AC cell grade ($p = 0.218$)], macular oedema [change in central retinal thickness ($p = 0.451$)], VFQ-25 composite score ($p = 0.160$) or EQ-5D score ($p = 0.836$).

In the HURON trial[48] there were significant benefits of DEX 700 compared with the sham procedure for the following (measured in the study eye only): percentage of patients with a VH score of zero at 8 weeks ($p < 0.001$) and 26 weeks ($p = 0.014$), percentage of patients with a VH improvement of ≥ 2 units at 8 weeks ($p < 0.001$) and 26 weeks ($p = 0.001$), percentage of patients with a BCVA improvement of three or more lines over weeks 3–26 ($p < 0.001$), mean BCVA improvement over weeks 3–26 ($p \leq 0.002$), central retinal thickness at 8 weeks ($p \leq 0.004$) although not 26 weeks ($p \geq 0.227$), change in VFQ-25 composite score (per patient as opposed to study eye) at 8 weeks ($p = 0.007$) and 26 weeks ($p = 0.001$) and percentage of patients with a ≥ 5-point improvement in VFQ-25 score at 8 weeks ($p < 0.001$) and 26 weeks ($p < 0.05$). Rescue medication (corticosteroid injections in the study eye or new/increased use of systemic corticosteroids or immunosuppressants) were required in 22% of participants in the DEX 700 arm and 38% of participants in the sham arm ($p = 0.030$).

As ADA affects the immune system, the potential risks of treatment with ADA include infections and malignancy.[44] The rate of serious infections was higher in the ADA group than in the placebo group in the VISUAL I trial[46] (4.5% vs. 1.8%) but not the VISUAL II trial[47] (1.7% vs. 1.8%). Malignancies and chronic renal failure each occurred in a total of three patients across both trials in the ADA group, with no cases in the placebo group. Systemic AEs that had a higher rate of occurrence in the ADA group than in the placebo group in at least one of the VISUAL trials[46,47] included infections, injection site reactions, fatigue, arthralgia, myalgia, paraesthesia, hypertension and elevations of liver enzymes. Anti-ADA antibodies in patients receiving ADA occurred in 2.7% in the VISUAL I trial[46] and 5% in the VISUAL II trial.[47] There was little difference between ADA and placebo in the rates of ocular AEs.

In terms of safety, the risks of DEX 700 include those associated with intraocular steroids, that is, increased IOP, cataract and glaucoma, as well as infection and bleeding.[45] In the HURON trial,[48] raised IOP occurred in 25% of participants in the DEX 700 group compared with 7% of participants in the sham group, whereas IOP of ≥ 25 mmHg occurred in 7.1% of participants in the DEX 700 group compared with 1.4% of participants in the sham group. Glaucoma rates were lower in the DEX 700 group (0%) than in the sham group (2.7%); no patients required incisional surgery for glaucoma, whereas 2.6% of participants in the DEX 700 group required a laser iridotomy and, at any single time point, up to 23% of participants in the DEX 700 group required IOP-lowering medication (not reported for the sham group). Cataracts in eyes that were phakic (had a natural lens) at baseline occurred in 15% of participants in the DEX 700 group compared with 7% of participants in the sham group and cataract surgery was carried out in 1.6% and 3.6% of the DEX 700 and sham groups respectively. Endophthalmitis (severe eye infection) and severe uveitis worsening occurred in one patient each in the DEX 700 group; there were no cases in the sham group. Conjunctival haemorrhage occurred in 30% of participants in the DEX 700 group compared with 21% of participants in the sham group. No systemic AEs had a substantially higher rate in the DEX 700 group than in the sham group.

Chapter 4 Assessment of cost-effectiveness

This chapter first presents a systematic review of existing cost-effectiveness evidence for treatments given to mainly adult patients with non-infectious uveitis. This is followed by a description of the de novo model developed by the AG to assess the cost-effectiveness of DEX in patients with active uveitis, ADA in patients with active uveitis and ADA in patients with inactive uveitis, all compared with current practice, and the results of the model and discussion of the analysis. Finally, a summary of the key model results is presented.

Systematic review of existing cost-effectiveness evidence

Methods

A comprehensive search was undertaken to systematically identify economic evaluations and quality-of-life studies in patients with active non-infectious intermediate uveitis, posterior uveitis and/or panuveitis.

The following electronic databases and clinical trials registries were searched from inception:

- MEDLINE (via Ovid) (1946–2016)
- MEDLINE Epub Ahead of Print, MEDLINE In-Process & Other Non-Indexed Citations (via Ovid) (1946–2016)
- EMBASE (via Ovid) (1980–2016)
- The Cochrane Library (via Wiley Online Library)
    - HTA database (1995–2016)
    - NHS EED (1995–2015)
- CINAHL (via EBSCO*host*) (1982–2016)
- Web of Science Citation Index (Thomson Reuters) (1899–2016)
- CPCI (Thomson Reuters) (1990–2016)

The search strategy consisted of MeSH or EMTREE Thesauri terms and free-text synonyms for 'uveitis'. Searches were translated across databases and were limited by neither language nor publication date. The search strategies are presented in *Appendix 1*. Search filters designed to identify economic evaluations and quality-of-life studies were used on MEDLINE and other databases when appropriate. Reference and citation searching of included papers was undertaken.

The inclusion criterion was economic evaluations of treatments given to mainly adult patients for non-infectious uveitis. This took a deliberately broad perspective and was not limited to treatment with ADA or DEX. Studies that reported only costs were excluded, although these were marked as being potentially useful for informing the model parameters. Study selection was undertaken by one reviewer (IB) and checked by a second reviewer (HS). Critical appraisal of the included studies was undertaken using a combination of key components of the BMJ checklist for economic evaluations[93] together with the Eddy checklist for mathematical models[94] (see *Table 28*).

Results

The electronic literature searches identified 1177 potentially relevant economic analyses of treatment for non-infectious uveitis. Of these, only seven studies appeared to relate to the economic evaluation of non-infectious uveitis and full texts of these papers were obtained.[95–101] Two of these studies met the inclusion criteria,[100,101] one of which was published only as a conference abstract.[100] The numbers of studies screened and included within the review are shown in *Figure 7*.

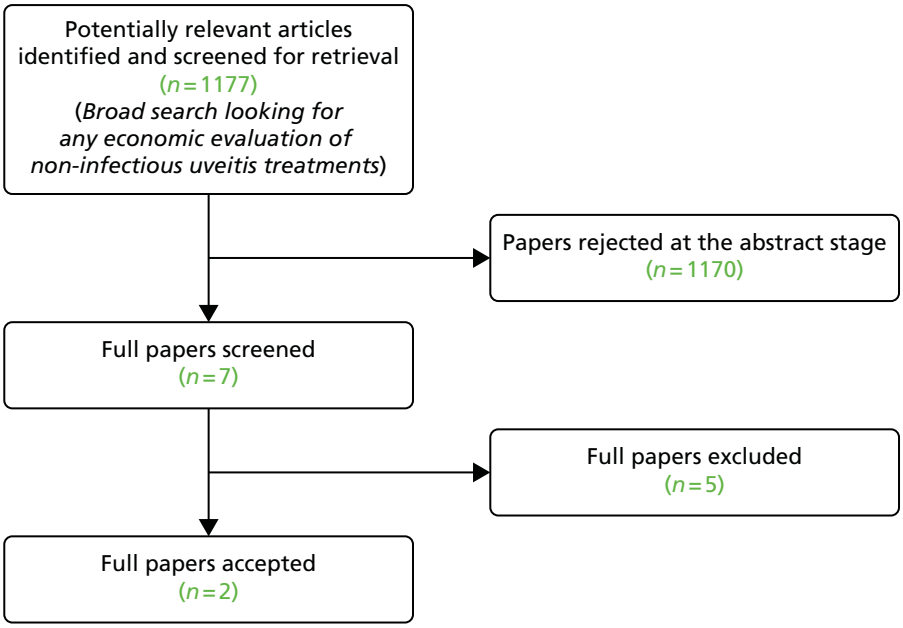

FIGURE 7 Summary of selection and exclusion of economic evaluation studies.

Justification for excluding studies at the full paper screening stage

The review by the Health Technology Inquiry Service[95] was excluded following full paper screening as it did not identify any cost-effectiveness studies. The study reported by Ang *et al.*[96] was excluded because it related to an analysis of interventions for tuberculous uveitis rather than non-infectious uveitis and compared diagnostic testing strategies rather than treatments for diagnosed disease. The studies by Ramanan *et al.*[97] and Ramanan *et al.*[98] were excluded because they were limited to children and they did not include an economic analysis. The study reported by Nguyen *et al.*[99] was excluded because it was not an economic evaluation.

Included economic evaluations

The key characteristics of the two studies[100,101] identified for inclusion within the review are shown in *Table 28* and are discussed briefly below. Neither of these studies included ADA or DEX as interventions or comparators. One of the economic analyses was based on a semi-Markov model[100] whereas the other[101] extrapolated cost and HRQoL data collected during the MUST trial.[57,102] The two economic evaluations compared a different set of treatments.

Padula et al.*:[100] a cost-effectiveness analysis of off-label biologics to treat sarcoid posterior uveitis versus standard of care: comparing infliximab to methotrexate and systemic steroids*

The study by Padula *et al.*[100] was reported only as a conference abstract. The authors presented the methods and results of a cost-effectiveness analysis of infliximab compared with methotrexate and systemic steroids over a lifetime horizon. The economic evaluation used a semi-Markov approach to estimate health outcomes and costs. Patients entered the model following the onset of sarcoid posterior uveitis. No further information was provided about the population reflected in the model. Cost-effectiveness was evaluated in terms of the incremental cost per quality-adjusted life-year (QALY) gained from a societal perspective.

Probabilities, health utilities and costs used in the model were reported to be taken from the literature, although parameter values were not reported in the abstract. It was not specified whether or not a systematic review was conducted. Costs and health outcomes were discounted at a rate of 3% per annum. Costs were expressed in 2010 US dollars. The authors conducted univariate sensitivity analyses, threshold analyses and probabilistic sensitivity analysis (PSA) using 10,000 simulations.

TABLE 28 Characteristics of studies included in the cost-effectiveness review

Characteristics	Study	
	Padula *et al.*[100]	Sugar *et al.*[101]
Country and year of publication	USA, 2011	USA, 2014
Type of economic analysis	Cost–utility analysis	Cost–utility analysis
Health economic perspective	Societal	Payer's perspective for costs and the patient's perspective for outcomes
Health economic comparisons (listed interventions)	Infliximab, systemic steroids, methotrexate	Fluocinolone acetonide intraocular implant, oral corticosteroid with immunosuppressive agents as needed
Population	Patients with sarcoid posterior uveitis	Patients aged ≥ 13 years with non-infectious intermediate uveitis, posterior uveitis or panuveitis in one or both eyes (active within ≤ 60 days) for which systemic corticosteroids were indicated (excluding those requiring systemic therapy for non-ocular indications)
Time horizon	Lifetime	3 years
Health economic outcomes	Incremental cost per QALY gained	Incremental cost per QALY gained
Modelling approach	Semi-Markov model	Extrapolation of trial data

QALY, quality-adjusted life-year.

The incremental cost-effectiveness ratio (ICER) for methotrexate compared with systemic steroids was estimated to be US$10,053 per QALY gained. Methotrexate dominated infliximab in the base case. However, if a patient's health utility after successful recovery was < 0.750 (base-case value of 0.84), then infliximab produced a greater net benefit than methotrexate, assuming a willingness-to-pay (WTP) threshold of US$50,000 per QALY gained. The PSA suggested that the probability of methotrexate dominating infliximab was 0.60.

It is not possible to assess the validity of the model as only limited information is provided within the conference abstract. The AG notes that this analysis does not include either of the interventions being assessed within this appraisal (DEX and ADA) and the model does not appear to differentiate between unilateral and bilateral uveitis, which may be associated with different cost-effectiveness results. There is insufficient information provided within the abstract for this analysis to be useful in the current appraisal.

Sugar et al.*:*[101] *cost-effectiveness of fluocinolone acetonide implant versus systemic therapy for noninfectious intermediate, posterior, and panuveitis*

Sugar *et al.*[101] presented a cost-effectiveness analysis of fluocinolone acetonide intraocular implant compared with oral corticosteroids and immunosuppressive agents. Costs and health benefits were estimated from data collected during the MUST trial.[57] The economic analysis used a time horizon of 3 years and costs and benefits were discounted at a rate of 3% per annum. Costs were expressed in US dollars (year unclear). The authors used a payer's perspective for costs and the patient's perspective for outcomes. The authors estimated the cost to a payer to maximise health benefits by using the more effective, but more expensive, treatment.

The within-trial data (differences in costs and utilities), reported at 2 years' follow-up, were extrapolated by a further year for a 3-year time horizon. The difference in the mean total costs of the treatments was determined with a linear regression with a saturated means model. The history of the disease was modelled through a sequence of utility values measured during the trial at different points in time. No health states were used. Uncertainty was assessed using bootstrapping and was represented using cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs).

For bilateral uveitis, the fluocinolone acetonide implant for both eyes was estimated to generate 0.057 additional QALYs at an additional cost of US$16,900; the ICER was reported to be US$297,800 per QALY gained. The probabilities of the fluocinolone acetonide implant being cost-effective compared with systemic therapy at WTP thresholds of US$50,000 and US$100,000 per QALY gained were 0.003 and 0.04 respectively. For unilateral uveitis, the implant resulted in 0.130 additional QALYs at an additional cost of US$5300; the ICER was reported to be US$41,200 per QALY. The probabilities of the implant being cost-effective compared with systemic therapy at WTP thresholds of US$50,000 and US$100,000 per QALY gained were 0.53 and 0.74 respectively.

The study highlights the importance of considering unilateral and bilateral uveitis separately within future economic evaluations in terms of (1) the cost difference between types of treatments, (2) quality-of-life impacts and (3) the greater risk to vision of an operative procedure on both eyes compared with one eye. However, this study does not consider the cost-effectiveness of the implant in one eye for patients with bilateral uveitis as all patients with bilateral uveitis within the MUST trial were given an implant in both eyes.[57] The model has several additional key limitations:

- All relevant comparators were not included in the model. Systemic steroids and immunosuppressants were assumed to be the gold standard as they were the only included comparators of the fluocinolone acetonide implant, with no discussion about whether or not this was appropriate.
- AEs were not taken into consideration.
- It is not clear how the 2 years of data from the MUST trial were extrapolated to the 3-year time horizon.
- It is not clear whether or not the implant would have benefits after this 3-year period.
- No model validation was reported.
- The analysis of uncertainty was not well described.

Company submissions

Neither AbbVie[55] (ADA) nor Allergan[43] (DEX) submitted a health economic model. Within its submission, AbbVie provided no discussion of cost-effectiveness and presented a budget impact estimate based on the acquisition costs of ADA only.[55]

Within its submission, Allergan argued that DEX has been recommended by NICE for the treatment of macular oedema secondary to retinal vein occlusion[103] and that the costs per patient associated with DEX are comparable for posterior segment uveitis and patients with macular oedema secondary to retinal vein occlusion, whereas the incremental gains in visual acuity are greater in posterior segment uveitis based on the trial data from the individual trials. This argument fails to consider the incremental (rather than absolute) cost of DEX treatment compared with current treatment. Allergan also submitted a budget impact model, which takes into account the costs of treatment and monitoring but not the costs of treating events associated with uveitis or AEs associated with treatment.

Summary of the review of existing cost-effectiveness studies

No existing studies have assessed the cost-effectiveness of either DEX or ADA within this patient population. Only one published health economic model of non-infectious uveitis exists. This study was subject to several limitations, including poor reporting of some of the methods, validation and uncertainty analysis, not taking into account AEs and the use of a 3-year time horizon, which may not fully capture all impacts of the treatments.

Independent economic assessment

Methods

This section provides details of the Markov model developed by the AG, which was used to evaluate the cost-effectiveness of ADA and DEX within their licensed indications for non-infectious posterior segment-involving uveitis compared with current practice, from a NHS and PSS perspective. A cohort of patients with

a mean age of 44.8 years was followed over a lifetime. All costs and QALYs were discounted at a rate of 3.5% per year. ADA and DEX were not compared against each other. This is because of their different use in clinical practice (see *Chapter 1*, *Description of the technologies under assessment*) and because, for the limited indications for which the clinician has a choice regarding which treatment to use, there is a lack of evidence, as detailed in *Chapter 3* (see *Indirect comparison of treatments: rationale for not undertaking*). *Table 29* describes the key features of the model for both ADA and DEX.

Because of the substantial uncertainties associated with the above assumptions because of the limited evidence base, most of the assumptions were altered within exploratory analyses to test their impact on the model results.

Model description

Patient population

The model population consists of people with non-infectious intermediate uveitis, posterior uveitis or panuveitis. Patients receiving DEX were assumed to have active disease, whereas the model assessed the

TABLE 29 Model summary (base-case analysis)

	Intervention	
Characteristic	**ADA**	**DEX**
Population	People with non-infectious intermediate uveitis, posterior uveitis or panuveitis with (1) active disease (VISUAL I[46]) and (2) inactive disease (VISUAL II[47])	People with non-infectious intermediate uveitis, posterior uveitis or panuveitis with active disease (HURON[48])
Intervention	ADA until treatment failure + LCP(VI), ADA until treatment failure + LCP(VII)	One DEX implant + LCP(H)
Comparator	LCP(VI), LCP(VII)	LCP(H)
Outcome used from trial	EQ-5D	VFQ-25
Time horizon	Lifetime	Lifetime
Discounting	3.5% per year for costs and QALYs	3.5% per year for costs and QALYs
Treatment discontinuation	Parametric survival curve of time to treatment failure fitted to VISUAL I and II trial data	Patients are given only one DEX implant
Method for estimating QALYs during the trial period	Use directly measured EQ-5D scores at each time point until treatment failure, when patients revert to baseline utility, adjusted for age	Use VFQ-25 data captured at each time point in the trial mapped onto EQ-5D scores
Method for estimating QALYs following the trial period	Patients who have not failed treatment retain the averaged utility from months 12–18 of the trial (because of small patient numbers), adjusted for age. Patients who fail treatment revert to baseline utility, adjusted for age	Assumes that utility remains the same for 4 weeks following the trial and then returns to baseline by week 30, adjusted for age
AEs (except blindness)	Cataract, raised IOP, glaucoma, serious infections, hypertension, fractures, diabetes. Impact on HRQoL associated with these AEs was assumed to be captured within the VFQ-25/EQ-5D scores	
Permanent blindness (comparator)	No blindness prior to treatment failure. Constant rate of blindness after treatment failure based on Dick *et al.*[19]	Constant rate of blindness based on Dick *et al.*[19]
Permanent blindness (intervention)	No blindness prior to treatment failure. Constant rate of blindness after treatment failure based on Dick *et al.*[19]	RR for blindness of 0.5 for 30 weeks following implantation
Treatment following remission	For all patients, treatment will continue until treatment failure	For all patients, treatment will continue until treatment failure

LCP(H), limited current practice based on the HURON trial; LCP(VI), limited current practice based on the VISUAL I trial; LCP(VII), limited current practice based on the VISUAL II trial.

cost-effectiveness of ADA separately for patients with active and inactive disease. An analysis was undertaken to explore the cost-effectiveness of DEX use in one eye in patients with unilateral disease as a separate subgroup; the trial did not provide data separately for this group and hence this analysis is considered to be exploratory. Because of a lack of evidence, it was not possible to explore additional subgroups. A cohort of uveitis patients was assumed to enter the model with a mean age of 44.8 years, based on the mean age within the HURON trial,[48] and was followed over a lifetime. The model population was limited to adults aged ≥ 18 years because the marketing authorisations for the technologies being considered relate only to this group.

Interventions

The two technologies considered were ADA (40 mg every 2 weeks until treatment failure) and the DEX implant (0.7 mg, once only in the base case).

Within the clinical trials of ADA (VISUAL I[46] and II[47]), patients were already receiving high-dose corticosteroids at randomisation, with a corticosteroid burst given to all patients at the start of the VISUAL I trial; corticosteroids were tapered to zero by week 15 (VISUAL I) or week 19 (VISUAL II). Clinical advisors to the AG suggested that this is also likely to reflect clinical practice, although the SmPC suggests that ADA may be given alongside corticosteroids or alone.[44] Given the evidence available, for patients with active disease, the model considers the cost-effectiveness of ADA plus an initial oral corticosteroid burst, rather than ADA alone.

The DEX implant can be administered in the affected eye to unilateral patients, in one eye for patients with bilateral disease or in both eyes at staggered intervals for patients with bilateral disease. Patients could also receive more than one consecutive implant. Clinical advisors to the AG suggested that the DEX implant would most probably be used when disease affects only one eye (or is more severe in one eye in the case of asymmetric disease), or to treat a temporary flare-up in one or both eyes, when systemic disease is not present or is well controlled. The base-case model assumed that patients would receive one DEX implant in one affected eye, as in the HURON trial.[48] There are no RCTs that assess the use of more than one consecutive implant or the use of implants in two affected eyes. However, there are several non-randomised trials, with 12–24 months of follow-up, that allow the use of repeat implants.[18,50,51] These studies consistently report that, after around 6 months, patients' outcomes return to those at baseline and that up to three repeat implants are each likely to have a similar treatment effect. Given the limited evidence around repeat implants, this was explored within sensitivity analysis. In one of the studies that assessed implants in both eyes, 3 out of 11 patients (27%) receiving implants had a response (reduced central retinal thickness and improved BCVA) in the second eye.[18] Clinical advisors to the AG suggested that it is more likely that systemic treatment would be used if both eyes required treatment; however, the direction of the ICER for treatment in both eyes compared with one eye is considered in *Chapter 6*.

Comparators

The two technologies were compared independently with current practice, which includes a range of immunosuppressants (such as methotrexate, mycophenolate mofetil, ciclosporin and azathioprine) and corticosteroids. Given the concerns regarding the robustness of undertaking a NMA (see *Chapter 3*, *Indirect comparison of treatments: rationale for not undertaking*), within the base-case analysis, current practice was assumed to be equivalent to practice in the control arm (sham or placebo) of the clinical trials of the interventions. In the VISUAL trials of ADA,[46,47] patients received initial corticosteroids, which were tapered by 15 weeks (VISUAL I[46]) and 19 weeks (VISUAL II[47]), and 32% in the VISUAL I trial[46] and 48% in the VISUAL II[47] study were receiving one immunosuppressant at baseline (across arms), which they were able to maintain according to the study protocol. Given that a greater proportion of patients in practice are likely to receive systemic corticosteroids, these comparators are denoted throughout as limited current practice based on the VISUAL I trial [LCP(VI)] or the VISUAL II trial [LCP(VII)]. In the HURON trial of DEX,[48] patients were allowed to receive rescue therapy with corticosteroids or immunosuppressants and 25% were using systemic immunosuppressants or anti-inflammatory treatment at baseline, which they were able to maintain according to the study protocol. This comparator is denoted throughout as limited current practice based on the HURON trial [LCP(H)]. Apart from rescue therapy with immunosuppressants within

the HURON trial, the proportions receiving immunosuppressants and corticosteroids were similar across the arms of the HURON[48] and VISUAL I[46] and II[47] trials. In current practice, a greater proportion of patients would receive systemic immunosuppressants or anti-inflammatory treatment than in the control arms of the pivotal studies; consequently, the base-case analysis is likely to underestimate both the effectiveness and the AE profile of current practice, as well as the costs associated with treatment. Within exploratory analyses, the AG assessed the impact on the results of increasing the value of these parameters within the model. However, it should also be noted that in clinical practice a greater proportion of patients being treated with ADA and DEX are also likely to receive concomitant treatment.

Outcomes

The model was used to estimate the incremental cost per QALY gained for each intervention compared with current practice.

The VISUAL trials and the HURON trial[48] each reported VFQ-25 HRQoL data at baseline and at each follow-up visit. The VISUAL trials[46,47] also reported EQ-5D data at baseline and at each follow-up visit. The model used the EQ-5D data directly for modelling the effectiveness of ADA. The HURON trial[48] reported EQ-5D data at baseline but not at subsequent time points. It was therefore not possible to use the EQ-5D data directly; however, Allergan shared patient-level data from the HURON trial with the AG, which allowed an analysis of the relationship between the VFQ-25 and the EQ-5D using the baseline data (see *Model structure*). It was necessary to convert VFQ-25 data to EQ-5D utilities to estimate QALYs associated with treatment with DEX and LCP(H).[104]

The use of the outcomes from the HURON trial[48] representing vision and inflammation (visual acuity, VH) was considered by the AG as an alternative to the use of the VFQ-25 for estimating QALYs; however, the VFQ-25 outcome was preferred because of the difficulties associated with using vision as an outcome in uveitis and capturing all impacts of the interventions (see *Chapter 1*, *Description of the health problem*). Clinical advisors to the AG suggested that clinicians measure ocular outcomes based on multiple factors, including visual acuity, VH and macular oedema. The VFQ-25 captures multiple components of vision, as well as broader considerations such as general health and the vision-related impact on the ability to drive and undertake normal activities. It is also essential to capture the AEs associated with the treatments and it is difficult to determine the utility decrements associated with the multiple interacting AEs associated with these treatments. The AG considered that the VFQ-25 should largely capture the impact of AEs, as well as treatment effects, on HRQoL.

The presence of unilateral or bilateral uveitis is important in terms of estimating outcomes for several reasons. The BCVA in the better-seeing eye is more representative of quality of life than the BCVA in the worst-seeing eye.[105] In addition, a patient with bilateral disease is expected to have a lower quality of life on average than a patient with unilateral disease. Thus, a person with bilateral disease has more scope to benefit from treatment. However, in patients with bilateral disease receiving local treatment, the choice of study eye is important in determining the extent to which quality of life can increase.

In the VISUAL I[46] and VISUAL II[47] trials, 91% and 96% of patients had bilateral disease respectively. Clinical advice received by the AG suggests that this is representative of patients who would be given ADA in practice because it is a systemic treatment. Within the HURON trial[48] it was not recorded whether patients had unilateral or bilateral disease. Based on the patient-level data provided by Allergan, the proportion of patients with VH that was greater than zero in the non-study eye was 51%; clinical advisors to the AG stated that this suggests that $\geq$ 51% of patients had bilateral disease. Within the HURON trial,[48] when patients had bilateral uveitis, the right eye was chosen for treatment. This resulted in the better-seeing eye being treated in 10.7% and 17.1% of cases for DEX 700 and the sham procedure respectively.

Given that the presence of unilateral or bilateral uveitis was not reported in the HURON trial,[48] it was not possible for the AG to undertake robust subgroup analysis around this factor. The base-case model is therefore dependent on the assumption that the patients included within the HURON trial and the way in

which DEX was used within the trial would be representative of current practice. It was not possible to draw robust conclusions about the subgroups separately in terms of cost-effectiveness; however, an exploratory subgroup analysis was undertaken (see *Model evaluation methods*). As described within *Chapter 1* (see *Description of the health problem*), it is expected that around 70–80% of this patient population would have bilateral disease. However, it may be that, because DEX is a local treatment, patients with unilateral disease would be more likely to be selected for DEX treatment, both within the trial and in practice. Given that patients with bilateral disease have a greater capacity to benefit from treatment because of the BCVA of the better-seeing eye being the best predictor of quality of life, and that treatment of one eye would cost the same whether given to a person with unilateral or bilateral disease, if the trial had a lower proportion of bilateral cases than in practice, the effectiveness of DEX may be underestimated. Conversely, if the trial had a higher proportion of bilateral cases than in practice, the effectiveness of DEX may be overestimated.

Time horizon

The time horizon of the model was the lifetime of patients (up to age 100 years) and a starting age of 44.8 years was used, representing the average age of patients with non-infectious posterior segment-involving uveitis within the HURON trial.[48] A cycle length of 2 weeks was chosen as this is the time between administration of ADA doses and assessment of patients for disease progression. This is also a sufficiently short cycle length to capture all relevant clinical events associated with DEX and current practice.

Discounting

All costs and QALYs were discounted at a rate of 3.5% per year.

Model structure

The structure of the AG model is presented in *Figure 8*. The model includes five health states: (1) treatment: no permanent blindness, (2) treatment failure: no permanent blindness, (3) permanent blindness, (4) remission (no treatment) and (5) death. For DEX, treatment was one implant, which was assumed to be effective for 6 months, at which time patients move to the treatment failure health state if they have remained in the treatment state until this time. Patients in the LCP(H) group begin in the treatment failure health state. Patients may discontinue ADA because of treatment failure, defined by the VISUAL trial criteria,[46,47] at which time they will move to the treatment failure health state if they have remained in the treatment state until this time. Patients in the LCP(VI) and LCP(VII) groups also begin in the treatment health state and move to the treatment failure health state once they have met criteria for treatment failure. Within the treatment health state, HRQoL (defined using the VFQ-25 or EQ-5D) can be improved as a result of the treatment effect or as a result of a reduction in AEs. The HRQoL estimates should capture any impacts of the interventions on visual loss while treatment is provided. However, treatment may also reduce the risk of experiencing permanent damage to the eye, resulting in a decreased risk of permanent legal blindness. Once a patient experiences legal blindness in the model, they can either remain in this health state or progress to death.

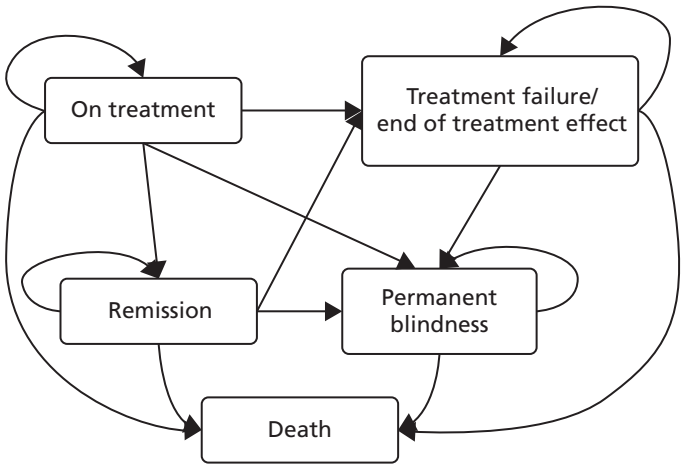

FIGURE 8 State transition diagram of the decision model.

Patients may also enter remission, whereby they do not receive further treatment but they continue to receive the benefits of the previous treatment. Within the base case, the proportion of patients experiencing remission was assumed to be zero; the impact of increasing this proportion was considered within the exploratory analyses.

Estimation of model parameters

Treatment discontinuation

In the base-case analysis, the DEX implant was assumed to be administered only once to one eye and to have an efficacy of 30 weeks, based on data from the HURON trial.[48]

Patients could discontinue ADA as a consequence of any of the four criteria for treatment failure used within the VISUAL trials,[46,47] including (1) the development of new inflammatory lesions, (2) worsening of AC cell grade, (3) worsening of VH grade or (4) worsening of visual acuity. Treatment discontinuation was modelled using parametric curves fitted to Kaplan–Meier curves for time to treatment failure from the trials. The Kaplan–Meier curves for time to treatment failure included in the VISUAL I[52] and II[72] clinical study reports were digitised and individual patient data were reconstructed using the methods described by Guyot *et al.*[106] A number of parametric curves were fitted to the data using the flexsurv R package (R version 3.3.2, flexsurv version 1.0.0; The R Foundation for Statistical Computing, Vienna, Austria). *Tables 30* and *31* present the Akaike information criterion (AIC) and Bayesian information criterion (BIC) scores for statistical goodness of fit.

It should be noted that these are relative measures of goodness of fit and it is possible that other models not tested here could provide a better fit to the data. *Figures 9–12* show the Kaplan–Meier data and the fitted parametric distributions for the VISUAL I[46] and II[47] trials for the ADA and comparator groups.

The statistical analysis suggested that, of those tested, the parametric distributions with the best fit to the data were the Gompertz and the log-normal distributions for both the ADA group and the placebo group in the VISUAL I[46] and II[47] trials. Clinical advisors to the AG suggested that it is clinically plausible that some patients would remain on ADA for years; hence, the plateauing of these curves seems potentially

TABLE 30 Akaike information criterion and BIC scores for parametric curves fitted to the Kaplan–Meier curves for time to treatment failure in the ADA arm in the VISUAL I trial[46]

Criterion	Arm	Log-normal	Gamma	Weibull	Gompertz	Exponential	Log-logistic
AIC	ADA	374.7	388.5	384.7	370.3	403.4	377.5
	Placebo	435.9	465.7	456.5	438.4	486.7	438.9
BIC	ADA	377.4	391.2	387.4	373.0	407.1	380.2
	Placebo	438.5	468.4	459.2	441.1	490.3	441.5

TABLE 31 Akaike information criterion and BIC scores for parametric curves fitted to the Kaplan–Meier curves for time to treatment failure in the ADA arm in the VISUAL II trial[47]

Criterion	Arm	Log-normal	Gamma	Weibull	Gompertz	Exponential	Log-logistic
AIC	ADA	370.6	378.9	377.3	364.9	382.2	373.1
	Placebo	403.5	408.4	406.1	403.7	428.5	403.2
BIC	ADA	373.3	381.6	380.0	367.7	385.9	375.8
	Placebo	406.2	411.2	408.8	406.4	432.3	406.0

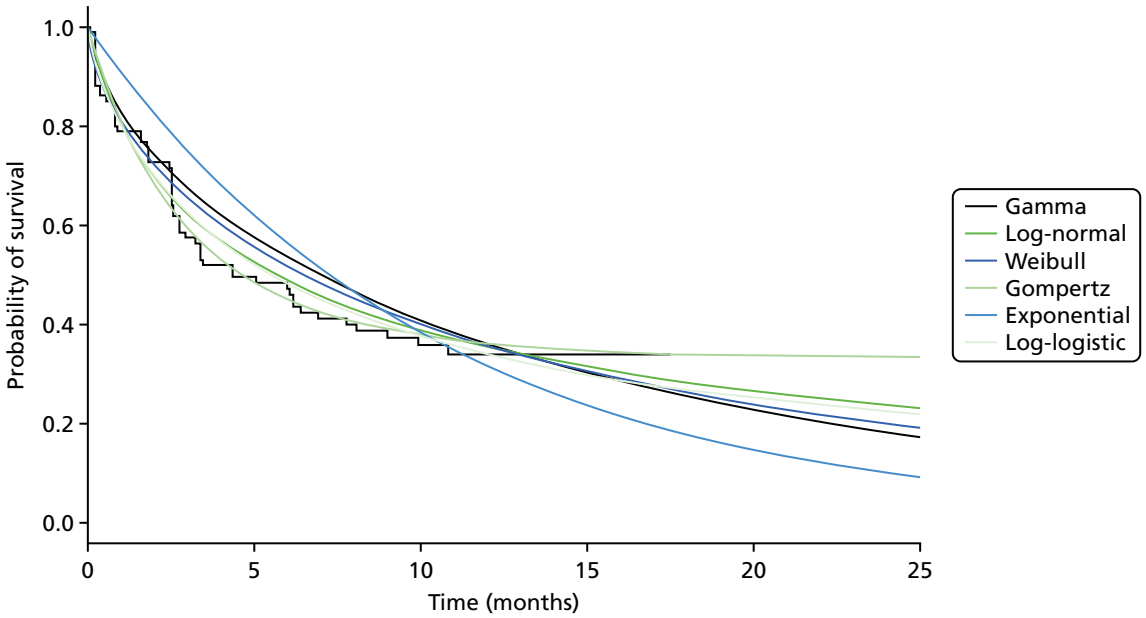

FIGURE 9 Observed and fitted curves for time to treatment discontinuation in the ADA arm in the VISUAL I trial.

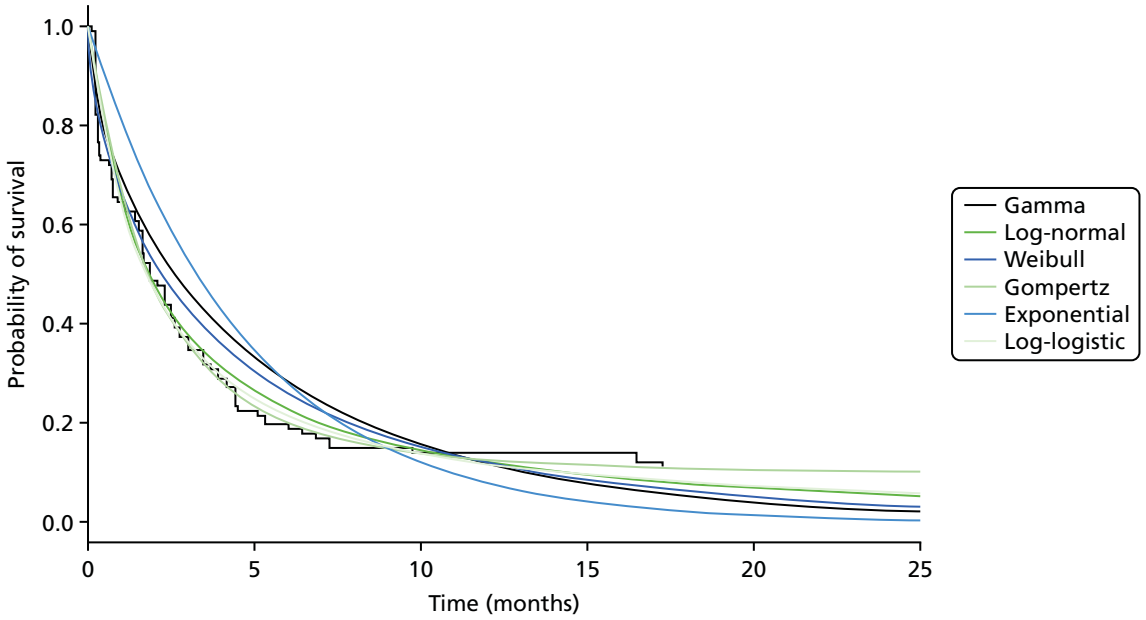

FIGURE 10 Observed and fitted curves for time to treatment discontinuation in the placebo arm in the VISUAL I trial.

reasonable. However, the Gompertz curve seems clinically implausible as observational studies of ADA in similar patient populations have suggested that patients are likely to continue to fail treatment in the longer term.[107,108] The log-normal distribution appears to be the most plausible for the placebo arm so that patients do fail on treatment relatively quickly. The log-normal distribution also appears clinically reasonable for the ADA group. It should be noted that, although based on these predictions alone some patients would continue to receive treatment for an implausibly long period of time, within the model patients may die of other causes, which negates the need for a cure model to be employed.

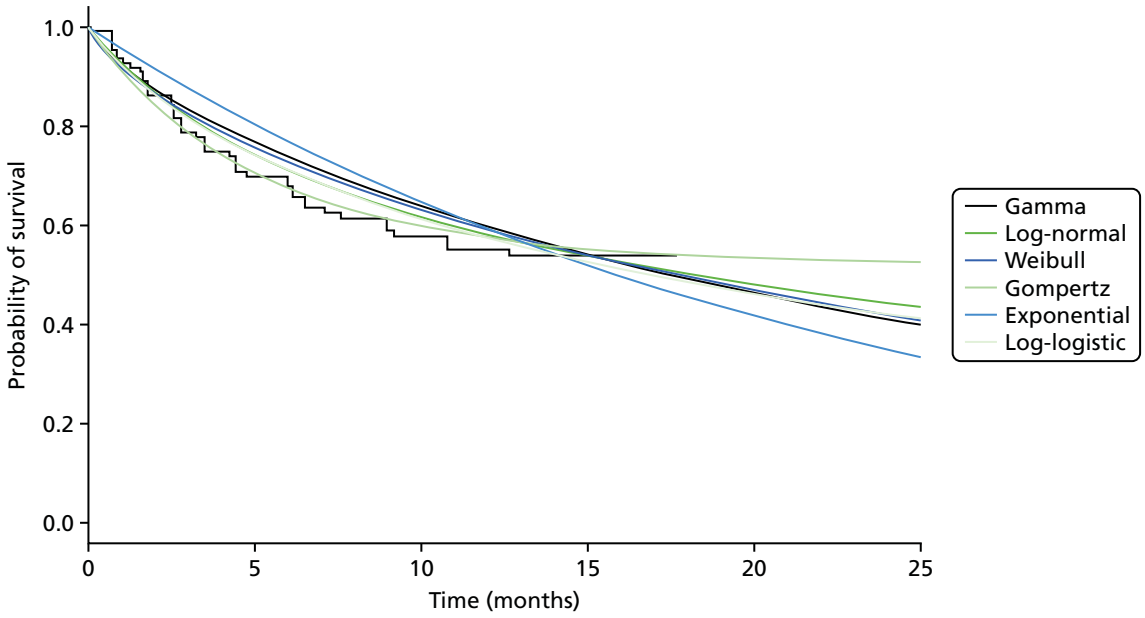

FIGURE 11 Observed and fitted curves for time to treatment discontinuation in the ADA arm in the VISUAL II trial.

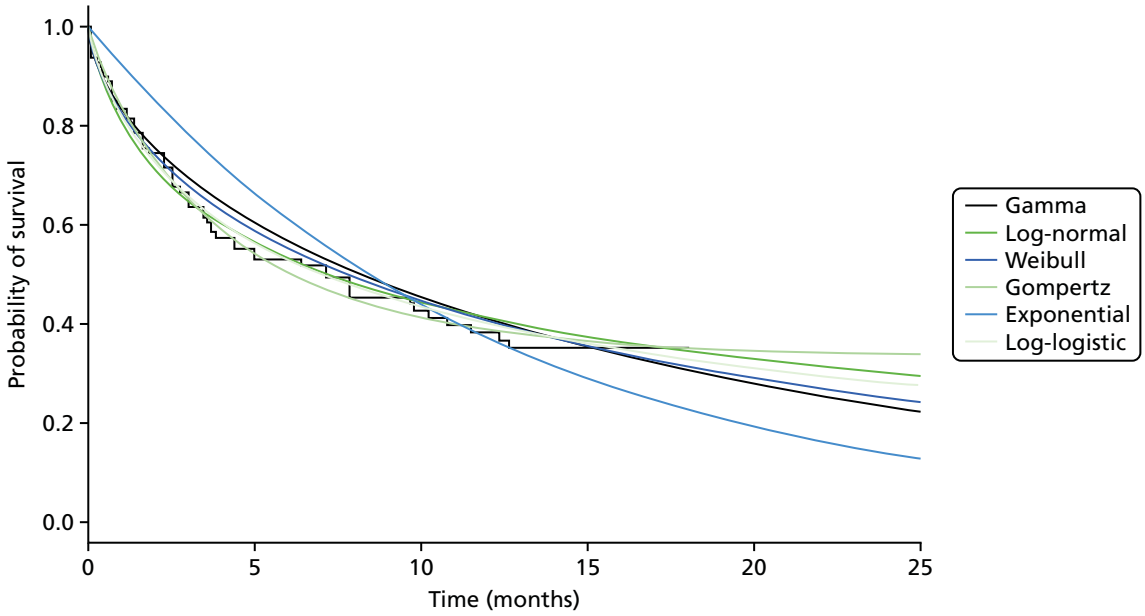

FIGURE 12 Observed and fitted curves for time to treatment discontinuation in the placebo arm in the VISUAL II trial.

It was assumed that after patients fail and discontinue treatment with ADA, or 6 months after the DEX implant is injected, patients receive limited current practice, which includes a range of immunosuppressants (such as methotrexate, mycophenolate mofetil, ciclosporin and azathioprine) and corticosteroids for a proportion of patients. It was also assumed that ADA and DEX are effective only while they are being given. Therefore, patients who are no longer being treated with ADA, and patients who received the DEX implant > 6 months ago, accrue no additional health gains.

Permanent legal blindness

The VISUAL[46,47] and HURON[48] trials did not report any occurrence of blindness, which is likely to be because of the short duration of these trials. However, it may be that the use of ADA or DEX could prevent damage to the eye, which may in turn prevent future blindness. Conversely, it is possible that the

AEs associated with treatment (such as raised IOP) could lead to an increased risk of blindness via glaucoma. There is no evidence about any longer-term (positive or negative) impacts of the interventions on vision loss beyond the treatment duration. As such, it was not possible to include a complex model of long-term outcomes associated with the interventions. However, as these interventions ultimately aim to reduce permanent damage to the eye, a state for becoming permanently legally blind was included as this has the largest impact on quality of life and costs.

We defined blindness as a BCVA of $\leq$ 20/200 in the better-seeing eye, according to the UK definition of legal blindness.[109] The AG considered two approaches for modelling permanent blindness based on the evidence from the key RCTs. The first was to extrapolate the decrease in BCVA over time using the mean change and distribution from the trials and estimate the proportion of patients who would go below the legal blindness threshold in each group. The AG considered that this approach had three weaknesses: (1) the follow-up period of the clinical trials was not long enough to capture the total impact on visual acuity because damage to the eye does not always immediately impact on visual acuity; (2) there are different trajectories according to the cause of the damage to the eye, which could not be appropriately captured by a single parametric distribution; and (3) for patients with unilateral disease, additional assumptions about the probability of blindness in both eyes would need to be made.

The second approach considered by the AG was to use outcomes from the trials such as glaucoma and macular oedema as surrogate outcomes for blindness in the future. In principle, this would allow a more accurate estimate of blindness over time to be made, and could exclude outcomes such as cataract, for which blindness is reversible through surgery. However, the AG did not identify any evidence that could provide a link between these shorter-term outcomes and blindness. The only evidence of blindness caused by uveitis identified by the AG was cross-sectional and did not specify time to blindness.[18,27] This means that populating the model would have required elicitation or an assumed distribution for how long it would take patients to become blind and for this to be extended beyond the period of the cross-sectional study data. In addition, the key long-term outcome to include in the model is blindness in both eyes, given that the BCVA in the better eye is the best predictor of quality of life and blindness in both eyes would incur the greatest costs. The cross-sectional studies do not provide sufficient information to estimate the probability of blindness in both eyes; hence, numerous assumptions would be required. The identified studies also include patients with anterior uveitis. The AG requested the patient-level data from the authors of one of the cross-sectional studies[18] to be able to predict blindness over time from the outcomes reported within the clinical trials; however, these data were not provided. Given the number of assumptions that would be required to undertake this analysis in the absence of patient-level data, and the low proportions of patients reported to have glaucoma (< 3% in any arm) and new cases of macular oedema (< 8% in any arm) in the clinical trials,[46–48] the AG decided that adopting such a complex analysis within the model may produce potentially misleading results.

Therefore, a simpler approach was taken and the assumptions were tested within exploratory analyses. For the base-case analysis, clinical experts to the AG helped to identify sources that could be used to estimate a constant blindness rate associated with (limited) current practice. All studies identified were cross-sectional rather than longitudinal. The best source of evidence was considered to be a study by Dick *et al.*,[19] a retrospective analysis of insurance claims data, because all patients ($n = 1769$) had posterior segment, non-infectious uveitis. A constant rate of blindness and uncertainty around this parameter was estimated by the AG based on the proportion of patients going blind within the study by Dick *et al.*[19] and the mean follow-up time. By 10 years, this study predicted that 6.6% of patients would go legally blind, in the absence of death from other causes. The proportions of patients who had unilateral and bilateral disease are not reported within the study. Two alternative similar sources were also identified as being potentially relevant, studies by Tomkins-Netzer *et al.*[18] and Durrani *et al.*[11] The constant blindness rate derived from the study by Tomkins-Netzer *et al.*[18] was deemed to be an underestimate by one of the clinicians consulted by the AG (Alastair Denniston, personal communication) and the study included a wider population than the target population of the current appraisal (including patients with infectious and anterior uveitis). The rate derived from the study by Durrani *et al.*[11] was substantially higher than the rate

derived from Dick *et al.*[19] but this study also included a wider population. As the authors warned, 'being a tertiary referral centre, more patients are likely to suffer from severe, often bilateral uveitis' and they acknowledged that the results of their study 'could not be applied to the general population because of the tertiary nature of the patient population'.[11] The AG explored the impact of using blindness rates based on these other two sources in exploratory analyses (see *Exploratory sensitivity analyses* and *Results*).

As discussed earlier, there is no evidence on the treatment effect of ADA or DEX on legal blindness. To model the impact of treatment with ADA on the rate of blindness, given the strict criteria for treatment failure within the VISUAL trials,[46,47] it was assumed that patients could not go blind before treatment failure. This was assumed for both the intervention and the comparator. The rate of blindness following treatment failure was then approximated so that the rate of blindness at each cycle in the placebo group was equivalent to the estimate from Dick *et al.*[19] It was not considered clinically reasonable that a DEX implant would prevent all cases of blindness during treatment, but it was deemed equally unreasonable to assume that it would prevent no cases of blindness. In light of the absence of evidence around this parameter, the AG sampled from a uniform distribution between 0 and 1 within the PSA and used the mean of this distribution (0.5) for the deterministic analysis. Therefore, the AG assumed that half of the cases of blindness in this group would be avoided for the period in which the treatment effect was applied (30 weeks in the base case). It was assumed that patients in the comparator group would have the same blindness rate as in the general population.

The AG heard from clinicians that around 20–30% of patients with uveitis remain unilateral and that patients treated with DEX are more likely to be unilateral. The AG assumed that patients who remained unilateral would not go blind and therefore the rate of blindness in the DEX target population would be lower than that in the general population and this is turn would be lower than that in the ADA target population. For the base case, the AG assumed that, in the general population, 25% of patients would remain unilateral whereas in the DEX target population 30% of patients would remain unilateral. For ADA, the proportions of patients with unilateral uveitis as reported in the VISUAL I[46] (9.2%) and VISUAL II[47] (4.4%) trials were used for active and inactive patients respectively. The blindness rate for bilateral patients was determined by dividing the blindness rate estimated from Dick *et al.*[19] by the proportion of bilateral patients in the general population. The incidence of blindness in each analysis was adjusted by multiplying the rate of blindness for bilateral patients by the proportion of bilateral patients in each population.

Adverse events

One of the key drivers for new treatment options is the substantial AE profile of existing treatments, which reduce HRQoL and incur treatment costs. In addition, treatment with ADA and DEX is associated with AEs. Given that the main outcome measures being used from the clinical trials were the VFQ-25 and EQ-5D, it was assumed that these will capture the quality-of-life impacts associated with AEs during the period in which the treatments are provided. The incidence of AEs from the trials was therefore used only to calculate the additional costs associated with their management. As such, AEs included within the model are limited to those for which the cost of treatment is substantial. Based on advice from the clinical experts to the AG, the AEs associated with substantial costs of treatment are cataract, raised IOP, glaucoma, serious infections, hypertension, fractures and diabetes.

There are no longer-term safety data for ADA and DEX for uveitis beyond the data reported within the key clinical trials.[46–48] However, Burmester *et al.*[110] reported the results of a study on the long-term safety of ADA in 23,458 patients with other indications compared with the general population in terms of the incidence of disease. The study found that overall malignancy and lymphoma rates were not increased as a result of ADA use. Although the incidence of non-melanoma skin cancer was greater for patients receiving ADA for some of the indications included, for all indications death rates were equivalent to or lower than those expected in the general population. Given the findings of this study, the model does not include any longer-term cumulative impacts of ADA on patient outcomes. For DEX, the model assumed that patients will receive only one implant. The application of more than one implant is considered later in the discussion section.

There is no clinical rationale for the AEs associated with corticosteroid use to differ between study arms because usage is similar between the arms within the trials. Therefore, although diabetes and osteoporosis are associated with substantial costs, there are no real differences in incidence between the arms of the trials. Within the exploratory analysis assessing the impact of greater corticosteroid use in the comparator groups, the proportion of patients with these AEs was increased according to their incidence in the MUST trial.[57]

The probabilities of AEs per cycle used in the model (*Table 32*) were calculated based on their incidence in the trials and the mean follow-up time of each trial.

Quality of life

Estimating the relationship between the Visual Function Questionnaire and the EuroQol-5 Dimensions The AG considered the published studies for mapping the VFQ-25 to the EQ-5D included in the database of mapping studies by Dakin.[111] However, none of the published mapping studies was based on a population with uveitis and, considering that the AG had access to the VFQ-25 and EQ-5D patient-level data at baseline from the HURON trial,[48] the AG decided to fit a new mapping model. The AG used the approach that produced the best fit according to Browne *et al.*[112] (ordinary least squares) and noticed that the mapping resulted in similar coefficient values to those presented by Payakachat *et al.*,[113] who used an alternative modelling method (censored least absolute deviation). The mapping was used for all of the analyses involving DEX, within the exploratory analyses comparing the interventions with current practice, as provided in the MUST trial,[57] and within a sensitivity analysis for ADA.

The patient-level data from the HURON trial[48] were used to test for a correlation between the VFQ-25 and the EQ-5D at baseline. The scatterplot is presented in *Figure 13*. A linear regression model was fitted to the data to predict EQ-5D utilities from VFQ-25 scores. One regression model was fitted to all three arms of the HURON trial (sham, DEX 350 implant and DEX 700 implant) to maximise the sample size for the regression analysis. The underlying assumption was that the relationship between VFQ-25 scores and EQ-5D utilities would be independent of treatment. The fitted regression used in the economic model was:

$$\text{EQ-5D utility} = 0.4454059 + \text{VFQ-25 score} \times 0.0051322. \quad (1)$$

It is recognised that a linear model is not bounded and is likely to have poor performance for utility values at the extremes. However, given that the mapping was only used for means, no extreme values were used. Alternative non-linear models (e.g. quadratic regression) were also tested but did not significantly improve the fit to the data. The variance–covariance matrix of the slope and the intercept of the regression model is presented in *Table 33*. To represent the uncertainty in the regression model, the matrix was used to

TABLE 32 Probability of AEs per cycle

			Active uveitis		Inactive uveitis		
AE	DEX 700	LCP(H)	ADA	LCP(VI)	ADA	LCP(VII)	SSI
Raised IOP	0.019	0.005	0.002	0.002	0.001	0.001	0.001
Cataract	0.016	0.011	0.002	0.002	0.001	0.003	0.008
Glaucoma	0.000	0.002	0.001	0.000	0.000	0.000	0.001
Hypertension	0.002	0.003	0.002	0.001	0.003	0.003	0.002
Serious infections	0.000	0.000	0.003	0.003	0.001	0.001	0.000
Fracture	0.000	0.000	0.000	0.000	0.000	0.000	0.002
Diabetes	0.000	0.000	0.000	0.000	0.000	0.000	0.001

SSI, systemic steroids and immunosuppressants.

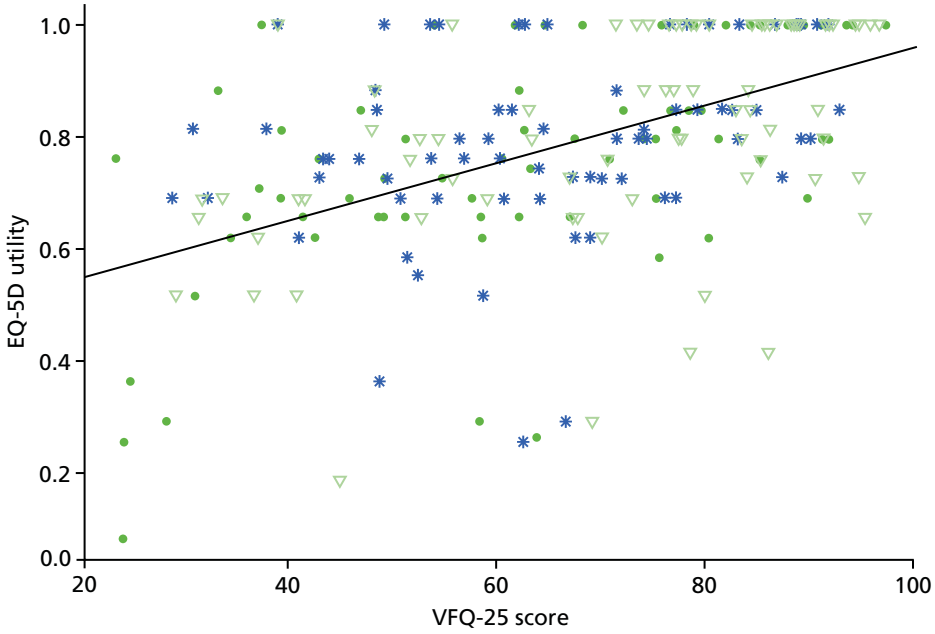

FIGURE 13 The relationship between the VFQ-25 and the EQ-5D based on patient-level data from the HURON trial.[48]

TABLE 33 Variance–covariance matrix of the intercept and the covariate of the regression model

	Intercept	VFQ-25
Intercept	1.75E-03	
VFQ-25	–2.42E-05	3.63E-07

sample the two coefficients of the regression model in the PSA. The baseline utilities, that is, the utilities for patients at week 0, were estimated based on the patient-level data from each trial: the HURON trial[48] for DEX and its comparator [LCP(H)], the VISUAL I trial[46] for ADA and its comparator in active patients [LCP(VI)] and the VISUAL II trial for ADA and its comparator in inactive patients [LCP(VII)]. In the HURON trial,[48] the baseline utility and visual acuity were substantially different between the sham arm and the DEX arm (visual acuity was 71.3 for the sham arm and 63.7 for the DEX 700 arm). Clinical advisors to the AG were asked to consider whether or not the baseline difference in both utility and visual acuity were reasonably due to random variation. All three experts agreed that a difference in visual acuity of $\geq$ 10 letters is considered to be clinically significant and a difference below this level could be owing to random variation and therefore it is plausible that the difference between the arms at baseline in the HURON trial was due to random variation. The baseline utilities were not varied to represent any population subgroups because these data were not available from the trials. The impact of changing the baseline utility has been assessed within the univariate sensitivity analysis; however, this analysis assumes that the relative treatment effect remains the same. This is unlikely to be the case for subgroups with differing baseline utilities such as patients with unilateral or bilateral uveitis. However, there is no evidence from the trials around outcomes for these subgroups that would enable a robust subgroup analysis.

Estimating utility over time The VFQ-25 data from each follow-up point within the HURON trial[48] (weeks 0, 8, 16 and 26) and the EQ-5D data from each follow-up point of the VISUAL trials[46,47] (weeks 0, 1, 4, 6, 8, 12, 16, 20, 24, 27 and 32 and then every 4 weeks until week 80) were used to estimate the change in utility for each treatment group over the time period of the trials. These were adjusted according to the average baseline utilities but maintaining the change from baseline in each arm.

When comparing DEX with its comparator, the AG assumed that the utility of patients who received DEX would drop to that of patients in the comparator arm after the duration of the treatment effect. Within the base-case analysis, the treatment effect was assumed to last for 30 weeks (4 weeks longer than the trial period). Within the sensitivity analyses the utility was assumed to decrease to the baseline utility over varying time periods. When comparing ADA with its comparator, for patients who fail and hence discontinue treatment it was assumed that utility returns to the baseline utility score, adjusted for any reduction in utility associated with age. For patients who receive ADA beyond the duration of the trial (80 weeks), it was assumed that their utility remains constant after the last follow-up point until treatment discontinuation. This utility is based on the mean of the last 6 months of data. *Figures 14–16* present the predicted mean utility values over time, excluding any adjustments for blindness, for DEX compared with LCP(H) for active patients, ADA compared with LCP(VI) for active patients and ADA compared with LCP(VII) for inactive patients respectively.

Age adjustments to utility were based on the regression equation reported by Ara and Brazier.[114] Age-related utility was calculated using the following formula:

$$\text{Utility} = A \times (\text{Male}) + B \times (\text{Age}) + C \times (\text{Age} \times \text{Age}) + D, \quad (2)$$

where $A = 0.0212126$, $B = -0.0002587$, $C = -0.0000332$ and $D = 0.9508566$.

The ratio between the utility for the general population at the starting age and that of the mean cohort age at each cycle was applied within the model.

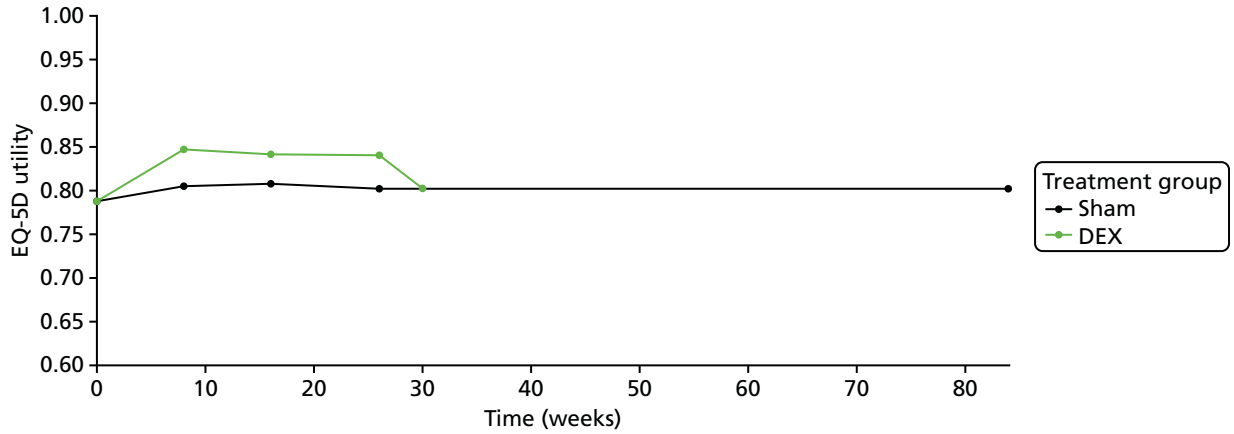

FIGURE 14 Mean utilities for DEX compared with LCP(H) for active patients over time.

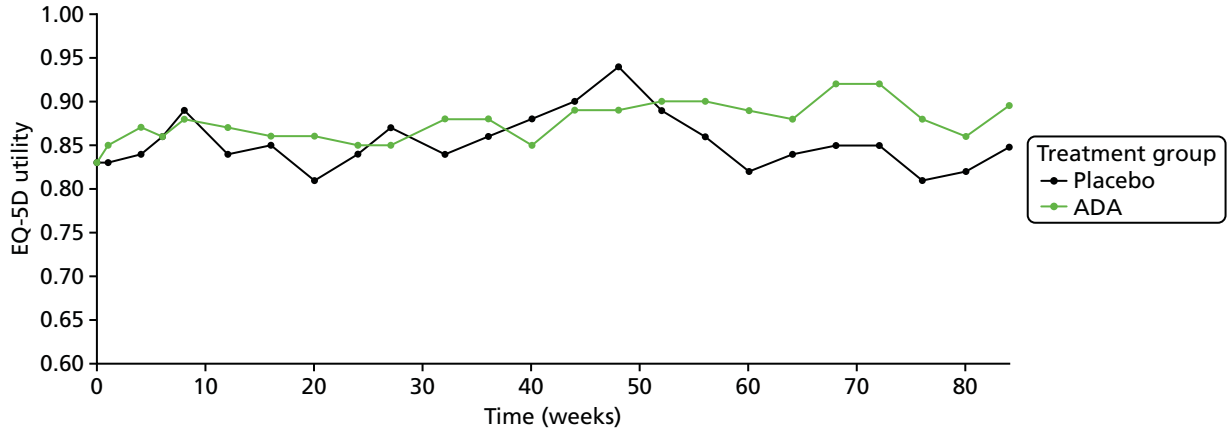

FIGURE 15 Mean utilities for ADA compared with LCP(VI) for active patients over time.

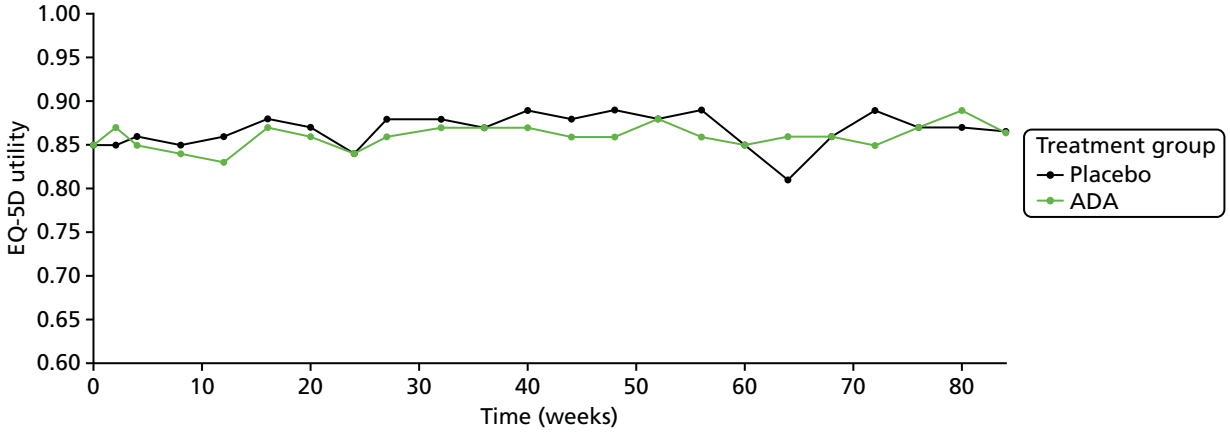

FIGURE 16 Mean utilities for ADA compared with LCP(VII) for inactive patients over time.

Adverse events Given that the main outcome measures being used from the clinical trials are the VFQ-25 and EQ-5D, it was assumed that these will capture the quality-of-life impacts associated with AEs during the period in which the treatments are provided.

Utilities associated with blindness Two UK-based studies report utilities associated with blindness,[109,115] which the AG thought to be the best sources of evidence. Both studies have been used within previous NICE appraisals.[116–120] Czoski-Murray *et al.*[109] used contact lenses to simulate blindness associated with macular degeneration, whereas Brown[115] estimated utilities according to valuations by patients with a range of conditions associated with blindness. The AG used the time trade-off values reported in these studies. Each study provided utilities for different levels of blindness and the AG calculated a weighted average based on the number of patients within the studies falling into each category. This assumed that patients with uveitis would have a similar distribution for the severity of blindness. The study by Czoski-Murray *et al.*[109] was used in the base-case analysis as it was based on public valuations of utility; however, it does not provide utilities for the worst states of blindness and may therefore overestimate the overall utility associated with blindness. This resulted in a utility associated with blindness of 0.38. Uncertainty around this parameter was modelled using the variance–covariance matrix provided within the study. The utility estimated from the study by Brown[115] (0.57) was employed within sensitivity analysis.

Resource use and costs

Treatment costs The costs of ADA, DEX, immunosuppressants and corticosteroids were based on the latest drug tariff.[49] Drug acquisition costs included within the model are presented in *Table 34*.

TABLE 34 Drug acquisition costs

Drug	Dose	Brand name	6-monthly cost (£)
ADA	40 mg every 2 weeks	Humira	4578
DEX	One 0.7-mg implant	Ozurdex	870
Mycophenolate mofetil	1 g twice daily	NA	136
Methotrexate	15 mg weekly	NA	16
Ciclosporin	2 mg/kg twice daily	NA	985
Azathioprine	1 mg/kg daily	NA	27
Systemic prednisolone	7.5 mg daily	NA	12

NA, not applicable.

The cost of treatment with immunosuppressants was calculated separately for each comparison [DEX vs. LCP(H), ADA vs. LCP(VI) and ADA vs. LCP(VII)] as a weighted average of mycophenolate mofetil, methotrexate, ciclosporin and azathioprine, based on their usage in the relevant trials (HURON,[48] VISUAL I[46] and VISUAL II[47]).

The two arms of each clinical trial were similar in terms of the use of corticosteroids and other medications, when reported. There was, however, an imbalance in the use of rescue therapy within the HURON trial.[48] The clinical study report states that the proportions of patients who received rescue therapy, which involved systemic and local corticosteroid use and immunosuppressants, in the DEX arm and the sham arm were 22.1% and 38.2% respectively.[71] Based on the patient-level data from the HURON trial,[48] the largest imbalance is in the provision of immunosuppressants as rescue therapy; these therapies are also more costly than corticosteroids. Of those patients who were not already taking immunosuppressants at baseline, only one patient from the DEX arm (1.3%) received an immunosuppressant whereas eight patients in the sham arm (10.5%) received an immunosuppressant. Of these, three patients received an immunosuppressant for 1–2 months and the remaining five patients did not stop immunosuppressant use within the trial period. This suggests that DEX may reduce the need for immunosuppressants. The model includes the costs of the additional immunosuppressants provided to the proportion of patients receiving this rescue therapy. The use of corticosteroid rescue therapy within the HURON trial[48] was more similar between the DEX group and the sham group (20.7% for DEX vs. 27.7% for sham) and such therapy is generally provided for only 2–4 weeks based on the patient-level data. Given that corticosteroids are inexpensive, this would result in a minimal cost difference between the groups and hence these costs have not been incorporated within the model. Within the base case, all other treatment costs were assumed to be the same between the DEX group and the LCP(H) group and between the ADA group and the LCP(VI)/LCP(VII) groups. An exploratory analysis was undertaken to explore the impact of an increase in the costs and utilities of the comparators.

Administration costs The DEX implant was assumed to be administered within one outpatient appointment at a cost of £113.42, based on *NHS Reference Costs 2014–15*[121] (minor vitreous retinal procedures, ≥ 19 years). ADA was assumed to be self-administered; the base-case model assumed that 10% of patients will need help from a district nurse to administer the injections, at a cost of £44, based on *Unit Costs of Health and Social Care 2015*[122] (district nurse cost per hour). All other treatments would be administered by the patient and therefore there would be no extra costs of administration for corticosteroids or immunosuppressants.

Monitoring costs The model assumed that all patients would receive monitoring every 6 weeks, irrespective of treatment. Monitoring consists of outpatient visits for visual function monitoring to assess the efficacy of the treatments and to monitor the risk of AEs. The AG assumed that monitoring for AEs was conducted alongside regular visual function monitoring follow-ups. It was also assumed that patients receiving immunosuppressants would receive six additional blood monitoring visits annually. Both regular monitoring and blood monitoring appointments were assumed to cost £96.11, based on *NHS Reference Costs 2014–15*[121] (outpatient attendance visit, ophthalmology, face-to-face visit).

Cost of adverse events The management of cataract and glaucoma was based on surgery costs taken from *NHS Reference Costs 2014–15*.[121] Raised IOP was assumed to be treated with two doses of bimatoprost (Lumigan®, Allergan) on average (most patients will need just one dose but others will need many). Serious infection was assumed to be treated with hospitalisation and the cost was based on an average of *NHS Reference Costs 2014–15* for the infections reported within the VISUAL trials.[46,47] Treatment for hypertension was based on the cost of antihypertensive treatment taken from the study by Breeze *et al.*[123]

A focused search was undertaken in October 2016 to identify cost and utility studies of blindness (see *Appendix 1* for the MEDLINE search strategy). Free-text terms for blindness and sight or vision loss (in the titles field) were combined with either an economic filter (balance of sensitivity and sensitivity) or a sensitive quality-of-life studies filter. The search was carried out in MEDLINE and MEDLINE-in-Process &

Other Non-Indexed Citations (Ovid). The search for cost studies was limited from 2006 until 2016. Based on this review, the AG considered that the most recent good-quality evidence associated with the costs of blindness was presented within a health technology assessment of treatment for age-related macular degeneration.[124] The costs of each component included within the calculation of the total annual cost of blindness to the NHS and PSS have been updated with the most recent data and uplifted to 2015 prices using the Hospital & Community Health Services index,[122] as shown in *Table 35*.

Fracture and diabetes have been shown to be the largest cost items associated with the long-term use of corticosteroids.[31] The cost of fracture was based on evidence from a HTA monograph by Davis *et al.*[127] and includes the costs of hospitalisations, accident and emergency visits, referrals, prescriptions and general practitioner contacts. The cost of diabetes was based on the annual hospitalisation cost from the UK Prospective Diabetes Study, which is the largest study of the costs of diabetes and its complications in the UK,[128] and the treatment costs from the study by Breeze *et al.*[123] *Table 36* summarises the resource use and costs associated with the AEs included in the model.

Corticosteroid sparing An important reason for developing new technologies is that existing treatments for non-infectious uveitis are associated with substantial AEs. In particular, long-term high-dose systemic corticosteroid use is associated with significant morbidity, including glaucoma, raised blood pressure, diabetes and osteoporosis.[41,42] Ideally, corticosteroid-sparing benefits would be taken into account in the comparison with current treatment. However, the VISUAL trials[46,47] did not allow corticosteroid use in either arm following the initial corticosteroid burst and taper and in the HURON trial[48] there was a minimal difference in corticosteroid usage between the arms of the trial. If corticosteroid usage is higher in clinical practice than in the trials, the effectiveness of the comparator may also increase, as well as the AE rate. Corticosteroid-sparing treatment was considered only within the exploratory analyses, in which the comparator was based on the MUST trial.[57]

Remission Based on advice received from the clinical advisors to the AG, an additional state was added to the model to reflect the possibility of patients achieving remission after a stable period, for example after 2 years on ADA. This would mean that patients would discontinue treatment on achieving remission but continue to experience the benefits of ADA until they were predicted to fail treatment from the extrapolated survival curves. Given that there is no evidence around this, within the base case we assumed that no patients would be taken off treatment because of remission; however, alternative assumptions around continued benefit following discontinuation because of remission were considered within the exploratory analyses.

TABLE 35 Costs of blindness

Component	% of patients receiving service	Cost (£)	Source
Blind registration[a]	95	146	Meads and Hyde[125]
Low-vision aids[a]	33	191	Meads and Hyde[125]
Low-vision rehabilitation[a]	11	329	Meads and Hyde[125]
Depression	39	2378[c]	McCrone *et al.*[126]
Hip replacement	5	4086[c]	*NHS Reference Costs 2014–15*[121]
Community care	6	281[c]	Curtis and Burns[122] (social care for older people)
Residential care	30	21,732[b,c]	Curtis and Burns[122] (private residential care)
Annual total		7659	

a One-off cost.
b This cost assumes that 30% of patients receiving this service pay for themselves.
c Annual cost.

TABLE 36 Resource use and costs associated with the included AEs

AE	Resource use	Cost (£)	Frequency	Source
Cataract	Cataract surgery	852.40	One-off cost	*NHS Reference Costs 2014–15*[121]
Raised IOP	Treatment with two doses of bimatoprost	23.42	One-off cost	*British National Formulary*[49]
Glaucoma	Glaucoma surgery	581.25	One-off cost	*NHS Reference Costs 2014–15*[121]
Serious infection	Hospitalisation	5940.50	One-off cost	*NHS Reference Costs 2014–15*[121]
Hypertension	Antihypertensive prescription	7.04	One-off cost	Breeze *et al.*[123]
Permanent blindness	See *Table 35*	237	Transition	See *Table 35*
		7659	Annual	
Fracture	Hospitalisations, accident and emergency visits, referrals, prescriptions and general practitioner contacts	2116.17–6022.62 depending on age and sex	One-off fracture cost	Davis *et al.*[127]
Diabetes	Diabetes treatment and hospitalisation for complications of diabetes	1521.46	Annual	Alva *et al.*[128] and Breeze *et al.*[123]

Mortality

Mortality rates within the model were assumed to reflect those of the general population, based on the most recent Office for National Statistics life tables for England.[129]

The model assumed that AEs have no impact on mortality, although it is recognised that in practice diabetes, osteoporosis and blindness would have some impact on mortality.

Model evaluation methods

The cost-effectiveness results for DEX and ADA compared with limited current practice are presented based on both the probabilistic and the deterministic versions of the model. In total, 5000 probabilistic samples were run to estimate the expected costs and QALYs. Uncertainty surrounding incremental costs, outcomes and cost-effectiveness was represented using CEACs and cost-effectiveness planes. It should, however, be noted that the uncertainty analysis is likely to underestimate the true uncertainty surrounding the cost-effectiveness of each option because of the numerous structural uncertainties associated with the model that are not captured within the PSA. A range of exploratory scenario analyses were undertaken to explore the sensitivity of the model results to key structural assumptions. A univariate sensitivity analysis was also undertaken to explore the impact of alternative plausible parameters on the model results.
All model results are presented for the entire patient population of interest as evidence did not allow a subgroup analysis to be undertaken; the potential direction of the results for key subgroups such as patients with unilateral and bilateral uveitis are considered in the discussion section.

Probabilistic sensitivity analysis

To assess the uncertainty around the parameters used in the model, the AG defined probability distributions for most parameters using the available evidence and undertook PSA. Gamma distributions were generally used for costs and beta distributions for utility values and probabilities. The RR of blindness for DEX was based on a uniform distribution because of a lack of evidence. *Table 37* summarises the input parameters and their base-case mean values and distributions used in the PSA. In addition to the parameters listed in *Table 37*, beta distributions were defined for utility scores at each time point in each arm, as well as the prevalence of concomitant therapy and the incidence of AEs and rescue therapy. Multivariate normal distributions were used for the parameters of the survival curves used to determine time to treatment failure. A Dirichlet distribution was used for the weight distribution of the cohort, which determined the mean dose cost of azathioprine and ciclosporin.

TABLE 37 Model input parameters for the base-case scenario

Parameter	Mean	Distribution	Source
Age (years)	44.8	Fixed	
Discount rate (costs and utilities) (%)	3.5	Fixed	NICE[104]
Sex, male (%)	36.7	Fixed	HURON trial[48]
Cycle length (weeks)	2	Fixed	
Utilities			
Baseline VFQ-25 score for DEX and LCP(H) arms	66.63	Beta	HURON trial (data on file)
Baseline EQ-5D score for patients with active uveitis	0.83	Beta	AbbVie[52]
Baseline EQ-5D score for patients with inactive uveitis	0.85	Beta	AbbVie[72]
Blindness utility	0.38	Multivariate normal (using variance–covariance matrix)	Czoski-Murray *et al.*[109]
Regression model for relationship between VFQ-25 and EQ-5D scores			
Intercept	0.445	Multivariate normal (using variance–covariance matrix in *Table 33*)	Based on patient-level data from the HURON trial (data on file)
Slope	0.005		
Proportion of bilateral patients (%)			
General population	75	Beta	Assumption
DEX population	70	Beta	Assumption
Active uveitis population	90.8	Beta	AbbVie[52]
Inactive uveitis population	95.6	Beta	AbbVie[72]
Blindness			
Probability of blindness (annual)	0.0068	Beta	Dick *et al.*[19]
RR of blindness for DEX during 6-month period following implantation	0.5	Uniform	Assumption
RR of blindness for ADA while on treatment	0	Fixed	Assumption
Remission			
Rate of remission when treatment is stopped but the treatment effect continues	0	Fixed	Assumption
Drug costs (£)			
DEX 700 mg	870	Fixed	BNF[49]
ADA 40 mg	352.14	Fixed	BNF[49]
Prednisolone	1.24	Fixed	BNF[49]
Mycophenolate mophetil	9.31	Fixed	BNF[49]

continued

TABLE 37 Model input parameters for the base-case scenario (*continued*)

Parameter	Mean	Distribution	Source
Methotrexate	2.40	Fixed	BNF[49]
Ciclosporin	48.50	Fixed	BNF[49]
Azathioprine	3.24	Fixed	BNF[49]
Bimatoprost	11.71	Fixed	BNF[49]
Adcal D3® (NextPharma, Göttingen, Germany)	7.49	Fixed	BNF[49]
Omeprazole	1.17	Fixed	BNF[49]
Administration and monitoring			
Monitoring visit frequency (weeks)	6		Jabs *et al.*[130]
Monitoring visit cost (£)	96.11	Gamma	*NHS Reference Costs 2014–15*[121] (outpatient attendance, ophthalmology, consultant-led)
DEX implant administration cost (£)	113.42	Gamma	*NHS Reference Costs 2014–15*[121] (minor vitreous retinal procedures)
% of self-injectors needing district nurse for ADA	10	Beta	NICE[131]
ADA administration cost (£) (patients who need help from a nurse)	44	Gamma	Curtis and Burns[122] and *NHS Reference Costs 2014–15*[121] (district nurse)
AE costs (£)			
Cataract surgery	852.40	Gamma	*NHS Reference Costs 2014–15*[121] (phacoemulsification cataract extraction and lens implant, with CC score 4+)
Raised IOP	23.42	Gamma	BNF[49]
Glaucoma procedure	581.25	Gamma	*NHS Reference Costs 2014–15*[121] (weighted average of glaucoma procedures)
Serious infection	5940.50	Gamma	*NHS Reference costs 2014–15*[121] [average of infection hospitalisations (based on the proportions of each infection in the VISUAL trials[46,47])]
Hypertension	7.04	Gamma	Breeze *et al.*[123]
Blindness (transition)	237	Gamma	See *Table 35*
Blindness (annual)	7659	Gamma	See *Table 35*
Fracture	2116.17–6022.62	Gamma	Davis *et al.*[127]
Diabetes	1521.46	Gamma	Alva *et al.*[128] and Breeze *et al.*[123]

BNF, *British National Formulary*.

Exploratory sensitivity analyses

A number of exploratory analyses were undertaken to explore the uncertainties within the model. Although there was a lack of evidence to fully inform these exploratory analyses, the aim was to provide an indication of the impact of alternative assumptions on the results.

1. *A greater proportion of patients are treated with immunosuppressants and corticosteroids in the comparator groups*. In clinical practice it would be expected that a higher proportion of patients would receive systemic therapy. This would result in greater efficacy associated with the comparator, with a higher AE rate and higher costs.
   As discussed in *Chapter 3* (see *Indirect comparison of treatments: rationale for not undertaking*), it was not possible to undertake a NMA to compare DEX or ADA with an alternative comparator, which might be more representative of current practice. However, the comparator arm of the MUST trial[57] (identified within the systematic review) was made up of patients who received systemic corticosteroids, supplemented in 86% of cases with immunosuppressants, and was thought by the clinical experts to the AG to be reasonably representative of clinical practice. Hence, this study was used to inform an exploratory analysis. This exploratory analysis was not undertaken for patients with inactive uveitis because the MUST trial included only patients with active uveitis. For active patients, data from the comparator arm of the MUST trial were used relating to (1) an estimate of the total proportion of patients receiving (i) corticosteroids and (ii) immunosuppressants, to estimate costs; (2) an estimate of the HRQoL of patients; and (3) the rates of any AEs associated with substantial resource use. With respect to the total proportion of patients receiving corticosteroids and immunosuppressants, it was unclear from the MUST trial publication exactly which immunosuppressants were used[57] and hence the composition was assumed to be the same as that for the VISUAL I trial.[46] It should be noted that using the data from the MUST trial without performing any formal mixed treatment comparison assumes that the trial population was comparable with the populations within the VISUAL and HURON trials and does not include any measure of uncertainty around the comparison. Within the base-case analysis, HRQoL was assumed to return to baseline levels following treatment failure with ADA or after 6 months following DEX implantation. Given that the comparator arm patients were able to receive immunosuppressants and corticosteroids, it was assumed within this exploratory analysis that patients treated with ADA or DEX were also able to receive immunosuppressants and corticosteroids, as in the comparator arm of the MUST trial following the end of treatment with the intervention. Therefore, the overall effectiveness of DEX and ADA was expected to increase as well as the effectiveness of the comparator.
   The analysis assumed that treatment with prednisolone includes concomitant therapy with Adcal D3 (£47.58) and 20 mg of omeprazole once daily (£15.25).
2. *Incidence and HRQoL impact of blindness*. As there is limited evidence around the rate of legal blindness for this patient group, and there is no evidence around the impact of treatment on this rate, the AG performed exploratory analyses around these parameters. This was done by varying the rate of legal blindness in patients with uveitis who are treated with (limited) current practice (from 0 to 0.0374) based on alternative sources[11,18] (see *Permanent legal blindness*) and varying the RR of legal blindness cases avoided as a result of treatments (from 0 to 1).
   These analyses were also undertaken using (1) alternative utilities from Brown[115] and (2) a higher cost of blindness based on the upper bound of the 95% CI for this parameter.
3. *Patients who go into remission after ADA treatment*. A proportion of patients who continue treatment with ADA may achieve remission. The base-case analysis assumed that these patients would continue to receive ADA until treatment failure; however, the clinical advisors to the AG suggested that, after around 2 years of stable disease, patients may no longer require treatment but because they are in remission they may maintain the same level of HRQoL as that while on treatment. This sensitivity analysis therefore assessed the impact of assuming that, after 2 years on treatment, a varying proportion of patients (0–1) would no longer receive ADA but their HRQoL would decrease only with age, until the treatment failure curve predicts failure or they die from other causes.
4. *Using the VFQ-25 data from the VISUAL trials of ADA*[46,47] *to map to EQ-5D utility data*. This sensitivity analysis assessed the impact of using the regression analysis of the HURON trial data[48] to map the VFQ-25 data from the VISUAL trials[46,47] to EQ-5D utilities.

5. *Extrapolation of time to treatment discontinuation for ADA*. The impact of using alternative plausible parametric distributions (Weibull, Gompertz) for time to treatment discontinuation was explored.
6. *Varying the time period over which the utility decreases to that of baseline after treatment*. The treatment effect beyond 6 months for DEX and beyond treatment discontinuation for ADA is unknown. Within the base case, patients receiving DEX were assumed to take 4 weeks to return to baseline utility beyond the trial follow-up of 6 months. HRQoL for patients receiving ADA was assumed to return to baseline levels immediately on treatment discontinuation. Within this exploratory analysis the treatment effect beyond 6 months for DEX was varied from 0 to 8 weeks and the treatment effect beyond discontinuation for ADA was increased to 4 weeks.

Univariate sensitivity analyses

Each parameter within the base case was varied to assess its impact on the model results, as shown in *Table 38*.

TABLE 38 Univariate sensitivity analyses

Parameters	Mean	Lower value	Upper value	Source
Utilities				
Baseline	0.79	0.77	0.80	HURON trial individual patient data (data on file)
	0.83	0.81	0.85	AbbVie[52]
	0.85	0.83	0.87	AbbVie[72]
Blindness	0.35	0.28	0.42	Czoski-Murray *et al.*[109]
Administration and monitoring				
Monitoring visit frequency (weeks)	6	4	8	Jabs *et al.*[130]
Monitoring visit cost (£)	96.11	77.27	114.95	*NHS Reference Costs 2014–15*[121] (outpatient attendance, ophthalmology, consultant-led)
DEX implant administration cost (£)	113.42	91.15	135.65	*NHS Reference Costs 2014–15*[121] (minor vitreous retinal procedures)
% of self-injectors needing district nurse for ADA	10	0	20	NICE[131]
ADA administration cost (£) (patients who need help from a nurse)	44	29.96	44.56	Curtis and Burns[122]
AE costs (£)				
Raised IOP	23.42	11.71	46.84	BNF[49]
Cataract surgery	852.40	658.33	1019.47	*NHS Reference Costs 2014–15*[121] (phacoemulsification cataract extraction and lens implant, with CC score 4+)
Glaucoma procedure	581.25	467.32	695.17	*NHS Reference Costs 2014–15*[121] (weighted average of glaucoma procedures)
Hypertension	7.04	5.66	8.42	Breeze *et al.*[123]
Serious infections	5940.50	4776	7105	*NHS Reference Costs 2014–15*[121] [average of infection hospitalisations (based on the proportions of each infection in the VISUAL trials[46,47])]
Blindness (transition)	236.95	191	283	See *Table 35*
Blindness (annual)	7658.71	6158	9160	See *Table 35*

Results

Dexamethasone

Base case

The base-case results are presented in *Table 39*. Based on the probabilistic version of the model, a single DEX implant combined with limited current practice as provided in the HURON trial[48] [DEX 700 + LCP(H)] was estimated to produce 0.029 incremental QALYs compared with LCP(H) alone at an additional cost of £573, resulting in an ICER of £19,509 per QALY gained. *Figure 17* presents the CEAC. Assuming WTP thresholds of £20,000 and £30,000 per QALY gained, the probability that a single DEX implant produces more net benefit than LCP(H) is estimated to be 0.47 and 0.72 respectively. The deterministic results were similar to those generated using the probabilistic model (*Table 40*), with an estimated ICER of £20,058 per QALY gained for DEX 700 + LCP(H) compared with LCP(H). A breakdown of the results of the deterministic analysis is provided in *Appendix 7*.

The small differences in both costs and QALYs between the two groups mean that the ICER is very sensitive to alternative model parameters and assumptions, as shown within subsequent sensitivity analyses.

TABLE 39 Results of the base-case analysis comparing DEX 700 with LCP(H): probabilistic model

Treatment group	Total QALYs	Total costs (£)	Incremental QALYs	Incremental costs (£)	ICER (£)	Probability of cost-effectiveness at WTP threshold of	
						£20,000	£30,000
LCP(H)[a]	14.599	39,992				0.53	0.28
DEX 700 + LCP(H)[a]	14.629	40,565	0.029	573	19,509	0.47	0.72

a Limited current practice, as provided in the HURON trial:[48] 25% of patients on anti-inflammatory or immunosuppressant medication.

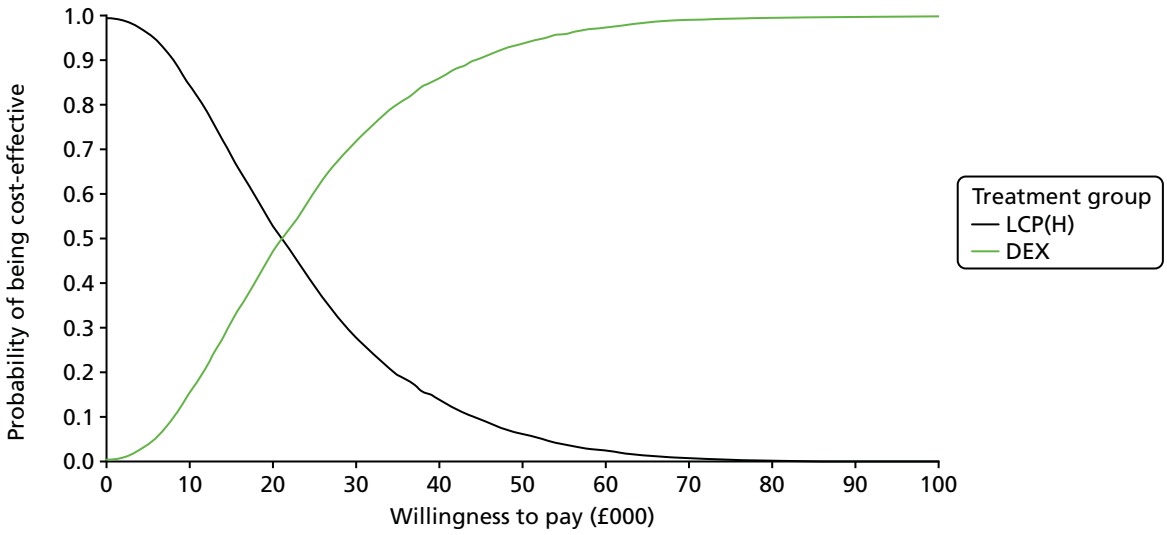

FIGURE 17 Cost-effectiveness acceptability curve for DEX 700 + LCP(H) vs. LCP(H).

TABLE 40 Results of the base-case analysis comparing DEX 700 with LCP(H): deterministic model

Treatment group	Total QALYs	Total costs (£)	Incremental QALYs	Incremental costs (£)	ICER (£)
LCP(H)[a]	14.613	39,655			
DEX 700 + LCP(H)[a]	14.641	40,235	0.029	580	20,058

a Limited current practice, as provided in the HURON trial:[48] 25% of patients on anti-inflammatory or immunosuppressant medication.

Figure 18 shows the cost-effectiveness scatterplot for DEX 700 + LCP(H) compared with LCP(H). The scatterplot shows that there is a negative correlation between incremental costs and incremental QALYs. The AG believes that this is because blindness has a strong impact both on QALYs gained and on costs, and the impact of DEX on blindness is very uncertain. A low RR of blindness would lead to increased QALY gains and important cost savings.

Exploratory analyses

Exploratory analysis 1: a greater proportion of patients are treated with immunosuppressants and corticosteroids in the comparator groups This exploratory analysis suggests that injecting a DEX implant before applying a treatment considered to be current practice (a mix of systemic steroids and immunosuppressants, based on the comparator within the MUST trial[57]) is expected to produce 0.011 additional QALYs at an incremental cost of £216 compared with current practice, resulting in an ICER of £19,899 per QALY gained, as shown in *Table 41*.

Within this exploratory analysis, the total QALYs associated with DEX 700 increase compared with the base case because of the assumption that patients would be able to receive more immunosuppressants and corticosteroids (equivalent to the comparator group) after 6 months following the DEX implant. It should be noted that the ICER estimated for DEX 700 compared with current practice as provided in the MUST trial[57] [CP(M)] is only slightly higher than that estimated for DEX 700 compared with LCP(H). The difference would be higher if different rates of blindness had been applied for CP(M) and LCP(H). It is reasonable to

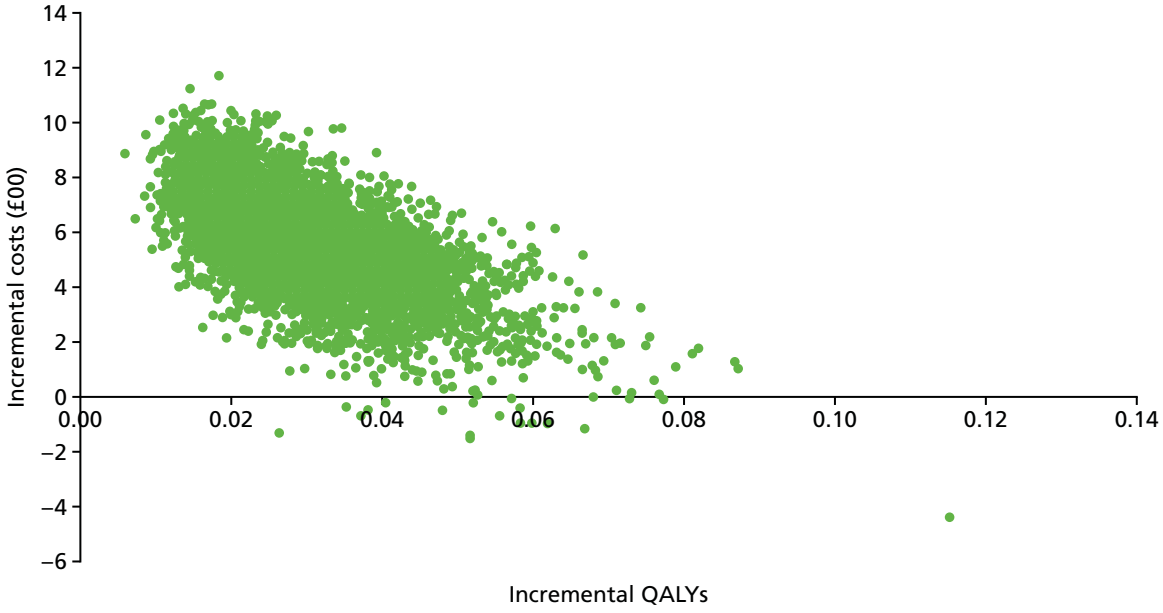

FIGURE 18 Cost-effectiveness plane scatterplot of DEX 700 + LCP(H) vs. LCP(H).

TABLE 41 Results of the exploratory analysis comparing DEX 700 with LCP(H): probabilistic model

Treatment group	Total QALYs	Total costs (£)	Incremental QALYs	Incremental costs (£)	ICER (£)	Probability of cost-effectiveness at WTP threshold of	
						£20,000	£30,000
CP(M)[a]	15.152	63,465				0.54	0.45
DEX 700 + LCP(H)[b] before CP(M)[a]	15.163	63,681	0.011	216	19,899	0.47	0.55

a Current practice as provided in the MUST trial:[57] all patients on systemic steroids and 86% on systemic immunosuppressants.
b Limited current practice, as provided in the HURON trial:[48] 25% of patients on anti-inflammatory or immunosuppressant medication.

assume that CP(M) would lead to a lower incidence of blindness than LCP(H) because of the more intensive treatment, but the AG assumed the same rate of blindness for both given the absence of evidence to estimate rates for both.

Exploratory analysis 2: incidence and health-related quality-of-life impact of blindness The AG analysed the combined impact of different blindness rates based on different sources in the literature and assuming different RRs for blindness on DEX. As shown in *Table 42*, the impact of the RR of blindness on the ICER for DEX 700 + LCP(H) compared with LCP(H) alone is very important and there is no evidence describing the impact that DEX will have on the rate of blindness. The higher the rate of blindness, the greater the impact of the RR on the model results. Assuming a rate of blindness from Durrani *et al.*[11] and a RR of 1 (i.e. a DEX implant has no effect on blindness), the ICER for DEX 700 + LCP(H) compared with LCP(H) alone is £56,329 per QALY gained, whereas DEX 700 dominates if the RR is ≤ 0.25 based on the same rate of blindness.

The AG also explored the impact of assuming a different source for the utility for patients following the onset of blindness. The base case used an estimate based on the study by Czoski-Murray *et al.*;[109] the exploratory analysis was undertaken using an estimate reported by Brown[115] The results of these exploratory analyses are presented in *Table 43*, showing that the ICERs for DEX 700 + LCP(H) compared with LCP(H) were higher than those based on the study by Czoski-Murray *et al.*[109] (in cases in which the rate of blindness is higher than zero and DEX 700 has an impact on the rate of blindness). This is because the utility for blindness based on the study by Czoski-Murray *et al.*[109] (0.38) was lower than that based on the study by Brown[115] (0.57).

TABLE 42 Incremental cost-effectiveness ratios (£) for DEX 700 + LCP(H) vs. LCP(H) with different blindness rates and RRs of blindness for patients while on DEX

Annual rate of blindness (source)	RR of blindness on DEX				
	0 (no blindness)	0.25	0.50[a]	0.75	1 (no effect)
0 (assumption)	48,937	48,937	48,937	48,937	48,937
0.0038 (Tomkins-Netzer *et al.*[18])	17,100	21,816	28,089	36,844	49,915
0.0066[a] (Dick *et al.*[19])	8688	13,314	20,058[a]	30,805	50,627
0.0374 (Durrani *et al.*[11])	Dominates	Dominates	557	10,900	56,329

a Base case.

TABLE 43 Incremental cost-effectiveness ratios (£) for DEX 700 + LCP(H) vs. LCP(H) with different blindness rates and RRs of blindness for patients on DEX and using the utility estimate for blindness from Brown[115]

	RR of blindness on DEX				
Annual rate of blindness (source)	0 (no blindness)	0.25	0.50[a]	0.75	1 (no effect)
0 (assumption)	48,937	48,937	48,937	48,937	48,937
0.0038 (Tomkins-Netzer *et al.*[18])	22,015	26,972	32,988	40,440	49,915
0.0066[a] (Dick *et al.*[19])	12,108	17,782	25,257[a]	35,550	50,627
0.0374 (Durrani *et al.*[11])	Dominates	Dominates	853	15,198	56,329

a Base case.

To explore the impact of the cost of blindness, the AG undertook an analysis using the upper bounds of the 95% CIs for the annual cost of blindness and the cost of the transition to blindness. *Table 44* presents the result of these exploratory analyses, which lead to lower ICERs for DEX 700 + LCP(H) compared with LCP(H) than in the analyses using the mean costs of blindness (in cases in which the rate of blindness is higher than zero and DEX 700 has an impact on the rate of blindness).

For the above analyses, when the annual rate of blindness is set to 0, the results could be used to give an indication of the cost-effectiveness of DEX for patients with unilateral disease (as patients with unilateral disease are unlikely to become legally blind, unless their disease progresses to become bilateral). The ICER when the annual rate of blindness is set to 0 is £48,937. It is important to note that the treatment effect may also be different (expected to be reduced) for unilateral patients compared with a pooled group of unilateral and bilateral patients; however, there is no evidence available to model this.

Exploratory analysis 6: varying the time period over which the utility decreases to that of baseline after treatment In the base case it was assumed that the health-related gain from DEX as measured at the end of the HURON trial[48] (week 26) is maintained for 4 weeks (up to week 30) and then falls to that of the comparator arm. *Table 45* shows the impact of varying the treatment effect duration on the cost-effectiveness estimates. The ICER for DEX 700 + LCP(H) compared with LCP(H) varies from £24,715 per QALY gained assuming 26 weeks of treatment effect to £12,154 per QALY gained assuming 42 weeks of treatment effect.

Univariate sensitivity analyses

The AG explored the impact of different parameters on the results of the model, as shown in *Table 46*.

TABLE 44 Incremental cost-effectiveness ratios (£) for DEX 700 + LCP(H) vs. LCP(H) with different blindness rates and RRs of blindness for patients on DEX using high costs of blindness (upper bounds of the 95% CIs)

	RR of blindness on DEX				
Annual rate of blindness (source)	0 (no blindness)	0.25	0.50[a]	0.75	1 (no effect)
0 (assumption)	48,937	48,937	48,937	48,937	48,937
0.0038 (Tomkins-Netzer *et al.*[18])	15,195	20,185	26,822	36,085	49,915
0.0066[a] (Dick *et al.*[19])	6283	11,174	18,305[a]	29,668	50,627
0.0374 (Durrani *et al.*[11])	Dominates	Dominates	Dominates	8534	56,329

a Base case.

TABLE 45 Results of the exploratory analysis comparing the effect of varying durations of treatment effect on HRQoL: deterministic model

Treatment group	Total QALYs	Total costs (£)	Incremental QALYs	Incremental costs (£)	ICER (£)
LCP(H)	14.613	39,655			
DEX 700: 26 weeks	14.637	40,256	0.024	600	24,715
DEX 700: 30 weeks[a]	14.641	40,235	0.029	580	20,058
DEX 700: 34 weeks	14.646	40,214	0.033	559	16,692
DEX 700: 42 weeks	14.655	40,173	0.043	518	12,154

a Base case.

TABLE 46 Univariate sensitivity analyses for DEX 700 + LCP(H) vs. LCP(H)[a]

Parameter	Base case, lower value, upper value	ICER based on lower value (£)	ICER based on upper value (£)
Utilities			
Baseline	0.79, 0.77, 0.80	20,346	19,783
Blindness	0.38, 0.31, 0.57	18,551	25,257
Administration and monitoring			
Monitoring visit frequency (weeks)	6, 4, 8	20,545	19,814
Monitoring visit cost (£)	44, 35.80, 53.03	19,854	20,282
DEX implant administration cost (£)	113.42, 91.15, 135.65	19,326	20,863
AE costs (£)			
Raised IOP	23.42, 19.06, 28.23	20,024	20,095
Cataract surgery	852.40, 658.33, 1019.47	19,534	20,635
Glaucoma procedure	581.25, 467.32, 695.17	20,173	19,931
Hypertension	7.04, 5.66, 8.42	20,058	20,057
Blindness (transition)	237, 191, 283	20,061	20,054
Blindness (annual)	7659, 6158, 9160	21,807	18,308

a Base-case ICER: £20,058 per QALY (deterministic analysis).

The model results were generally robust to changes in the values of these parameters. The model was most sensitive to assumptions around the comparator, assumptions around permanent blindness and the duration of the treatment effect.

Adalimumab: active uveitis patients

Base case

The base-case results are presented in *Table 47*. In the base case, ADA + LCP(VI), as provided in the VISUAL I trial,[46] was estimated to produce 0.194 incremental QALYs compared with LCP(VI) alone in patients with active uveitis at an additional cost of £18,321, resulting in an ICER of £94,523 per QALY gained. The ICER generated using the deterministic version of the model (£95,506) (*Table 48*) was similar to that in the probabilistic model. A breakdown of the results of the deterministic analysis is provided in *Appendix 7*. *Figure 19* shows the CEAC for ADA + LCP(VI) compared with LCP(VI) in patients with active

TABLE 47 Results of the base case analysis comparing ADA + LCP(VI) with LCP(VI) in patients with active uveitis: probabilistic model

Treatment group	Total QALYs	Total costs (£)	Incremental QALYs	Incremental costs (£)	ICER (£)	Probability of cost-effectiveness at WTP threshold of £20,000	Probability of cost-effectiveness at WTP threshold of £30,000
LCP(VI)[a]	14.897	47,776				1.00	1.00
ADA + LCP(VI)[a]	15.091	66,098	0.194	18,321	94,523	0.00	0.00

a Limited current practice as provided in the VISUAL I trial:[46] initial systemic steroid burst tapered by week 15 and around 30% of patients on systemic immunosuppressants.

TABLE 48 Results of the base case analysis comparing ADA + LCP(VI) with LCP(VI) in patients with active uveitis: deterministic model

Treatment group	Total QALYs	Total costs (£)	Incremental QALYs	Incremental costs (£)	ICER (£)
LCP(VI)[a]	14.919	47,186			
ADA + LCP(VI)[a]	15.110	65,401	0.191	18,215	95,506

a Limited current practice as provided in the VISUAL I trial:[46] initial systemic steroid burst tapered by week 15 and around 30% of patients on systemic immunosuppressants.

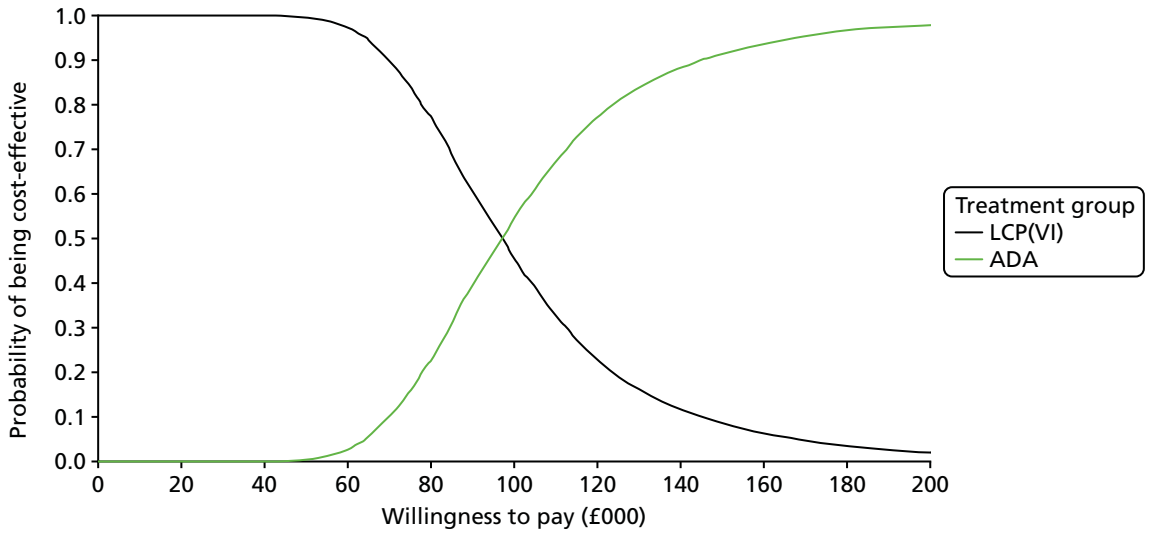

FIGURE 19 Cost-effectiveness acceptability curve for ADA + LCP(VI) vs. LCP(VI) in patients with active uveitis.

uveitis. It should be noted that within the VISUAL I trial[46] both treatment groups included an initial systemic steroid burst, which was tapered by week 15, and around 30% of patients in both arms received systemic immunosuppressants.

Figure 20 shows the cost-effectiveness plane for ADA + LCP(VI) compared with LCP(VI). The scatterplot shows that there is a positive correlation between the incremental costs and the incremental QALYs. The AG believes that this is because longer ADA treatments lead to more QALYs but also incur important additional costs.

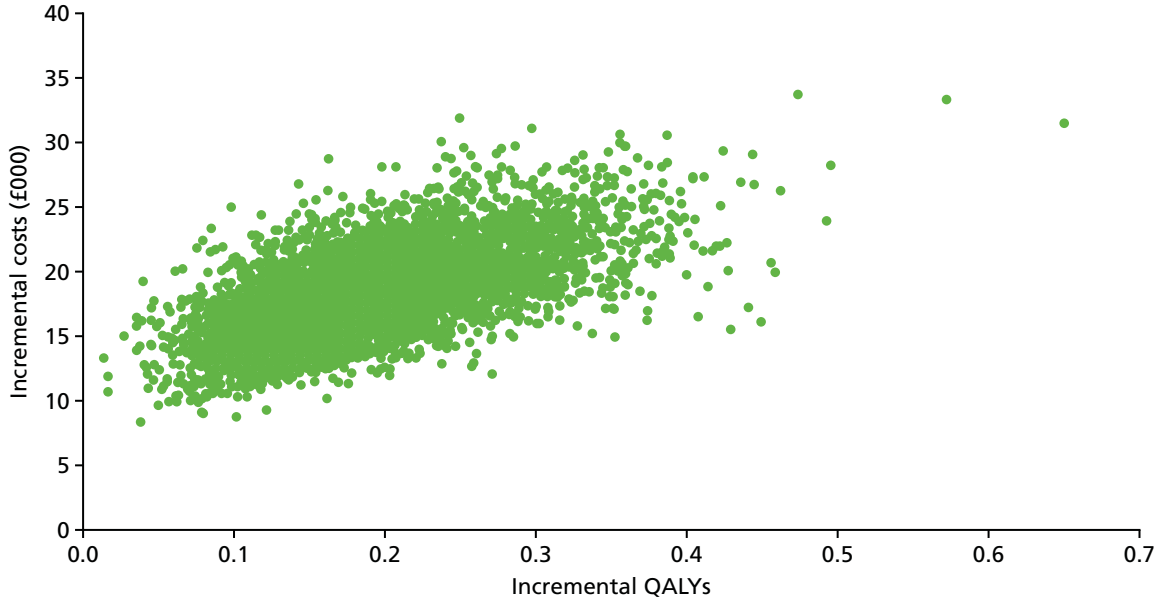

FIGURE 20 Cost-effectiveness plane scatterplot of ADA + LCP(VI) vs. LCP(VI) in patients with active uveitis.

Exploratory analyses

Exploratory analysis 1: a greater proportion of patients are treated with immunosuppressants and corticosteroids in the comparator groups The AG undertook an exploratory analysis (*Table 49*) whereby patients who fail ADA are assumed to receive a treatment that the AG considered representative of current practice, a mix of systemic steroids and immunosuppressants based on the MUST trial[57] [CP(M)]. The analysis shows that ADA + LCP(VI) before CP(M) is expected to produce 0.0159 additional QALYs at an incremental cost of £17,183 compared with CP(M), resulting in an ICER of £109,044 per QALY gained.

Within this exploratory analysis, the total QALYs associated with the ADA group increase compared with the base case because of the assumption that more patients would be able to receive immunosuppressants and corticosteroids (equivalent to the proportion in the comparator group) after ADA treatment failure. It should be noted that the ICER estimated for ADA compared with CP(M) is only slightly higher than that for ADA compared with LCP(VI). The difference would be higher if different rates of blindness had been applied for CP(M) and LCP(VI). It is reasonable to assume that CP(M) would lead to a lower incidence of blindness than LCP(VI) because of the more intensive treatment, but the AG assumed the same rate of blindness for both given the absence of evidence to estimate rates for both.

TABLE 49 Results of the exploratory analysis comparing ADA + LCP(VI) before CP(M) with CP(M) alone: probabilistic model

Treatment group	Total QALYs	Total costs (£)	Incremental QALYs	Incremental costs (£)	ICER (£)	Probability of cost-effectiveness at WTP threshold of	
						£20,000	£30,000
CP(M)[a]	15.655	66,171				1.00	1.00
ADA + LCP(VI)[b] before CP(M)[a]	15.813	83,355	0.158	17,183	109,044	0.00	0.00

a Current practice as provided in the MUST trial:[57] all patients on systemic steroids and 86% on systemic immunosuppressants.
b Limited current practice, as provided in the VISUAL I trial:[46] initial systemic steroid burst tapered by week 15 and around 30% of patients on systemic immunosuppressants.

Exploratory analysis 2: incidence and health-related quality-of-life impact of blindness The AG analysed the combined impact of different blindness rates based on different sources in the literature and assuming different RRs for patients before treatment failure. As shown in *Table 50*, the impact of the RR of blindness on the ICER for ADA + LCP(VI) compared with LCP(VI) in patients with active uveitis is highly influential. The higher the rate of blindness, the greater the impact of the RR. Assuming the highest rate of blindness from the literature (based on the study by Durrani *et al.*[11]) resulted in an ICER for ADA + LCP(VI) compared with LCP(VI) of £202,592 per QALY gained for a RR of 1 (i.e. ADA has no effect on blindness) and £33,003 per QALY gained for a RR of 0 (i.e. no patient goes blind before treatment failure).

The AG also explored the impact of assuming a different source for the utility for patients following the onset of blindness. In the base case the utility estimate was based on the study by Czoski-Murray *et al.*;[109] the exploratory analysis was undertaken using the utility estimate reported by Brown[115] The results of this exploratory analysis are shown in *Table 51*. The ICERs for ADA + LCP(VI) compared with LCP(VI) were higher using the utility estimate from Brown[115] than when using the utility estimate from Czoski-Murray *et al.*[109] This is because the utility estimate for blindness is lower in the study by Czoski-Murray *et al.*[109] (0.38) than in the study by Brown[115] (0.57).

To explore the impact of the cost of blindness, the AG undertook an analysis using the upper bounds of the 95% CIs for the annual cost of blindness and the cost of the transition to blindness. *Table 52* presents the results of this exploratory analysis, which show that the ICERs for ADA + LCP(VI) compared with LCP(VI) are lower than in the analyses using the mean costs of blindness, except when a blindness rate of 0 or a RR before treatment failure of 1 is assumed.

TABLE 50 Incremental cost-effectiveness ratios (£) for ADA + LCP(VI) vs. LCP(VI) with varying blindness rates and RRs of blindness for patients before treatment failure

	RR of blindness before treatment failure				
Annual rate of blindness (source)	0 (no blindness)[a]	0.25	0.50	0.75	1 (no effect)
0 (assumption)	192,808	192,808	192,808	192,808	192,808
0.0038 (Tomkins-Netzer *et al.*[18])	121,908	134,773	150,325	169,503	193,740
0.0066[a] (Dick *et al.*[19])	95,506[a]	110,263	129,611	156,077	194,471
0.0374 (Durrani *et al.*[11])	33,003	44,570	63,587	100,494	202,592

a Base case.

TABLE 51 Incremental cost-effectiveness ratios (£) for ADA + LCP(VI) vs. LCP(VI) with varying blindness rates and RRs of blindness for patients before treatment failure and using the utility estimate for blindness from Brown[115]

	RR of blindness before treatment failure				
Annual rate of blindness (source)	0 (no blindness)[a]	0.25	0.50	0.75	1 (no effect)
0 (assumption)	192,808	192,808	192,808	192,808	192,808
0.0038 (Tomkins-Netzer *et al.*[18])	142,399	152,827	164,646	178,154	193,740
0.0066[a] (Dick *et al.*[19])	119,012[a]	132,539	148,886	169,031	194,471
0.0374 (Durrani *et al.*[11])	48,876	63,923	86,679	124,952	202,592

a Base case.

TABLE 52 Incremental cost-effectiveness ratios (£) for ADA + LCP(VI) vs. LCP(VI) with varying blindness rates and RRs of blindness for patients before treatment failure using high costs of blindness (upper bounds of the 95% CIs)

	RR of blindness before treatment failure				
Annual rate of blindness (source)	0 (no blindness)[a]	0.25	0.50	0.75	1 (no effect)
0 (assumption)	192,808	192,808	192,808	192,808	192,808
0.0038 (Tomkins-Netzer *et al.*[18])	120,637	133,725	149,546	169,056	193,712
0.0066[a] (Dick *et al.*[19])	93,765[a]	108,775	128,453	155,372	194,422
0.0374 (Durrani *et al.*[11])	30,187	41,936	61,245	98,713	202,352

a Base case.

Exploratory analysis 3: patients who go into remission after adalimumab treatment In the base case, the AG assumed that patients would stay on ADA until treatment failure. However, based on clinical advice received by the AG, an additional analysis was undertaken assuming that, after 2 years of successful treatment, a proportion of patients discontinue treatment as they are in remission and retain the benefits of treatment. *Table 53* presents the results for different annual discontinuation rates for patients who have completed 2 years of successful treatment. As expected, only the cost of treatment with ADA varies with the different rates of treatment discontinuation after remission: the cost of ADA treatment decreases as the rate of discontinuation increases and therefore the ICER for ADA + LCP(VI) compared with LCP(VI) also decreases. If all patients who have not failed treatment (according to the discontinuation criteria defined in the VISUAL trials[46,47]) by 2 years could discontinue ADA and retain the benefits accrued from treatment, the ICER for ADA + LCP(VI) compared with LCP(VI) would be £35,299 per QALY gained.

It should be noted that the clinical advisors to the AG suggested that the treatment failure criteria for the VISUAL trials[46,47] are more strict than would be used in clinical practice and hence it is possible that a greater proportion of patients would still be receiving ADA treatment at 2 years. However, there is no evidence around the extent of the benefit of ADA in these patients.

TABLE 53 Results of the exploratory analysis of different annual discontinuation rates for patients who have completed 2 years of successful treatment

Annual rate of treatment discontinuation	Treatment group	Total QALYs	Total costs (£)	Incremental QALYs	Incremental costs (£)	ICER (£)
0.00[a]	LCP(VI)[b]	14.919	47,186			
	ADA + LCP(VI)[b]	15.110	65,401	0.191	18,215	95,506
0.10	LCP(VI)[b]	14.919	47,186			
	ADA + LCP(VI)[b]	15.110	60,034	0.191	12,848	67,363
0.25	LCP(VI)[b]	14.919	47,186			
	ADA + LCP(VI)[b]	15.110	57,239	0.191	10,052	52,707
1.00	LCP(VI)[b]	14.919	47,186			
	ADA + LCP(VI)[b]	15.110	53,918	0.191	6732	35,299

a Base case.
b Limited current practice, as provided in the VISUAL I trial:[46] initial systemic steroid burst tapered by week 15 and around 30% of patients on systemic immunosuppressants.

Exploratory analysis 4: using the Visual Function Questionnaire data from the VISUAL trials of adalimumab[46,47] to map to EuroQol-5 Dimensions utility data The AG undertook an exploratory analysis using EQ-5D scores mapped from VFQ-25 scores captured in the VISUAL I trial[46] instead of directly measured EQ-5D scores. This analysis resulted in a higher incremental QALY gain and therefore a slightly lower ICER for ADA + LCP(VI) compared with LCP(VI) than in the base case (*Table 54*).

Exploratory analysis 5: extrapolation of the time to treatment discontinuation for adalimumab To assess the impact of uncertainty around the extrapolation of time to treatment failure, the AG undertook an exploratory analysis using alternative parametric curves (*Table 55*). The ICER for ADA + LCP(VI) compared with LCP(VI) was considerably higher when using a Gompertz distribution (£101,429 per QALY) and a Weibull distribution (£103,369 per QALY) than when using a log-normal distribution, as in the base case (£95,506 per QALY).

Univariate sensitivity analyses

The AG explored the impact of different parameters on the results of the model, as shown in *Table 56*.

Of those parameters tested within the univariate sensitivity analysis, the parameters relating to baseline utility and the utility of blindness had the greatest impact on the ICER for ADA + LCP(VI) compared with LCP(VI). However, the model was most sensitive to assumptions around the comparator, assumptions around permanent blindness and the proportion of patients who would discontinue treatment on achieving remission and retain the benefits of treatment.

TABLE 54 Results of the exploratory analysis using EQ-5D scores captured in the VISUAL I trial[46]

Treatment group	Total QALYs	Total costs (£)	Incremental QALYs	Incremental costs (£)	ICER (£)
LCP(VI)[a]	14.350	47,186			
ADA + LCP(VI)[a]	14.546	65,401	0.196	18,215	92,884

a Limited current practice, as provided in the VISUAL I trial:[46] initial systemic steroid burst tapered by week 15 and around 30% of patients on systemic immunosuppressants.

TABLE 55 Results of the exploratory analysis of different parametric curves to extrapolate time to treatment failure

Parametric curve	Treatment group	Total QALYs	Total costs (£)	Incremental QALYs	Incremental costs (£)	ICER (£)
Log-normal[a]	LCP(VI)[b]	14.919	47,186			
	ADA + LCP(VI)[b]	15.110	65,401	0.191	18,215	95,506
Gompertz	LCP(VI)[b]	14.947	47,186			
	ADA + LCP(VI)[b]	15.569	110,215	0.621	63,029	101,429
Weibull	LCP(VI)[b]	14.917	47,186			
	ADA + LCP(VI)[b]	15.031	58,938	0.114	11,751	103,369

a Base case.
b Limited current practice, as provided in the VISUAL I trial:[46] initial systemic steroid burst tapered by week 15 and around 30% of patients on systemic immunosuppressants.

TABLE 56 Univariate sensitivity analyses for ADA + LCP(VI) vs. LCP(VI) in patients with active uveitis[a]

Parameters	Base case, lower value, upper value	ICER based on lower value (£)	ICER based on upper value (£)
Utilities			
Baseline	0.83, 0.81, 0.85	97,804	93,419
Blindness	0.38, 0.31, 0.57	88,602	119,012
Administration and monitoring			
Monitoring visit frequency (weeks)	6, 4, 8	95,983	95,267
Monitoring visit cost (£)	96.11, 77.27, 114.95	95,290	95,744
ADA administration cost (£) (help from a nurse)	44, 35.80, 53.03	95,272	95,763
% of self-injectors needing district nurse for ADA	10, 0, 20	94,253	96,758
AE costs (£)			
Cataract surgery	852.40, 658.33, 1019.47	95,465	95,551
Glaucoma procedure	581.25, 467.32, 695.17	95,487	95,527
Serious infections	5940, 4776, 7105	95,272	95,763
Hypertension	7.04, 5.66, 8.42	95,505	95,506
Blindness (transition)	237, 191, 283	95,510	95,502
Blindness (annual)	7659, 6158, 9160	97,243	93,769

a Base-case ICER: £95,506 (deterministic model).

Adalimumab: inactive uveitis patients

Base case

In the base case, ADA plus limited current practice as provided in the VISUAL II trial[47] [LCP(VII)] was estimated to produce 0.118 incremental QALYs compared with LCP(VII) alone at an extra cost of £37,432, resulting in an ICER of £317,547 per QALY gained in patients with inactive uveitis, as shown in *Table 57*. The deterministic analysis produced a slightly higher ICER (£321,405), as shown in *Table 58*. A breakdown of the results of the deterministic analysis is provided in *Appendix 7*. *Figure 21* shows the CEAC for ADA + LCP(VII) compared with LCP(VII) in patients with inactive uveitis and *Figure 22* shows the cost-effectiveness plane scatterplot of ADA + LCP(VII) compared with LCP(VII). The scatterplot shows a positive correlation between incremental costs and incremental QALYs, as was the case for patients with active uveitis. However, in patients with inactive uveitis, the comparator was more effective than the intervention arm. It should be noted that around 47% of patients in both arms received systemic immunosuppressants.

TABLE 57 Results of the base-case analysis comparing ADA + LCP(VII) with LCP(VII) in patients with inactive uveitis: probabilistic model

Treatment group	Total QALYs	Total costs (£)	Incremental QALYs	Incremental costs (£)	ICER (£)	Probability of cost-effectiveness at WTP threshold of	
						£20,000	£30,000
LCP(VII)[a]	15.221	48,642				1.00	1.00
ADA + LCP(VII)[a]	15.339	86,074	0.118	37,432	317,547	0.00	0.00

a Limited current practice, as provided in the VISUAL II trial:[47] on systemic steroids at baseline, which were tapered by week 19, and around 47% of patients on systemic immunosuppressants.

TABLE 58 Results of the base-case analysis comparing ADA + LCP(VII) with LCP(VII) in patients with inactive uveitis: deterministic model

Treatment group	Total QALYs	Total costs (£)	Incremental QALYs	Incremental costs (£)	ICER (£)
LCP(VII)[a]	15.244	48,111			
ADA + LCP(VII)[a]	15.361	85,462	0.116	37,351	321,405

a Limited current practice, as provided in the VISUAL II trial:[47] on systemic steroids at baseline, which were tapered by week 19, and around 47% of patients on systemic immunosuppressants.

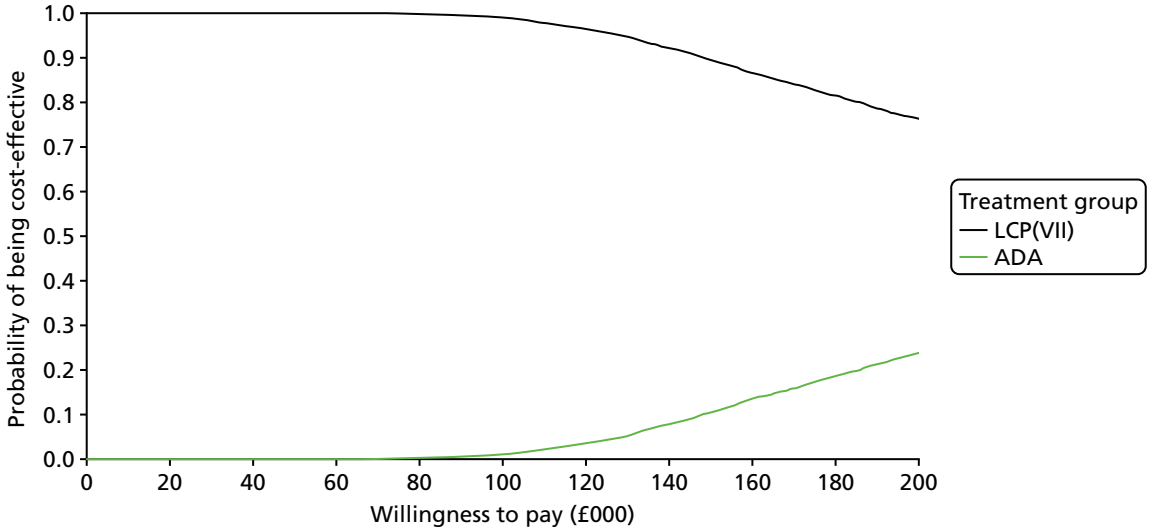

FIGURE 21 Cost-effectiveness acceptability curve for ADA + LCP(VII) compared with LCP(VII) in patients with inactive uveitis.

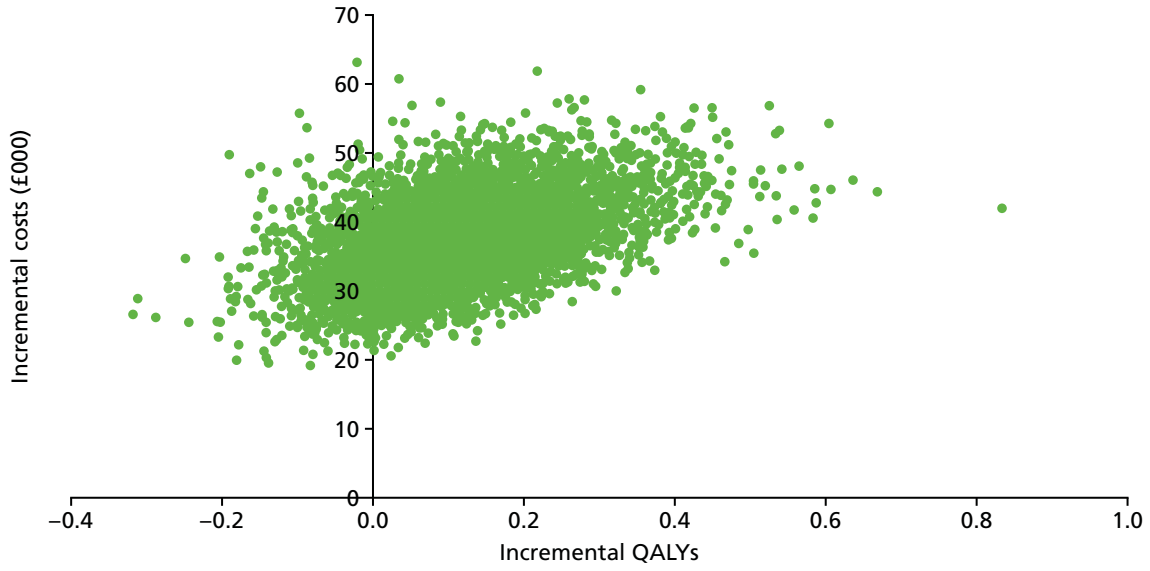

FIGURE 22 Cost-effectiveness plane scatterplot of ADA + LCP(VII) compared with LCP(VII) in patients with inactive uveitis.

Exploratory analyses

Exploratory analysis 2: incidence and health-related quality-of-life impact of blindness The AG analysed the combined impact of different blindness rates based on different sources in the literature and assuming different RRs for patients before treatment failure. As shown in *Table 59*, the impact of the RR of blindness on the ICER for ADA + LCP(VII) compared with LCP(VII) in patients with inactive uveitis is very important. The higher the rate of blindness, the greater the impact of the RR. Assuming the highest rate of blindness from the literature (based on the study by Durrani *et al.*[11]) resulted in an ICER for ADA + LCP(VII) compared with LCP(VII) of £7,411,362 per QALY gained for a RR of 1 (i.e. assuming that ADA has no effect on blindness) and an ICER of £85,544 per QALY for a RR of 0 (i.e. assuming that no patient goes blind before treatment failure).

The AG also explored the impact of assuming a different source for the utility for patients following the onset of blindness. In the base case the utility estimate was based on the study by Czoski-Murray *et al.*;[109] the exploratory analysis was undertaken using the utility estimate reported by Brown.[115] The results of this exploratory analysis are shown in *Table 60*. The ICERs for ADA + LCP(VII) compared with LCP(VII) were higher using the utility estimate from Brown[115] than when using the utility estimate from Czoski-Murray *et al.*[109] This is because the utility estimate for blindness is lower in the study by Czoski-Murray *et al.*[109] (0.38) than in the study by Brown[115] (0.57).

To explore the impact of the cost of blindness, the AG undertook an analysis using the upper bounds of the 95% CIs for the annual cost of blindness and the cost of the transition to blindness. *Table 61* presents the results of this exploratory analysis, which show that the ICERs for ADA + LCP(VI) compared with LCP(VI) are lower than in the analyses using the mean costs of blindness, except when a blindness rate of 0 or a RR before treatment failure of 1 is assumed.

TABLE 59 Incremental cost-effectiveness ratios (£) for ADA + LCP(VII) vs. LCP(VII) with varying blindness rates and RRs of blindness for patients before treatment failure

	RR of blindness before treatment failure				
Annual rate of blindness (source)	0 (no blindness)[a]	0.25	0.50	0.75	1 (no effect)
0 (assumption)	4,814,459	4,814,459	4,814,459	4,814,459	4,814,459
0.0038 (Tomkins-Netzer *et al.*[18])	527,056	679,863	956,162	1,606,857	4,988,973
0.0066[a] (Dick *et al.*[19])	321,405[a]	420,805	607,928	1,089,865	5,133,625
0.0374 (Durrani *et al.*[11])	85,544	112,594	167,837	331,006	7,411,362

a Base case.

TABLE 60 Incremental cost-effectiveness ratios (£) for ADA + LCP(VII) vs. LCP(VII) with varying blindness rates and RRs of blindness for patients before treatment failure and using the utility estimate for blindness from Brown[115]

	RR of blindness before treatment failure				
Annual rate of blindness (source)	0 (no blindness)[a]	0.25	0.50	0.75	1 (no effect)
0 (assumption)	4,814,459	4,814,459	4,814,459	4,814,459	4,814,459
0.0038 (Tomkins-Netzer *et al.*[18])	821,798	1,040,149	1,414,808	2,206,843	4,988,973
0.0066[a] (Dick *et al.*[19])	514,958[a]	665,947	940,350	1,593,079	5,133,625
0.0374 (Durrani *et al.*[11])	141,538	185,892	275,797	536,245	7,411,362

a Base case.

TABLE 61 Incremental cost-effectiveness ratios (£) for ADA + LCP(VII) vs. LCP(VII) with varying blindness rates and RRs of blindness for patients before treatment failure using high costs of blindness (upper bounds of the 95% CIs)

	RR of blindness before treatment failure				
Annual rate of blindness (source)	0 (no blindness)[a]	0.25	0.50	0.75	1 (no effect)
0 (assumption)	4,814,459	4,814,459	4,814,459	4,814,459	4,814,459
0.0038 (Tomkins-Netzer *et al.*[18])	523,933	676,848	953,341	1,604,491	4,988,973
0.0066[a] (Dick *et al.*[19])	318,140[a]	417,608	604,860	1,087,124	5,133,625
0.0374 (Durrani *et al.*[11])	82,177	109,245	164,519	327,767	7,411,362

a Base case.

Exploratory analysis 3: patients who go into remission after adalimumab treatment In the base case, the AG assumed that patients would stay on ADA until treatment failure. However, based on clinical advice received by the AG, a further analysis was undertaken assuming that, after 2 years of successful treatment, a proportion of patients discontinue treatment as they are in remission and retain the benefits of treatment. *Table 62* presents the results for different annual discontinuation rates for patients after 2 years of successful treatment. As expected, only the cost of treatment with ADA varies with the different rates of treatment discontinuation after remission: the cost of ADA treatment decreases as the rate of discontinuation increases and therefore the ICER for ADA + LCP(VII) compared with LCP(VII) also decreases. It is worth noting that, if all patients could discontinue ADA treatment after 2 years and still retain the benefits of treatment, the ICER for ADA + LCP(VII) compared with LCP(VII) would be £84,132 per QALY gained.

Exploratory analysis 4: using the Visual Function Questionnaire data from the VISUAL trials of adalimumab[46,47] to map to EuroQol-5 Dimensions utility data The AG undertook an exploratory analysis using EQ-5D scores mapped from VFQ-25 scores captured in the VISUAL II trial[47] instead of directly measured EQ-5D scores. This analysis resulted in lower QALY gains and therefore a higher ICER for ADA + LCP(VII) compared with LCP(VII) than in the base case (*Table 63*).

TABLE 62 Results of the exploratory analysis of different annual discontinuation rates for patients who have completed 2 years of successful treatment

Rate of remission	Treatment group	Total QALYs	Total costs (£)	Incremental QALYs	Incremental costs (£)	ICER (£)
0.00[a]	LCP(VII)[b]	15.244	48,111			
	ADA + LCP(VII)[b]	15.361	85,462	0.116	37,351	321,405
0.10	LCP(VII)[b]	15.244	48,111			
	ADA + LCP(VII)[b]	15.361	71,241	0.116	23,130	199,031
0.25	LCP(VII)[b]	15.244	48,111			
	ADA + LCP(VII)[b]	15.361	64,710	0.116	16,599	142,832
1.00	LCP(VII)[b]	15.244	48,111			
	ADA + LCP(VII)[b]	15.361	57,888	0.116	9777	84,132

a Base case.
b Limited current practice, as provided in the VISUAL II trial:[47] on systemic steroids at baseline, which are tapered by week 19, and around 47% of patients on systemic immunosuppressants.

TABLE 63 Results of ADA + LCP(VII) compared with LCP(VII) in patients with inactive uveitis using EQ-5D scores captured in the VISUAL II trial

Treatment group	Total QALYs	Total costs (£)	Incremental QALYs	Incremental costs (£)	ICER (£)
LCP(VII)[a]	15.100	48,111			
ADA + LCP(VII)[a]	15.207	85,462	0.107	37,351	348,094

a Limited current practice, as provided in the VISUAL II trial:[47] on systemic steroids at baseline, which are tapered by week 19, and around 47% of patients on systemic immunosuppressants.

Exploratory analysis 5: extrapolation of the time to treatment discontinuation for adalimumab To assess the impact of uncertainty around the extrapolation of the time to treatment failure, the AG undertook an exploratory analysis using alternative parametric curves. The ICER for ADA + LCP(VII) compared with LCP(VII) was lower when using a Gompertz distribution (£297,746 per QALY) or a Weibull distribution (£235,916 per QALY) than when a log-normal distribution was used, as in the base case (£321,405 per QALY) (*Table 64*).

Univariate sensitivity analyses

The AG explored the impact of different parameters on the results of the model, as shown in *Table 65*.

As for patients with active disease, of those parameters tested within the univariate sensitivity analysis, the parameters relating to the baseline utility and the utility of blindness had the greatest impact on the ICER for ADA + LCP(VII) compared with LCP(VII). However, the ICER for ADA + LCP(VII) compared with LCP(VII) in patients with inactive uveitis did not fall below £84,000 per QALY gained for any of the analyses considered.

Discussion

Model results and key uncertainties

The base-case analysis undertaken by the AG estimated the ICER for one DEX implant in one eye for a combination of patients with unilateral and bilateral uveitis compared with limited current practice, as per the HURON trial,[48] to be £19,509 per QALY gained. The ICER for ADA (systemic, therefore treatment for both eyes) for patients with mainly bilateral uveitis compared with limited current practice, as per the VISUAL trials,[46,47] was estimated to be £94,523 and £317,547 per QALY gained in patients with active and inactive uveitis respectively.

TABLE 64 Results of the exploratory analysis of different parametric curves to extrapolate time to treatment failure

Rate of remission	Treatment group	Total QALYs	Total costs (£)	Incremental QALYs	Incremental costs (£)	ICER (£)
Log-normal[a]	LCP(VII)[b]	15.244	48,111			
	ADA + LCP(VII)[b]	15.361	85,462	0.116	37,351	321,405
Gompertz	LCP(VII)[b]	15.305	48,101			
	ADA + LCP(VII)[b]	15.628	144,266	0.323	96,166	297,746
Weibull	LCP(VII)[b]	15.225	48,114			
	ADA + LCP(VII)[b]	15.325	71,577	0.099	23,463	235,916

a Base case.
b Limited current practice, as provided in the VISUAL II trial:[47] on systemic steroids at baseline, which were tapered by week 19, and around 47% of patients on systemic immunosuppressants.

TABLE 65 Univariate sensitivity analyses for ADA + LCP(VII) vs. LCP(VII) in patients with inactive uveitis[a]

Parameters	Base case, lower value, upper value	ICER based on lower value (£)	ICER based on upper value (£)
Utilities			
Baseline	0.85, 0.83, 0.87	334,704	309,733
Blindness	0.38, 0.31, 0.57	279,904	514,958
Administration and monitoring			
Monitoring visit frequency (weeks)	6, 4, 8	322,313	320,952
Monitoring visit cost (£)	96.11, 77.27, 114.95	320,956	321,900
ADA administration cost (£) (help from a nurse)	44, 35.80, 53.03	320,628	322,262
% of self-injectors needing district nurse for ADA	10, 0, 20	317,234	325,577
AE costs (£)			
Cataract surgery	852.40, 658.33, 1019.47	321,741	321,035
Glaucoma procedure	581.25, 467.32, 695.17	321,405	321,405
Serious infections	5940, 4776, 7105	321,620	321,169
Hypertension	7.04, 5.66, 8.42	321,405	321,406
Blindness (transition)	237, 191, 283	321,409	321,402
Blindness (annual)	7659, 6158, 9160	324,667	318,144

a Base-case ICER: £321,405 (deterministic model).

The results of the model are highly uncertain because of the limited availability of evidence. There are three major issues with the existing evidence: (1) there is no evidence comparing DEX or ADA with current practice; (2) long-term outcomes, in particular the incidence of permanent blindness, are uncertain; and (3) there is no evidence around the proportion of patients who would experience remission and be taken off ADA (or an alternative) treatment or around long-term outcomes for these patients. These are structural uncertainties within the model and the complexity of these issues in combination with the lack of data meant that it was not possible to appropriately quantify the uncertainty associated with them within the PSA, as would be ideal. Instead, the potential impacts of these factors on the model results have been dealt with using exploratory analysis.

These analyses suggest that the rate of blindness in the comparator group and the RR of blindness for DEX and ADA substantially affect the ICER. The cost per QALY gained compared with the comparator within the HURON trial[48] ranged from dominating to £56,329 for DEX. Under all assumptions tested for these parameters, the ICER associated with ADA compared with (limited) current practice remained above £30,000 and £82,000 for patients with active and inactive uveitis respectively. The choice of comparator did not have a substantial impact on the ICER, although it should be noted that the rate of blindness was assumed to be the same for all comparators independent of the proportion of patients receiving systemic treatment, which may have slightly overestimated the QALYs associated with the placebo and sham groups and hence the ICERs for these comparisons may be slightly overestimated. The exploratory analyses also suggest that the proportion of patients who would be taken off ADA treatment following remission and who would maintain the same quality of life is a key driver of the model results. Under the assumption that all patients who remain on ADA at 2 years achieve remission and are taken off treatment while retaining quality of life, the ICER for ADA compared with (limited) current practice decreases to £35,299 and £84,132 per QALY for patients with active and inactive uveitis respectively.

Use of adalimumab and dexamethasone in clinical practice

The clinical advisors to the AG suggested that there are several differences between the way in which the treatments are provided within the RCTs and the way in which they would be provided in practice. The clinical experts suggested that the proportion of patients who remain on ADA treatment is likely to be underestimated within the clinical trial because of the strict criteria for treatment failure. If more people were to remain on treatment, the additional group of patients on treatment would incur the same costs as those who remain on treatment in the VISUAL trial, whereas the effectiveness of ADA is likely to be reduced in these patients who were considered to have failed treatment in the trial and hence the ICER would increase for these patients.

The model predicts that ADA would have a substantially higher ICER for inactive patients than active patients. The VISUAL II trial[47] captures the benefits of ADA over placebo for preventing the recurrence of uveitis symptoms in patients who were inactive while on high-dose steroids, once the steroids have been tapered and discontinued. However, our clinical advisors suggested that, for the 'inactive' group of patients, ADA is more likely to be used in patients who have to discontinue existing immunosuppressants because they are ineffective or not tolerated. However, there are no clinical data for this group of patients.

The model assumes that only one DEX implant would be provided to patients. There is no RCT evidence to assess the comparative effectiveness or safety of more than one DEX implant; however, there are several non-randomised trials with 12–24 months' follow-up that have allowed repeat implants.[18,50,51] These studies consistently report that, after around 6 months, patients' outcomes return to those at baseline and that up to three repeat implants are each likely to have a similar treatment effect. Each additional implant is associated with a higher incidence of AEs such as raised IOP and cataract.[18,50,51] The univariate sensitivity analyses suggested that the model is not sensitive to the costs of treating raised IOP or cataract and, hence, given that the cost of each implant is the same, the cost-effectiveness of up to three consecutive implants is expected to be similar to the cost-effectiveness of one implant. The ICER would be expected to decrease if there was also a cumulative impact on the reduction in blindness or if patients were to achieve remission after consecutive implants. The clinical experts to the AG suggested that the maximum number of implants likely to be provided to one eye per patient is four because of the increasing rate of raised IOP for each implant. Clinicians suggested that the increasing rate of cataract would not affect their decision regarding additional implants because the condition is reversible with surgery. If DEX implants were repeated at < 6 months following the previous implant, the DEX implants would be less cost-effective than currently predicted.

The clinical advisors suggested that patients would not usually receive an implant in both eyes because they are more likely to have a systemic treatment if both eyes require treatment; however, this may occur in some cases. There was insufficient evidence to assess the cost-effectiveness of using DEX implants in both eyes; however, because the costs would essentially be doubled (with the exception of some monitoring costs) and the increment in HRQoL is likely to be lower for the second eye, it is expected to be less cost-effective than treatment in one eye for a patient with bilateral disease.

The clinical experts to the AG suggested that ADA and DEX are likely to be provided alongside other treatment options in practice. In the clinical trials, around one-third of patients did receive other treatments in both arms. However, it is unclear whether or not the relative effectiveness of ADA and DEX predicted within the trials would be the same if the use of alternative treatments in both the intervention group and the comparator group was increased. If the relative effectiveness and costs remained the same, then the ICER would not change from the base-case predicted ICER. However, because of the lack of evidence for a comparator that represents current practice, it is unclear how both ADA and DEX may have an impact on the use of other treatments. The model incorporates the impact of DEX on use of rescue therapy, but this is based on the analysis using a sham comparator. If treatment with DEX or ADA led to a reduction in the use of immunosuppressants and/or corticosteroids without this having an impact on efficacy in these treatment groups, then DEX and ADA would be more cost-effective than currently predicted.

Potentially important subgroups

The model includes a heterogeneous population and it may be that the interventions are more cost-effectiveness in some groups than others. However, there was insufficient evidence to undertake any formal subgroup analyses. This discussion considers the key subgroups for which the interventions may be more cost-effective. Almost all patients receiving ADA will have bilateral uveitis; however, DEX may be given to patients with unilateral and bilateral uveitis. DEX is likely to be more cost-effective when given in one eye to patients with bilateral uveitis because BCVA in the better-seeing eye is the best predictor of quality of life and hence bilateral uveitis patients are generally able to benefit more from treatment than unilateral uveitis patients, for the same cost of treatment. When the annual rate of blindness is set to 0, the results can be used to give an indication around the cost-effectiveness of DEX for patients with unilateral disease (as patients with unilateral disease are unlikely to become legally blind, unless their disease progresses to become bilateral). The ICER in this case was £48,937. It is important to note that the treatment effect may also be different (expected to be reduced) for unilateral patients compared with a pooled group of unilateral and bilateral patients; however, there was no evidence available to model this.

Patients also have the potential to benefit more from treatment with ADA or DEX if they have more severe uveitis and hence the treatments are likely to be more cost-effective as the baseline disease worsens. In addition, patients with macular oedema are more likely to go blind and therefore the interventions of interest, in particular ADA, because of the longer duration of treatment, are more likely to prevent cases of blindness and hence are likely to be more cost-effective in this group.

Model perspective

The base-case analysis took a NHS and PSS perspective. However, sight problems and sight damage caused by uveitis can affect every aspect of daily life. The quality-of-life measures used within the health economic model aimed to largely capture these effects. However, if a societal perspective was taken, the cost-effectiveness of the interventions would be reduced. A societal perspective would capture the additional cost savings associated with increased leisure time and workplace productivity resulting from the benefits of the interventions. Given that non-infectious uveitis affects a working-age population, these cost savings would not be negligible. Therefore, there are likely to be additional non-NHS and -PSS cost savings of the interventions that are not captured within our analyses; however, analysis of these additional cost savings are beyond the scope of this NICE appraisal.

Chapter 5 Assessment of factors relevant to the NHS and other parties

Many uveitis treatments used in clinical practice are not licensed for uveitis and injections of triamcinolone are contraindicated in the eye [Kenalog® formulation (Bristol-Myers Squibb Pharmaceuticals Ltd, Princeton, NJ, USA)] or are not available in the UK [Trivaris® (Allergan, Irvine, CA, USA)/Triesence® (Alcon Canada Inc., Mississauga, ON, Canada) formulation]. DEX implants and ADA are both used variably in current practice, depending on funding availability. Posterior segment-involving uveitis covers a broad spectrum of patients. DEX implants and ADA would generally be used in different populations in clinical practice (DEX for local disease or local flare-up and in unilateral cases; ADA for severe refractory disease, often bilateral and/or related to a systemic condition). There are few trial data relating to patients who have very severe uveitis or who are unresponsive to or contraindicated for immunosuppressants.

The prevalence of non-infectious posterior segment-involving uveitis is estimated to be between 3 and 10 in 100,000 people in the European Union, based on a population of 506,500,000, including people from the UK.[132] The mid-2015 estimate for the adult population of England is 43,108,471.[133] This results in an estimated prevalence of non-infectious posterior segment-involving uveitis in adults in England of between 1293 and 4311. Within its submission to NICE,[55] Allergan, however, estimated a higher prevalence of non-infectious posterior segment-involving uveitis in adults of 16.14 per 100,000, based on a US study, which would result in a higher estimate of 6958 adults affected by non-infectious posterior segment-involving uveitis in England. In its submission,[43] AbbVie predicted that 5389 adults would be affected by non-infectious posterior segment-involving uveitis in England. The proportion of patients who would receive DEX and ADA within this patient group is highly uncertain. Within its submission to NICE,[55] Allergan predicted that 589 patients would be eligible for DEX annually (8.0% of the predicted number of patients with non-infectious posterior segment-involving uveitis), whereas, within its submission,[43] AbbVie predicted that 175 patients would be eligible for ADA annually (3.2% of the predicted number of patients with non-infectious posterior segment-involving uveitis).

The provision of ADA and DEX does not usually engender significant additional management costs compared with current practice. Therefore, the burden on the NHS is generally related to the additional drug acquisition costs and differences in the treatment of AEs. Allergan and AbbVie submitted estimates of the annual additional cost to the NHS of DEX and ADA respectively. DEX was predicted by Allergan to cost an additional £74,672–1,057,706 in the first year, depending on whether the comparator was an immunosuppressant or a corticosteroid, rising to an additional £599,537–5,514,704 in year 5. These estimates were based on the costs of DEX (assuming that patients with unilateral and bilateral disease would have 1.64 implants and 3.28 implants on average annually respectively) minus the costs of immunosuppressants or corticosteroids, which assumes that DEX would eradicate the need for these comparators, and hence they are likely to be underestimates. They also include a reduction in monitoring costs for patients receiving DEX, but do not include the costs of the treatment of AEs. The increase in costs over time occurs because of the assumption that patients will continue to receive DEX implants, which is unlikely to be the case, and hence the first year cost is likely to be the most reasonable estimate.

Adalimumab was predicted by AbbVie to cost £1.55M in the first year, rising to £4.77M in year 5. This was based on the costs of ADA minus the costs of prednisolone (assuming that ADA would be given as third-line treatment and would eradicate the need for corticosteroids). It does not include the costs of the treatment of AEs. The increase in costs over time occurs because of an expected increase by the company in the use of biologics in this patient population. The calculation did not account for patients failing on treatment and hence the increase in costs over the 5 years is likely to have been overpredicted.

Given the substantial uncertainties around prevalence, the number of patients who would receive ADA and DEX, the impact of the interventions on existing immunosuppressant and corticosteroid use, the impact of the interventions on blindness, the number of DEX implants that patients would receive (bilateral and consecutive) in practice and whether or not patients would stop receiving ADA following remission, the AG has not undertaken an analysis of its own as the extent to which it could improve on the companies' estimates is unclear.

Chapter 6 Discussion

Statement of principal findings

One RCT of ADA in patients with active uveitis (VISUAL I;[46] $n = 223$, follow-up of up to 80 weeks) showed significant benefits over placebo for time to treatment failure as well as visual acuity, inflammation (VH and AC cell grade), macular oedema (change in central retinal thickness) and VFQ-25 score. Another RCT of ADA in patients with inactive uveitis controlled with corticosteroids (VISUAL II;[47] $n = 229$, follow-up of up to 80 weeks) showed significant benefits over placebo for time to treatment failure but not for the other outcomes. There were some concerns regarding the use of LOCF to account for missing data after patients experienced treatment failure in the ADA studies as these data were not missing at random as more patients experienced treatment failure in the placebo arms than in the ADA arms. The ICERs for ADA (systemic, therefore treatment of both eyes) for patients with mainly bilateral uveitis compared with limited current practice, as in the VISUAL trials,[46,47] were estimated to be £94,523 and £317,547 per QALY gained in patients with active and inactive uveitis respectively.

A 26-week study of DEX 700 compared with a sham procedure (HURON;[48] $n = 153$ for relevant groups) showed significant improvements in the DEX 700 group for measures of visual acuity, inflammation (VH and AC cell grade), macular oedema (central retinal thickness) and VFQ-25 score. The base-case analysis undertaken by the AG estimated that the ICER for one DEX implant in one eye for a combination of patients with unilateral and bilateral uveitis compared with limited current practice, as in the HURON trial,[48] was £19,509 per QALY gained.

Exploratory analyses suggest that two of the factors that have the largest impact on the ICERs, both of which are highly uncertain, are (1) the rate of blindness in the comparator group and (2) the RR of blindness for ADA and DEX. The ICER for DEX compared with (limited) current practice varied from dominating to £56,329 per QALY gained under different assumptions for these parameters. Setting the rate of legal blindness to zero was used to explore the potential cost-effectiveness of DEX for patients with unilateral uveitis; the ICER in this case was £50,627 per QALY gained. Under all assumptions tested for these parameters, the ICER associated with ADA compared with (limited) current practice remained above £30,000 and £82,000 per QALY gained for patients with active and inactive uveitis respectively. The proportion of patients taken off ADA treatment following remission and maintaining the same quality of life had the largest impact on the ICER for ADA, with ICERs of £35,299 and £84,132 per QALY gained for patients with active and inactive uveitis, respectively, when it was assumed that all patients go into remission after 2 years on ADA.

Strengths and limitations of the assessment

We have attempted to compare the two interventions being assessed with current practice; however, there is no RCT evidence comparing any two treatments within the scope of the assessment. ADA was compared with placebo in both studies of ADA identified (patients in both arms also received initial systemic corticosteroids, which were then tapered, and some also received an immunosuppressant) and DEX was compared with a sham procedure in the one study of DEX identified (25% also continued with a stable dose of systemic corticosteroids or immunosuppressants and 22% received rescue therapy, either a local steroid injection or new/increased systemic therapy, in both the DEX 700 arm and the sham arm). The placebo/sham arms could be considered to represent standard practice to some extent because other therapies were permitted in both the active treatment and the placebo arms in all three studies. However, the main comparison was with placebo/sham procedure as opposed to active management with other therapies.

It was not possible to conduct meta-analyses or NMAs because of clinical heterogeneity, lack of common comparators (disconnected network) and differences in the reported outcomes.

The health economic model is the first model that has attempted to assess the cost-effectiveness of ADA or DEX for the treatment of non-infectious uveitis. However, the results are highly uncertain because of the limited availability of evidence and the differences between the trial evidence and clinical practice (as discussed in *Chapter 4*, *Independent economic assessment*).

The model includes a heterogeneous population and it may be that the interventions are more cost-effective in some groups than others. However, there was no evidence from the trials to allow subgroup analyses to be undertaken. Patients have the potential to benefit more from treatment with ADA or DEX if they have more severe uveitis and hence the treatments are likely to be more cost-effective as the baseline disease worsens. In addition, patients with macular oedema are more likely to go blind and hence the interventions of interest, in particular ADA, because of the longer duration of treatment, are more likely to prevent cases of blindness and hence are likely to be more cost-effective in this group. The exploratory analysis in which the rate of blindness was varied to represent patients with unilateral uveitis suggests that the ICER for DEX compared with (limited) current practice increases substantially for this patient group; however, the treatment effect for this subgroup is assumed to remain unchanged.

The analysis presented here takes a NHS and PSS perspective. However, non-infectious uveitis affects a working-age population and can reduce workplace productivity. In addition, the disease can affect leisure time. Therefore, there are likely to be additional non-NHS and -PSS costs and benefits of the interventions not captured within our analyses.

Uncertainties

The key uncertainties associated with this evaluation are:

- the comparative effectiveness and cost-effectiveness of DEX and ADA and their effectiveness and cost-effectiveness compared with those of systemic immunosuppressants and corticosteroids, as would be used in practice
- how short-term improvements in visual acuity and inflammation relate to long-term effects on vision loss and blindness
- how ADA and DEX would be used in practice, particularly with regard to taking patients off treatment following remission and the number of DEX implants that would be provided
- the impact of the expected differences between clinical practice and the trial evidence on estimated outcomes
- the effectiveness and cost-effectiveness of ADA and DEX in subgroups of patients, including patients with unilateral and bilateral uveitis, those with more and less severe uveitis, patients who are unresponsive to or who are contraindicated for immunosuppressants, patients with macular oedema and patients with underlying autoimmune or inflammatory diseases
- the long-term impacts of corticosteroids.

Other relevant factors

The number of patients who would be eligible for these treatments is low. DEX implants and ADA are currently generally used in very different patient populations in clinical practice.

Chapter 7 Conclusions

Two RCTs of systemic ADA and one RCT of a unilateral, single DEX implant showed significant benefits over placebo or a sham procedure for outcomes including visual acuity, inflammation (VH and AC cell grade), macular oedema (central retinal thickness), VFQ-25 score and time to treatment failure. One DEX implant in a mixed group of unilateral and bilateral patients had an estimated ICER of £19,509 per QALY gained compared with (limited) current practice. The ICER associated with ADA compared with (limited) current practice did not fall below £30,000 per QALY gained in any of the analyses carried out.

There is substantial uncertainty around the evidence, in particular with regard to the comparative effectiveness and cost-effectiveness of DEX and ADA and their effectiveness and cost-effectiveness compared with those of systemic immunosuppressants and corticosteroids, as would be used in practice, and how short-term improvements in visual acuity and inflammation relate to long-term effects on vision loss and blindness. In addition, the way in which ADA and DEX would be used in practice and the impact of the expected differences between clinical practice and the trial evidence on estimated outcomes are uncertain. Finally, there are important subgroups for which the interventions may be more or less effective and cost-effective; however, there was insufficient evidence to make robust conclusions around this.

Implications for service provision

The provision of ADA and DEX does not usually engender significant additional management costs. Therefore, the burden on the NHS is generally related to the drug acquisition costs and the treatment of AEs.

Suggested research priorities

- Development of guidance on which outcomes should be used and how they should be reported in trials of non-infectious uveitis, outlining primary clinical outcomes as well as considering a standardised way of reporting reduction in corticosteroid use.
- Primary research comparing:
    - DEX with immunosuppressants over the long term in patients with localised (uveitis affecting one eye or a flare in one eye) active uveitis
    - ADA with immunosuppressants and other anti-TNFs over the long term in patients with systemic bilateral active uveitis
    - ADA, DEX, immunosuppressants and other anti-TNFs over the long term in patients with systemic unilateral uveitis (or a flare in one eye).
- Researchers should consult a statistician and follow the Consolidated Standards of Reporting Trials (CONSORT) statement[134] when designing and undertaking RCTs.[135]
- Research on how short-term improvements in visual acuity or inflammation relate to long-term effects on moderate-to-severe vision loss and blindness.
- An assessment of the impact of treatments within important subgroups, including patients with unilateral and bilateral uveitis, those with severe uveitis, patients who are unresponsive to or who are contraindicated for immunosuppressants, patients with macular oedema and patients with specific underlying autoimmune or inflammatory diseases.
- A study of the long-term impacts of corticosteroids to gain further data on health and utility decrements and costs.

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Katy Cooper (Senior Research Fellow, systematic reviewing) undertook the clinical effectiveness review.

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Jean Hamilton (Research Associate, statistics) commented on statistical issues and the feasibility of NMA.

Ruth Wong (Information Specialist) performed the literature searches.

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Data sharing statement

Data can be obtained from the corresponding author subject to them being non-confidential.

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Appendix 1 Literature search strategies

Clinical effectiveness searches

MEDLINE, Epub Ahead of Print, MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE(R) Daily and MEDLINE(R) (1946 to 2016) (via Ovid)

Date searched: 13 June 2016.

#	Searches
1	exp Uveitis/
2	uveiti*.mp.
3	(panuveitis or pars planitis or panophthalmitis or uveomeningoencephaliti*).tw.
4	(iridocycliti* or heterochromic cycliti* or anterior scleritis or iriti* or choroiditi* or retinochoroiditi* or retinochoroidopath* or chorioretinitis or chorioretinopath*).tw.
5	((vogt or harada or behcet* or blau* or jabs or reiter*) adj (disease or syndrome)).tw.
6	(vogt koyanagi harada or triple symptom complex).tw.
7	(ophthalm* adj2 sympathetic).tw.
8	exp Retinitis/
9	(retinitis or vitritis* or uveoretinitis or neuroretinitis).tw.
10	or/1-9
11	Meta-Analysis as Topic/
12	meta analy$.tw.
13	metaanaly$.tw.
14	Meta-Analysis/
15	(systematic adj (review$1 or overview$1)).tw.
16	exp Review Literature as Topic/
17	or/11-16
18	cochrane.ab.
19	embase.ab.
20	(psychlit or psyclit).ab.
21	(psychinfo or psycinfo).ab.
22	(cinahl or cinhal).ab.
23	science citation index.ab.
24	bids.ab.
25	cancerlit.ab.
26	or/18-25
27	reference list$.ab.
28	bibliograph$.ab.
29	hand-search$.ab.
30	relevant journals.ab.
31	manual search$.ab.

#	Searches
32	or/27-31
33	selection criteria.ab.
34	data extraction.ab.
35	33 or 34
36	Review/
37	35 and 36
38	Comment/
39	Letter/
40	Editorial/
41	animal/
42	human/
43	41 not (41 and 42)
44	or/38-40,43
45	17 or 26 or 32 or 37
46	45 not 44
47	Randomized Controlled Trials as Topic/
48	randomized controlled trial/
49	Random Allocation/
50	Double Blind Method/
51	Single Blind Method/
52	clinical trial/
53	clinical trial, phase i.pt.
54	clinical trial, phase ii.pt.
55	clinical trial, phase iii.pt.
56	clinical trial, phase iv.pt.
57	controlled clinical trial.pt.
58	randomized controlled trial.pt.
59	multicenter study.pt.
60	clinical trial.pt.
61	exp Clinical Trials as topic/
62	or/47-61
63	(clinical adj trial$).tw.
64	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
65	PLACEBOS/
66	placebo$.tw.
67	randomly allocated.tw.
68	(allocated adj2 random$).tw.
69	or/63-68
70	62 or 69

#	Searches
71	case report.tw.
72	letter/
73	historical article/
74	or/71-73
75	70 not 74
76	10 and (46 or 75)

EMBASE (1974–2016) (via Ovid)

Date searched: 13 June 2016.

#	Searches
1	exp uveitis/
2	uveiti*.mp.
3	(panuveitis or pars planitis or panophthalmitis or uveomeningoencephaliti*).tw.
4	(iridocycliti* or heterochromic cycliti* or anterior scleritis or iriti* or choroiditi* or retinochoroiditi* or retinochoroidopath* or chorioretinitis or chorioretinopath*).tw.
5	((vogt or harada or behcet* or blau* or jabs or reiter*) adj (disease or syndrome)).tw.
6	(vogt koyanagi harada or triple symptom complex).tw.
7	(ophthalm* adj2 sympathetic).tw.
8	exp retinitis/
9	(retinitis or vitritis* or uveoretinitis or neuroretinitis).tw.
10	or/1-9
11	exp Meta Analysis/
12	((meta adj analy$) or metaanalys$).tw.
13	(systematic adj (review$1 or overview$1)).tw.
14	or/11-13
15	cancerlit.ab.
16	cochrane.ab.
17	embase.ab.
18	(psychlit or psyclit).ab.
19	(psychinfo or psycinfo).ab.
20	(cinahl or cinhal).ab.
21	science citation index.ab.
22	bids.ab.
23	or/15-22
24	reference lists.ab.
25	bibliograph$.ab.
26	hand-search$.ab.
27	manual search$.ab.
28	relevant journals.ab.

#	Searches
29	or/24-28
30	data extraction.ab.
31	selection criteria.ab.
32	30 or 31
33	review.pt.
34	32 and 33
35	letter.pt.
36	editorial.pt.
37	animal/
38	human/
39	37 not (37 and 38)
40	or/35-36,39
41	14 or 23 or 29 or 34
42	41 not 40
43	Clinical trial/
44	Randomized controlled trial/
45	Randomization/
46	Single blind procedure/
47	Double blind procedure/
48	Crossover procedure/
49	Placebo/
50	Randomi?ed controlled trial$.tw.
51	Rct.tw.
52	Random allocation.tw.
53	Randomly allocated.tw.
54	Allocated randomly.tw.
55	(allocated adj2 random).tw.
56	Single blind$.tw.
57	Double blind$.tw.
58	((treble or triple) adj blind$).tw.
59	Placebo$.tw.
60	Prospective study/
61	or/43-60
62	Case study/
63	Case report.tw.
64	Abstract report/ or letter/
65	or/62-64
66	61 not 65
67	10 and (42 or 66)

Web of Science® Core Collection, Science Citation Index Expanded (1900–2016), Conference Proceedings Citation Index – Science (1990–2016) (Thomson Reuters)

Date searched: 13 June 2016.

#	Searches
#1	TOPIC: (uveiti*)
#2	TOPIC: ((panuveitis or pars planitis or panophthalmitis or uveomeningoencephaliti*))
#3	TOPIC: ((iridocycliti* or heterochromic cycliti* or anterior scleritis or iriti* or choroiditi* or retinochoroiditi* or retinochoroidopath* or chorioretinitis or chorioretinopath*))
#4	TOPIC: (((vogt or harada or behcet* or blau* or jabs or reiter*) near (disease or syndrome)))
#5	TOPIC: ((vogt koyanagi harada or triple symptom complex))
#6	TOPIC: ((ophthalm* near/2 sympathetic))
#7	TOPIC: ((retinitis or vitritis* or uveoretinitis or neuroretinitis)
#8	#7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
#9	TOPIC: (("clinic* trial*" or "randomi* controlled trial*")) OR TOPIC: (((singl* or doubl* or treb* or tripl*) and (blind* or mask*))) OR TOPIC: ((placebo*)) OR TOPIC: ((allocat* and random*))
#10	TOPIC: ((meta-analysis or meta analy* or metaanaly*)) OR TOPIC: (("review literature" or "literature review")) OR TOPIC: (("systematic review*" or "systematic overview*")) OR TOPIC: ((cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or bids or cancerlit)) OR TOPIC: (("reference list*" or bibliograph* or hand-search* or "relevant journals" or "manual search*")) OR TOPIC: ((("selection criteria" or "data extraction") and review))
#11	#10 OR #9
#12	#11 AND #8

Cochrane Database of Systematic Reviews (CDSR) (1996–2016), Cochrane Central Register of Controlled Trials (CENTRAL) (1898–2016), Health Technology Assessment (HTA) database (1995–2016), Database of Abstracts of Reviews of Effects (DARE) (1995–2015), NHS Economic Evaluation Database (NHS EED) (1995–2015) (Wiley Online Library)

Date searched: 13 June 2016.

#	Searches
#1	MeSH descriptor: [Uveitis] explode all trees
#2	uveiti*:ti,ab,kw
#3	(panuveitis or pars planitis or panophthalmitis or uveomeningoencephaliti*):ti,ab,kw
#4	(iridocycliti* or heterochromic cycliti* or anterior scleritis or iriti* or choroiditi* or retinochoroiditi* or retinochoroidopath* or chorioretinitis or chorioretinopath*):ti,ab,kw
#5	((vogt or harada or behcet* or blau* or jabs or reiter*) near (disease or syndrome)):ti,ab,kw
#6	(vogt koyanagi harada or triple symptom complex):ti,ab,kw
#7	(ophthalm* near/2 sympathetic):ti,ab,kw
#8	MeSH descriptor: [Retinitis] explode all trees
#9	(retinitis or vitritis* or uveoretinitis or neuroretinitis):ti,ab,kw
#10	#1 or #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9

Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1982–2016) (EBSCOhost)

Date searched: 6 October 2016.

#	Searches
S1	(MH "Uveitis+")
S2	uveiti*
S3	(panuveitis or pars planitis or panophthalmitis or uveomeningoencephaliti*)
S4	(iridocycliti* or heterochromic cycliti* or anterior scleritis or iriti* or choroiditi* or retinochoroiditi* or retinochoroidopath* or chorioretinitis or chorioretinopath*)
S5	((vogt or harada or behcet* or blau* or jabs or reiter*) N1 (disease or syndrome))
S6	(vogt koyanagi harada or triple symptom complex)
S7	(ophthalm* N2 sympathetic)
S8	(MH "Retinitis+")
S9	(retinitis or vitritis* or uveoretinitis or neuroretinitis)
S10	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9
S11	(MH "Meta Analysis")
S12	TI ((Meta analys* or Metaanaly*)) or AB ((Meta analys* or Metaanaly*))
S13	(MH "Literature Review+")
S14	systematic N2 review or systematic N2 overview
S15	S11 or S12 or S13 or S14
S16	PT Commentary or PT Letter or PT Editorial
S17	(MH "Animals")
S18	S16 or S17
S19	S15 not S18
S20	(MH "Clinical Trials+")
S21	PT Clinical trial
S22	TI Randomi?ed control* trial* or AB Randomi?ed control* trial*
S23	(MH "Random Assignment")
S24	(MH "Quantitative Studies")
S25	TI Allocat* random* or AB Allocat* random*
S26	TI Random* allocat* or AB Random* allocat*
S27	TI Placebo* or AB Placebo*
S28	TI Placebos or AB Placebos
S29	TI ((singl* or doubl* or trebl* or tripl*) and (blind* or mask*)) or AB ((singl* or doubl* or trebl* or tripl*) and (blind* or mask*))
S30	TI clinic* N1 trial* or AB clinic* N1 trial*
S31	S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30
S32	S10 and (S19 or S31)

Cost-effectiveness studies

MEDLINE, Epub Ahead of Print, MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE(R) Daily and MEDLINE(R) (1946–2016) (Ovid)

Date searched: 7 June 2016.

#	Searches
1	exp Uveitis/
2	uveiti*.mp.
3	(panuveitis or pars planitis or panophthalmitis or uveomeningoencephaliti*).tw.
4	(iridocycliti* or heterochromic cycliti* or anterior scleritis or iriti* or choroiditi* or retinochoroiditi* or retinochoroidopath* or chorioretinitis or chorioretinopath*).tw.
5	((vogt or harada or behcet* or blau* or jabs or reiter*) adj (disease or syndrome)).tw.
6	(vogt koyanagi harada or triple symptom complex).tw.
7	(ophthalm* adj2 sympathetic).tw.
8	exp Retinitis/
9	(retinitis or vitritis* or uveoretinitis or neuroretinitis).tw.
10	or/1-9
11	Economics/
12	"costs and cost analysis"/
13	Cost-benefit analysis/
14	Cost control/
15	Cost savings/
16	Cost of illness/
17	Cost sharing/
18	"deductibles and coinsurance"/
19	Medical savings accounts/
20	Health care costs/
21	Direct service costs/
22	Drug costs/
23	Employer health costs/
24	Hospital costs/
25	Health expenditures/
26	Capital expenditures/
27	Value of life/
28	exp economics, hospital/
29	exp economics, medical/
30	Economics, nursing/
31	Economics, pharmaceutical/
32	exp "fees and charges"/
33	exp budgets/
34	(low adj cost).mp.

#	Searches
35	(high adj cost).mp.
36	(health?care adj cost*).mp.
37	(fiscal or funding or financial or finance).tw.
38	(cost adj estimate*).mp.
39	(cost adj variable).mp.
40	(unit adj cost*).mp.
41	(economic* or pharmacoeconomic* or price* or pricing).tw.
42	or/11-41
43	10 and 42

EMBASE (1974–2016) (Ovid)

Date searched: 7 June 2016.

#	Searches
1	exp uveitis/
2	uveiti*.mp.
3	(panuveitis or pars planitis or panophthalmitis or uveomeningoencephaliti*).tw.
4	(iridocycliti* or heterochromic cycliti* or anterior scleritis or iriti* or choroiditi* or retinochoroiditi* or retinochoroidopath* or chorioretinitis or chorioretinopath*).tw.
5	((vogt or harada or behcet* or blau* or jabs or reiter*) adj (disease or syndrome)).tw.
6	(vogt koyanagi harada or triple symptom complex).tw.
7	(ophthalm* adj2 sympathetic).tw.
8	exp retinitis/
9	(retinitis or vitritis* or uveoretinitis or neuroretinitis).tw.
10	or/1-9
11	Socioeconomics/
12	Cost benefit analysis/
13	Cost effectiveness analysis/
14	Cost of illness/
15	Cost control/
16	Economic aspect/
17	Financial management/
18	Health care cost/
19	Health care financing/
20	Health economics/
21	Hospital cost/
22	(fiscal or financial or finance or funding).tw.
23	Cost minimization analysis/
24	(cost adj estimate*).mp.
25	(cost adj variable*).mp.

#	Searches
26	(unit adj cost*).mp.
27	or/11-26
28	10 and 27

Web of Science® Core Collection, Science Citation Index Expanded (1900–2016), Conference Proceedings Citation Index – Science (1990–2016) (Thomson Reuters)

Date searched: 7 June 2016.

#	Searches
#1	TOPIC: (uveiti*)
#2	TOPIC: ((panuveitis or pars planitis or panophthalmitis or uveomeningoencephaliti*))
#3	TOPIC: ((iridocycliti* or heterochromic cycliti* or anterior scleritis or iriti* or choroiditi* or retinochoroiditi* or retinochoroidopath* or chorioretinitis or chorioretinopath*))
#4	TOPIC: (((vogt or harada or behcet* or blau* or jabs or reiter*) near (disease or syndrome)))
#5	TOPIC: ((vogt koyanagi harada or triple symptom complex))
#6	TOPIC: ((ophthalm* near/2 sympathetic))
#7	TOPIC: ((retinitis or vitritis* or uveoretinitis or neuroretinitis))
#8	#7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
#9	TOPIC: ((cost* and (effective* or utilit* or benefit* or minimi*))) *OR* TOPIC: (cost*) *OR* TOPIC: ((economic* or pharmacoeconomic* or pharmaco-economic*)) *OR* TOPIC: ((financial or finance or finances or financed)) *OR* TOPIC: ((fee or fees)) *OR* TOPIC: ((value and (money or monetary))) *OR* TOPIC: ((economic* and (hospital or medical or nursing or pharmaceutical))) *OR* TOPIC: (("quality adjusted life year" or "quality adjusted life years")) *OR* TOPIC: ((qaly or qalys)) *OR* TOPIC: (budget*) *OR* TOPIC: ((price* or pricing*))
#10	#9 AND #8

Cochrane Database of Systematic Reviews (CDSR) (1996–2016), Health Technology Assessment (HTA) database (1995–2016), Database of Abstracts of Reviews of Effects (DARE) (1995–2015), NHS Economic Evaluation Database (NHS EED) (1995–2015) (Wiley Online Library)

Date searched: 7 June 2016.

#	Searches
#1	MeSH descriptor: [Uveitis] explode all trees
#2	uveiti*:ti,ab,kw
#3	(panuveitis or pars planitis or panophthalmitis or uveomeningoencephaliti*):ti,ab,kw
#4	(iridocycliti* or heterochromic cycliti* or anterior scleritis or iriti* or choroiditi* or retinochoroiditi* or retinochoroidopath* or chorioretinitis or chorioretinopath*):ti,ab,kw
#5	((vogt or harada or behcet* or blau* or jabs or reiter*) near (disease or syndrome)):ti,ab,kw
#6	(vogt koyanagi harada or triple symptom complex):ti,ab,kw
#7	(ophthalm* near/2 sympathetic):ti,ab,kw
#8	MeSH descriptor: [Retinitis] explode all trees
#9	(retinitis or vitritis* or uveoretinitis or neuroretinitis):ti,ab,kw
#10	#1 or #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9

Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1982–2016) (EBSCOhost)

Date searched: 6 October 2016.

#	Searches
S1	(MH "Uveitis+")
S2	uveiti*
S3	(panuveitis or pars planitis or panophthalmitis or uveomeningoencephaliti*)
S4	(iridocycliti* or heterochromic cycliti* or anterior scleritis or iriti* or choroiditi* or retinochoroiditi* or retinochoroidopath* or chorioretinitis or chorioretinopath*)
S5	((vogt or harada or behcet* or blau* or jabs or reiter*) N1 (disease or syndrome))
S6	(vogt koyanagi harada or triple symptom complex)
S7	(ophthalm* N2 sympathetic)
S8	(MH "Retinitis+")
S9	(retinitis or vitritis* or uveoretinitis or neuroretinitis)
S10	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9
S11	(MH "Costs and Cost Analysis+")
S12	(MH "Economics")
S13	(MH "Economics, Pharmaceutical")
S14	(MH "Fees and Charges+")
S15	(MH "Budgets")
S16	budget*
S17	cost*
S18	AB cost* and (effective* or utilit* or benefit* or minimi*)
S19	TI economic* or pharmacoeconomic* or pharmaco-economic*
S20	price* or pricing*
S21	financial or finance or finances or financed
S22	fee or fees
S23	value and (money or monetary)
S24	qaly or qalys
S25	quality adjusted life year or quality adjusted life years
S26	S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25
S27	S10 AND S26

Quality-of-life studies

MEDLINE, Epub Ahead of Print, MEDLINE In-Process & Other Non-Indexed Citations MEDLINE(R) Daily and MEDLINE(R) (1946–2016) (Ovid)

Date searched: 9 June 2016.

#	Searches
1	exp Uveitis/
2	uveiti*.mp.

#	Searches
3	(panuveitis or pars planitis or panophthalmitis or uveomeningoencephaliti*).tw.
4	(iridocycliti* or heterochromic cycliti* or anterior scleritis or iriti* or choroiditi* or retinochoroiditi* or retinochoroidopath* or chorioretinitis or chorioretinopath*).tw.
5	((vogt or harada or behcet* or blau* or jabs or reiter*) adj (disease or syndrome)).tw.
6	(vogt koyanagi harada or triple symptom complex).tw.
7	(ophthalm* adj2 sympathetic).tw.
8	exp Retinitis/
9	(retinitis or vitritis* or uveoretinitis or neuroretinitis).tw.
10	or/1-9
11	"Quality of Life"/
12	(qol or (quality adj2 life)).ab,ti.
13	(value adj2 (money or monetary)).tw.
14	value of life/
15	quality adjusted life year/
16	quality adjusted life.tw.
17	(qaly* or qald* or qale* or qtime*).tw.
18	disability adjusted life.tw.
19	daly*.tw.
20	health status indicators/
21	(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
22	(sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
23	(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
24	(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen).tw.
25	(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
26	(euroqol or euro qol or eq5d or eq 5d).tw.
27	(hql or hqol or h qol or hrqol or hr qol).tw.
28	(hye or hyes).tw.
29	health* year* equivalent*.tw.
30	health utilit*.tw.
31	(hui or hui1 or hui2 or hui3).tw.
32	disutilit*.tw.
33	rosser.tw.
34	(quality adj2 wellbeing).tw.
35	qwb.tw.
36	(willingness adj2 pay).tw.
37	standard gamble*.tw.
38	time trade off.tw.

#	Searches
39	time tradeoff.tw.
40	tto.tw.
41	letter.pt.
42	editorial.pt.
43	comment.pt.
44	41 or 42 or 43
45	or/11-40
46	45 not 44
47	10 and 46

EMBASE (1974–2016) (Ovid)

Date searched: 9 June 2016.

#	Searches
1	exp uveitis/
2	uveiti*.mp.
3	(panuveitis or pars planitis or panophthalmitis or uveomeningoencephaliti*).tw.
4	(iridocycliti* or heterochromic cycliti* or anterior scleritis or iriti* or choroiditi* or retinochoroiditi* or retinochoroidopath* or chorioretinitis or chorioretinopath*).tw.
5	((vogt or harada or behcet* or blau* or jabs or reiter*) adj (disease or syndrome)).tw.
6	(vogt koyanagi harada or triple symptom complex).tw.
7	(ophthalm* adj2 sympathetic).tw.
8	exp retinitis/
9	(retinitis or vitritis* or uveoretinitis or neuroretinitis).tw.
10	or/1-9
11	"Quality of Life"/
12	(qol or (quality adj2 life)).ti,ab.
13	(value adj2 (money or monetary)).tw.
14	socioeconomics/
15	quality adjusted life year/
16	(qaly$ or qald$ or qale$ or qtime$).tw.
17	disability adjusted life.tw.
18	daly$.tw.
19	health survey/
20	(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
21	(sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
22	(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
23	(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen).tw.

#	Searches
24	(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
25	(euroqol or euro qol or eq5d or eq 5d).tw.
26	(hql or hqol or h qol or hrqol or hr qol).tw.
27	(hye or hyes).tw.
28	health$ year$ equivalent$.tw.
29	health utilit$.tw.
30	(hui or hui1 or hui2 or hui3).tw.
31	disutilit$.tw.
32	rosser.tw.
33	(quality adj2 wellbeing).tw.
34	qwb.tw.
35	(willingness adj2 pay).tw.
36	standard gamble$.tw.
37	time trade off.tw.
38	time tradeoff.tw.
39	tto.tw.
40	letter.pt.
41	editorial.pt.
42	comment.pt.
43	40 or 41 or 42
44	or/11-39
45	44 not 43
46	10 and 45

Web of Science® Core Collection, Science Citation Index Expanded (1900–2016), Conference Proceedings Citation Index – Science (1990–2016) (Thomson Reuters)

Date searched: 9 June 2016.

#	Searches
#1	TOPIC: (uveiti*)
#2	TOPIC: ((panuveitis or pars planitis or panophthalmitis or uveomeningoencephaliti*))
#3	TOPIC: ((iridocycliti* or heterochromic cycliti* or anterior scleritis or iriti* or choroiditi* or retinochoroiditi* or retinochoroidopath* or chorioretinitis or chorioretinopath*))
#4	TOPIC: (((vogt or harada or behcet* or blau* or jabs or reiter*) near (disease or syndrome)))
#5	TOPIC: ((vogt koyanagi harada or triple symptom complex))
#6	TOPIC: ((ophthalm* near/2 sympathetic))
#7	TOPIC: ((retinitis or vitritis* or uveoretinitis or neuroretinitis))
#8	#7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1

#	Searches
#9	TOPIC: ((qol or "quality of life" or "quality adjusted life")) *OR* TOPIC: ((qaly* or qald* or qale* or qtime*)) *OR* TOPIC: (("disability adjusted life" or daly*)) *OR* TOPIC: ((sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six)) *OR* TOPIC: ((sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six)) *OR* TOPIC: ((sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve)) *OR* TOPIC: ((sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen)) *OR* TOPIC: ((sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty)) *OR* TOPIC: ((euroqol or euro qol or eq5d or eq 5d)) *OR* TOPIC: ((hql or hqol or h qol or hrqol or hr qol)) *OR* TOPIC: ((hye or hyes)) *OR* TOPIC: (("health* year* equivalent*")) *OR* TOPIC: (("health utilit*")) *OR* TOPIC: ((hui or hui1 or hui2 or hui3)) *OR* TOPIC: ((disutilit* or rosser)) *OR* TOPIC: (("quality of wellbeing" or qwb or "willingness to pay")) *OR* TOPIC: (("standard gamble*" or "time trade off" or "time tradeoff" or tto))
#10	#9 AND #8

Cochrane Database of Systematic Reviews (CDSR) (1990–2016), Cochrane Central Register of Controlled Trials (CENTRAL) (1898–2016), Health Technology Assessment (HTA) database (1995–2016), Database of Abstracts of Reviews of Effects (DARE) (1995–2015), NHS Economic Evaluation Database (NHS EED) (1995–2015) (Wiley Online Library)

Date searched: 9 June 2016.

#	Searches
#1	MeSH descriptor: [Uveitis] explode all trees
#2	uveiti*:ti,ab,kw
#3	(panuveitis or pars planitis or panophthalmitis or uveomeningoencephaliti*):ti,ab,kw
#4	(iridocycliti* or heterochromic cycliti* or anterior scleritis or iriti* or choroiditi* or retinochoroiditi* or retinochoroidopath* or chorioretinitis or chorioretinopath*):ti,ab,kw
#5	((vogt or harada or behcet* or blau* or jabs or reiter*) near (disease or syndrome)):ti,ab,kw
#6	(vogt koyanagi harada or triple symptom complex):ti,ab,kw
#7	(ophthalm* near/2 sympathetic):ti,ab,kw
#8	MeSH descriptor: [Retinitis] explode all trees
#9	(retinitis or vitritis* or uveoretinitis or neuroretinitis):ti,ab,kw
#10	#1 or #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9

*Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1982–2016) (EBSCO*host*)*

Date searched: 6 October 2016.

#	Searches
S1	(MH "Uveitis+")
S2	uveiti*
S3	(panuveitis or pars planitis or panophthalmitis or uveomeningoencephaliti*)
S4	(iridocycliti* or heterochromic cycliti* or anterior scleritis or iriti* or choroiditi* or retinochoroiditi* or retinochoroidopath* or chorioretinitis or chorioretinopath*)
S5	((vogt or harada or behcet* or blau* or jabs or reiter*) N1 (disease or syndrome))
S6	(vogt koyanagi harada or triple symptom complex)
S7	(ophthalm* N2 sympathetic)
S8	(MH "Retinitis+")

#	Searches
S9	(retinitis or vitritis* or uveoretinitis or neuroretinitis)
S10	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9
S11	(MH "Quality of Life")
S12	TI (qol or (quality N2 life)) or AB (qol or (quality N2 life))
S13	TI value and TI (money or monetary) or AB value and AB (money or monetary)
S14	(MH "Economic Value of Life")
S15	(MH "Quality-Adjusted Life Years")
S16	TI (qaly* or qald* or qale* or qtime*) or AB (qaly* or qald* or qale* or qtime*)
S17	TI disability adjusted life or AB disability adjusted life
S18	TI daly* or AB daly*
S19	(MH "Health Status Indicators")
S20	TI (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six) or AB (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six)
S21	TI (sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six) or AB (sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six)
S22	TI quality adjusted life or AB quality adjusted life
S23	TI (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve) or AB (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve)
S24	TI (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen) or AB (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen)
S25	TI (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty) or AB (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty)
S26	TI (euroqol or euro qol or eq5d or eq 5d) or AB (euroqol or euro qol or eq5d or eq 5d)
S27	TI (hql or hqol or h qol or hrqol or hr qol) or AB (hql or hqol or h qol or hrqol or hr qol)
S28	TI (hye or hyes) or AB (hye or hyes)
S29	TI health* year* equivalent* or AB health* year* equivalent*
S30	TI health utilit* or AB health utilit*
S31	TI (hui or hui1 or hui2 or hui3) or AB (hui or hui1 or hui2 or hui3)
S32	TI disutilit* or AB disutilit*
S33	TI rosser or AB rosser
S34	TI quality N2 wellbeing or AB quality N2 wellbeing
S35	TI qwb or AB qwb
S36	TI willingness N2 pay or AB willingness N2 pay
S37	TI standard gamble* or AB standard gamble*
S38	TI time trade off or AB time trade off
S39	TI time tradeoff or AB time tradeoff
S40	TI tto or AB tto
S41	PT letter
S42	PT editorial

#	Searches
S43	PT comment
S44	S41 or S42 or S43
S45	S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40
S46	S45 NOT S44
S47	S10 AND S46

Costs and utilities of blindness

MEDLINE, Epub Ahead of Print, MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE(R) Daily and MEDLINE(R) (1946–2016) (Ovid)

Date searched: 20 October 2016.

#	Searches
1	blindness.ti.
2	((sight or visual or vision) adj1 loss).ti.
3	1 or 2
4	exp "costs and cost analysis"/
5	costs.tw.
6	cost effective:.tw.
7	or/4-6
8	3 and 7
9	limit 8 to yr="2006 -Current"
10	"Quality of Life"/
11	(qol or (quality adj2 life)).ab,ti.
12	(value adj2 (money or monetary)).tw.
13	value of life/
14	quality adjusted life year/
15	quality adjusted life.tw.
16	(qaly$ or qald$ or qale$ or qtime$).tw.
17	disability adjusted life.tw.
18	daly$.tw.
19	health status indicators/
20	(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
21	(sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
22	(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
23	(sf6D or sf 6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form six D).tw.
24	(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
25	(euroqol or euro qol or eq5d or eq 5d).tw.

#	Searches
26	(hql or hqol or h qol or hrqol or hr qol).tw.
27	(hye or hyes).tw.
28	health$ year$ equivalent$.tw.
29	health utilit$.tw.
30	(hui or hui1 or hui2 or hui3).tw.
31	disutilit$.tw.
32	rosser.tw.
33	(quality adj2 wellbeing).tw.
34	qwb.tw.
35	(willingness adj2 pay).tw.
36	standard gamble$.tw.
37	time trade off.tw.
38	time tradeoff.tw.
39	tto.tw.
40	letter.pt.
41	editorial.pt.
42	comment.pt.
43	40 or 41 or 42
44	or/10-39
45	44 not 43
46	3 and 45

Appendix 2 Table of excluded studies with reasons

Reference	Intervention/conditions	Reason(s) for exclusion
***Population not non-infectious uveitis (intermediate/posterior/panuveitis)* (n = *28*)**		
Allegri 2014[136]	Indomethacin in macular oedema	Includes patients with anterior and postinfective uveitis (includes other ocular disease)
Alpsoy 2002[137]	Interferon-alpha-2a in Behçet's disease	Not a homogeneous group of patients with Behçet's uveitis
Biryukova 2015[138]	Simvastatin	Includes patients with anterior uveitis
Blumenkranz 2010[139]	DEX for macular oedema	Most patients did not have uveitis; no separate data
Boscia 2005[140]	Intravitreal triamcinolone for cystoid macular oedema	Not a RCT; not specific to uveitis
Buggage 2007[141]	Daclizumab in Behçet's disease	Uveitis or retinal vasculitis; no separate data. Daclizumab (anti-interleukin-2) not in scope
Dada 2007[142]	Triamcinolone post cataract	*n* = 28/40 anterior uveitis; no separate data
Davatchi 2004[143]	Cyclophosphamide in Behçet's disease	Population uveitis or retinal vasculitis; no separate data. Posterior uveitis recorded as an outcome not a population
Davatchi 2009[144]	Colchicine in Behçet's disease	Not specific to uveitis
Davatchi 2010[145]	Rituximab in Behçet's disease	Posterior uveitis recorded as an outcome not a population
Foster 1996[146]	Rimexolone vs. prednisolone	Anterior segment uveitis
Gupta 2013[147]	DEX in cataract	Population included patients with tuberculous uveitis and anterior uveitis; DEX administered during cataract surgery
Kuppermann 2007[148]	DEX in macular oedema	Patients (aged > 12 years) with macular oedema; not specific to uveitis
Landewé 2014[149]	Certolizumab pegol in axial spondyloarthritis	Data for new cases of uveitis only
Louis 2016[150]	ADA in Crohn's disease	No data for uveitis only
Parodi 2010[151]	Bevacizumab vs. photodynamic therapy	Neither treatment in scope; for treating neovascularisation. Population multifocal choroiditis
Perkins 1956[152]	Pyrimethamine	Includes patients with anterior uveitis and infectious uveitis. Intervention not in scope
Perkins 1965[153]	Indomethacin	Mostly anterior uveitis; some infectious uveitis
Roesel 2009[154]	Triamcinolone, two routes in cataract surgery	Includes patients with anterior uveitis and patients undergoing cataract surgery
Roesel 2010[155]	Triamcinolone vs. prednisolone in cataract surgery	Includes patients with anterior uveitis and patients undergoing cataract surgery
Rosenbaum 2004[156]	Etanercept and iritis	Summary of iritis cases across trials of etanercept in ankylosing spondylitis
Rudwaleit 2014[157]	Certolizumab pegol in axial spondyloarthritis	Not uveitis population. Data relate to uveitis flares (nine cases in total)

Reference	Intervention/conditions	Reason(s) for exclusion
Rudwaleit 2016[158]	Certolizumab pegol in axial spondyloarthritis	Not uveitis population. Data relate to uveitis flares (seven cases in total)
Schlaegel 1969[159]	Isoniazid	Mostly infectious uveitis (tuberculosis)
Sieper 2010[160]	Etanercept uveitis rates in trials of ankylosing spondylitis	Summary of uveitis cases across trials of etanercept in ankylosing spondylitis
Van den Bosch 2002[161]	Infliximab	Uveitis reported only as an AE (in one patient)
Williams 2009[162]	DEX	Patients with macular oedema as a result of uveitis or Irvine–Gass syndrome
Yates 2015[163]	Etanercept in ankylosing spondylitis	Uveitis reported only as an AE (in three patients)
Intervention not relevant (n = 25)		
Callanan 2008[164]	Fluocinolone (two doses, USA)	Compared with non-licensed dose
Choi 2005[165]	Vitrectomy vs. immunomodulatory treatment	Not in scope
de Smet 1992[166]	Ciclosporin and ketoconazole	High-dose ciclosporin vs. lower-dose ciclosporin plus ketoconazole
Dick 2013[167]	Secukinumab (three trials vs. placebo)	Not in scope
Farber 1994[168]	Acetazolamide in macular oedema	Not in scope
Haller 2009[169]	DEX	RCT comparing the effect of the insertion procedure
Ibrahim 2015[170]	SAVE trial	Not in scope
Jaffe 2006[171]	Fluocinolone (two doses, USA)	Compared with non-licensed dose
Lashay 2003[172]	Acetazolamide in uveitic macular oedema in Behçet's disease	Not in scope
Letko 2015[173]	Secukinumab (one trial of three doses)	Not in scope
Neri 2006[174]	Echinacea	Not in scope
Nguyen 2013[175]	SAVE trial	Not in scope
Nussenblatt 1997[176]	Retinal antigens	Not in scope
Nussenblatt 2006[177]	Vitamin E	Not in scope
Quinones 2010[178]	Vitrectomy	Not in scope
Rahimi 2012[179]	Bevacizumab vs. triamcinolone in uveitic macular oedema	Not in scope
Sangwan 2015[180]	Fluocinolone (two doses, Asia)	Compared with non-licensed dose; most data not from RCT
Soheilian 2010[181]	Bevacizumab vs. triamcinolone in uveitic macular oedema	Not in scope
Soheilian 2010[182]	Bevacizumab vs. triamcinolone in uveitic macular oedema	Not in scope
Soheilian 2013[183]	Diclofenac vs. triamcinolone in uveitic macular oedema	Not in scope
Soheilian 2013[184]	Diclofenac vs. triamcinolone in uveitic macular oedema	Not in scope
Tranos 2006[185]	Vitrectomy	Not in scope
van Kooij 2006[186]	Lisinopril	Not in scope
Vigil 2015[187]	SAVE trial	Not in scope

Reference	Intervention/conditions	Reason(s) for exclusion
Whitcup 1996[188]	Acetazolamide in uveitic macular oedema	Not in scope
No relevant outcomes or data (n = 15)		
Bodaghi 2001[16]	Various treatments	Retrospective analysis of causes of uveitis
Goldstein 2007[189]	Fluocinolone	Analysis of the results of three RCTs of fluocinolone
Holbrook 2016[190]	Fluocinolone (MUST trial)	Outcome was dissociation of the drug pellet
Mackensen 2008[191]	Methotrexate vs. interferon in uveitic macular oedema	Secondary publication; intermediate results only
Masuda 1989[192]	Ciclosporin vs. colchicine in Behçet's disease	Outcomes were 'frequency of ocular attack' and 'severity of ocular attack' but these were not defined
Mercante 2007[193]	Fluocinolone (two doses)	No comparison of data between groups
Muller 2004[194]	Fluocinolone (two doses)	In German; duplicate publication. Same as Sangwan *et al.*[180]
Multicenter Uveitis Steroid Treatment Trial Research Group 2010[102]	Fluocinolone (MUST) study design	Secondary publication; no additional data
Nussenblatt 1993[195]	Ciclosporin A and G	Compares two subtypes of same drug; cannot connect to network
Parekh 2015[196]	Fluocinolone (IOP risk in three trials)	Analysis of the results of three RCTs of fluocinolone
Pavesio 2006[197]	Fluocinolone	Secondary publication; preliminary data. Final data in Pavesio *et al.*[58]
Sheppard 2012[198]	Fluocinolone (two doses)	No comparison of data between groups. Secondary publication of Sangwan *et al.*[180]
Soheilian 2007[199]	Bevacizumab vs. triamcinolone in uveitic macular oedema	Secondary publication. Same as Soheilian *et al.*[181,182]
Waheed 2002[200]	Etanercept (abstract)	Secondary publication of Foster *et al.*[61]
Williams 2003[201]	DEX (Posurdex™, Oculex Pharmaceuticals, Sunnyvale, CA, USA)	Secondary publication of Kuppermann *et al.*;[148] no results reported
Not a RCT (n = 33)		
Abu El-Asrar 2012[202]	Mycophenolate mofetil in VKH	Not a RCT
Barreiro-de-Acosta 2012[203]	ADA for Crohn's disease	Not a RCT
Benitez-del-Castillo 2005[204]	Infliximab	Not a RCT
Bollinger 2009[205]	Management of IOP with fluocinolone implant	Review of three RCTs reporting the adverse effects of fluocinolone acetonide
Callejas-Rubio 2008[206]	ADA	Not a RCT (single-arm study)
Castellino 1994[207]	Ciclosporin	Not a RCT
Chavis 1992[208]	Ciclosporin	Not a RCT
Chinchurreta Capote 2014[209]	ADA in serpiginous choroiditis	Letter
Coskun 2015[210]	DEX in Behçet's disease uveitis	Retrospective analysis of a single DEX implant (posterior uveitis as a result of Behçet's disease)
Davatchi 2003[211]	Methotrexate in Behçet's disease	Not a RCT (controlled study)

Reference	Intervention/conditions	Reason(s) for exclusion
Denniston 2016[212]	ADA	News article
Ermertcan 2014[213]	ADA	Case report of patients with psoriatic uveitis
Frick 2012[39]	Fluocinolone (MUST)	No RCT data, only baseline data. Reports visual acuity and quality of life
Giardina 2011[214]	Infliximab in Behçet's disease	Not a RCT
Hamuryudan 1997[215]	Azathioprine in Behçet's disease	Reanalysis of patients in RCT by Yazici *et al.*[62]
Helveston 1996[216]	Intravenous immunoglobulin	Case report
Jaffe 2000[217]	DEX	Case report
Jaffe 2008[218]	Fluocinolone	Not a RCT
Khalil 2015[219]	Methotrexate in Behçet's disease	Case series
Mehryar 2001[220]	Sulfasalazine vs. cyclophosphamide in Behçet's disease	Not a RCT
Mochizuki 1993[221]	Tacrolimus (FK506) in Behçet's disease	Not a RCT. Also compares doses only (no placebo/other group). Same as Sakane *et al.*[227]
Multicenter Uveitis Steroid Treatment Trial Research Group 2014[101]	Fluocinolone (MUST)	Not a RCT; cost-effectiveness analysis
Murphy 2007[222]	Ciclosporin vs. tacrolimus	Not a RCT
Naik 2013[223]	DEX (HURON)	Not a RCT. Comparison of PROMs using baseline data from the HURON trial and national data
Nguyen 2009[224]	Fluocinolone	Not a RCT. Expert perspectives
Ozsahin 2012[225]	TNF inhibitor	Case report
Ozyazgan 1992[226]	Ciclosporin vs. cyclophosphamide	Not a RCT. Patients randomised but then could choose treatment
Sakane 1995[227]	Tacrolimus (FK506)	Not a RCT. Also compares doses only (no placebo/other group) and non-English-language study (Japanese). Same as Mochizuki[221]
Sen 2012[228]	Fluocinolone (MUST)	Not a RCT. Prevalence of hypotony at baseline in the MUST trial
Sen 2016[229]	Fluocinolone (MUST)	Not a RCT. Nested cohort study of visual acuity outcomes after cataract surgery
Suhler 2013[230]	ADA	Single-arm study
Tay-Kearney 2006[231]	Triamcinolone	Not a RCT. Clinical summary
Zlatanović 2012[232]	TNF-alpha antagonist	Not a RCT. Non-English publication (Serbian)
Other* (n = *16)		
Anonymous 2012[233]	Fluocinolone (MUST)	Letter to editor; erratum
Cunningham 2010[234]	TNF inhibitors	Editorial
Cunningham 2012[235]	TNF inhibitors	Editorial
Farber 1992[236]	Acetazolamide	Clinical trial record
Fraser-Bell 2008[237]	Various	Review of treatments in patients with uveitis
Goldstein 2009[238]	TNF inhibitors	Letter
Gonzalez 2005[239]	Fluocinolone	Editorial
Hall 2015[240]	Fluocinolone	Letter to editor (difference between Retisert and Iluvien)

Reference	Intervention/conditions	Reason(s) for exclusion
Lai 2005[241]	Periocular corticosteroids	Letter
Masuda 1986[242]	Ciclosporin	Non-English-language study (Chinese). Other report of this study[192] was excluded as the outcomes were not sufficiently robust
Puchalska-Niedbał 1989[243]	FIBS preparation (not defined)	Non-English-language study (Polish). Some patients with infectious uveitis; unlikely to be relevant intervention
Rho 1996[244]	Acetazolamide	Letter
Shimakawa 2002[245]	Corticosteroids (oral vs. topical)	Non-English-language study (Chinese). Likely non-RCT
Wiederholt 1986[246]	Ciclosporin vs. prednisolone	Non-English-language study (German). Only eight patients and data difficult to interpret
Wirostko 1997[247]	Scleritis-associated uveitis	Letter
Zhou 2010[248]	Traditional Chinese medicine	Non-English-language study (Chinese). Intervention not in scope

SAVE, Sirolimus as therapeutic Approach to uVEitis.

Appendix 3 Data extraction form

Reviewer:			
Study reference	Study name	Author year	Setting(s)
Study population			
Inclusion and exclusion criteria:			
Age:		Percentage males:	
Sample size (number of patients randomised):		Sample size (number of eyes randomised):	
Type of uveitis (intermediate uveitis, posterior uveitis, panuveitis/active, non-active/bilateral or unilateral):			
Cause of uveitis ('known systemic condition', 'no known systemic condition', 'not reported', 'unclear'):			
State known systemic condition(s):			
Prior treatment received (including treatment for any associated systemic condition)? Yes/no			
List prior treatment(s):			
Concomitant treatment(s) ('ALL' if treatment was received by all patients or 'PRN' if treatment was given as needed):			
List concomitant treatment(s):			
Baseline BCVA:		Baseline IOP:	
Baseline VH grade:		Baseline central macular thickness:	
Outcomes			
Outcomes reported in the study:		Follow-up schedule for assessments:	
Treatment arm and comparator arm			
Allocated treatment (dosing routine and duration of treatment):			
Number randomised (patients/eyes):			
Number analysed (patients/eyes):			
Details of any excluded/lost/withdrawn post randomisation and reasons:			
Vision or visual acuity outcomes reported:[a]			
Outcomes of intraocular inflammation activity (e.g. VH grade or AC cell grade) reported:[a]			
Reported outcomes of uveitis-related tissue damage or complications (e.g. cataract, macular oedema):[a]			
Other outcomes reported (e.g. composite outcomes):[a]			
Patient-reported outcomes reported:[a]			
Ocular and systemic adverse effects reported:[a]			
Relevance for network meta-analysis			
Clinically relevant? Yes/no			
Connects relevant treatments via network? Yes/no			

PRN, pro re nata.
a Comparisons between study arms were abstracted or calculated.

Appendix 4 Criteria for assessment of the methodological quality of included studies

Quality item	Reviewer's judgement	Details
1. Were participants assigned to study groups using an acceptable random method?	Yes	Use of centrally generated random numbers, random number tables, throwing dice
	No	Use of case record numbers, date of birth or alternation or rotation
	Unclear	Insufficient details to assess quality item
2. Was allocation concealment adequately conducted?	Yes	Allocation to study arms achieved by using interactive or web-based system or sequentially numbered opaque envelopes
	No	Allocation to study arms achieved without appropriate measures, e.g. unsealed, transparent envelopes, date of birth, alternation or rotation or other unconcealed methods
	Unclear	Insufficient details to assess quality item
3. Were eligibility criteria specified for selecting participants?	Yes	Eligibility criteria for study participants specified at study entry
	No	Eligibility criteria for study participants not specified at study entry
	Unclear	Insufficient details to assess quality item
4. Was the study adequately powered?	Yes	Sample size considered to be adequate (i.e. $\geq 80\%$) based on the a priori sample size calculation and significance level to detect a minimally clinically significant difference in the primary outcome of interest
	No	Sample size considered to be inadequate (i.e. $< 80\%$) based on the a priori sample size calculation and significance level to detect a minimally clinically significant difference in the primary outcome of interest
	Unclear	Insufficient details to assess quality item
5. Were study groups comparable for most prognostic indicators at baseline?	Yes	Key prognostic variables (e.g. age, visual acuity, IOP) were reported to be similar in relevant treatment groups at baseline
	No	Key prognostic variables (e.g. age, visual acuity, IOP) were reported to be different between relevant treatment groups at baseline
	Unclear	Insufficient details to assess quality item
6. Were patients and investigators/ outcome assessors blinded to treatment allocation?	Yes	Patients, investigators and/or outcome assessors could not identify administered study treatments
	No	Patients, investigators and/or outcome assessors may possibly identify administered study treatments
	Unclear	Insufficient details to assess quality item
7. Was follow-up adequate ($\geq 70\%$ randomised patients analysed)?	Yes	$\geq 70\%$ of randomised patients (or eyes) were included in the analysis
	No	<70% of randomised patients (or eyes) were included in the analysis
	Unclear	Insufficient details to assess quality item

Quality item	Reviewer's judgement	Details
8. Were reasons for attrition/exclusions stated?	Yes	Number of patients lost to follow-up (including withdrawals and those excluded from analysis) was reported to ensure completeness of data
	No	Incomplete data reporting noted because number of patients lost to follow-up (including withdrawals and those excluded from analysis) was not reported
	Unclear	Insufficient details to assess quality item
9. Was an intention-to-treat analysis included?	Yes	Outcome data for all patients initially randomised to a specific study arm were included in the analysis of the specified outcome
	No	Outcome data for selected patients initially randomised to a specific study arm were included in the analysis of the specified outcome
	Unclear	Insufficient details to assess quality item

Appendix 5 Effectiveness data from non-randomised studies of the dexamethasone implant

Study and design	Number of patients/eyes, follow-up and number of implants	BCVA	VH	CRT	Repeat implantations	Other
Adán 2013[85] retrospective study of DEX 700 after vitrectomy for uveitic macular oedema, Spain	• 13 patients, 17 eyes • 12 months • Single: 9 eyes; repeat: 8 eyes	Median improvement in BCVA at 1 month was one line (range 0–3; $n = 15$ eyes; $p < 0.01$), increasing to two lines by 3 months; 52.9% of eyes improved by two or more lines ($p < 0.01$). Improvement was maintained in 5 eyes (29.4%) at 6 months. No eyes lost more than one line of BCVA from baseline ($p = 0.003$)	NR	Mean (SD) CRT at baseline was 461.6 (121.7) µm, decreasing to 277.2 (66.5) µm at 1 month ($p < 0.01$); at 3 and 6 months mean (SD) CRT was 349.9 (143.2) µm ($p = 0.01$) and 394.1 (138.4) µm ($p = 0.14$) respectively. Reduction in CRT of > 100 µm in 10 eyes (62%) at 1 month, 8 eyes (47.1%) at 3 months and 5 eyes (29.4%) at 6 months	NR	Duration of response: over follow-up (mean 9.6 months, range 6–17 months), relapse of CMO (CRT increase of > 150 µm from lowest level post implant) in 8/17 eyes (47.1%) after mean of 6.5 months (range 3–11 months) follow-up. These eyes had a repeat implant
Khurana 2015[86] retrospective review of DEX 700 for cystoid macular oedema secondary to non-infectious uveitis, single centre, USA	• 13 patients, 18 eyes • 3 months • 1: 8 eyes; 2–4: 10 eyes	Mean BCVA at baseline 0.449 logMAR (Snellen 20/60); improved to 0.238 logMAR (20/30) by 1 month. Significant improvement at 1 month (2.0 lines; $p = 0.0016$), 3 months (2.1 lines; $p = 0.0051$), 6 months (2.1 lines; $p = 0.014$) and 12 months (1.4 lines; $p = 0.11$). Improvement of two or more lines in 47% of eyes at 1 month and 50% at 3 months	Baseline VH was grade 1 in 33% of eyes and grade 2 in 11% of eyes. Mean VH was grade 0 at 1, 3, 6 and 12 months of follow-up	After first implant, complete resolution of CMO in 89% of eyes at 1 month and 72% of eyes at 3 months. In eyes without epiretinal membrane, CRT decreased at 1 month (190 µm; $p = 0.00048$) and 3 months (228 µm; $p = 0.0039$). In eyes with epiretinal membrane, mean change was not significant at 1 month (100 µm; $p = 0.063$) or 3 months (33 µm; $p = 0.50$). In all patients, median ± SE time to CMO recurrence was 201 ± 62 days	Repeat implantation in patients with recurrence of CMO and decrease in VA from previous visit. Number of implants per patient during follow-up ranged from one to four; 56% (10/18 eyes) needed two or more implants. Among those with a second implant, median time to retreatment was 300 ± 71 days	NR

Study and design	Number of patients/eyes, follow-up and number of implants	BCVA	VH	CRT	Repeat implantations	Other
Lam 2015[81] retrospective review of DEX 700 for macular oedema, multicentre, Canada	• 20 patients, 23 eyes • 1–6 months • Mean implants: 1.7 ± 0.2	After first implant, 17/21 eyes (81%) gained one or more line of vision, 13 (62%) gained two or more lines and 12 (57%) gained three or more lines	NR	17/23 eyes showed improvement in CRT, with a mean (SE) peak improvement of 255.6 (43.6) µm. Eyes without prior pars plana vitrectomy showed a greater mean peak improvement than eyes with prior pars plana vitrectomy (295.1 ± 54.0 µm vs. 161.0 ± 20.4 µm)	• Mean ± SE number of implants was 1.7 ± 0.2. Mean ± SE time from first to second implant was 4.7 ± 0.3 months and from second to third implant was 3.4 ± 0.4 months • BCVA: second implant – 9 (90%), 7 (70%) and 5 (50%) out of 10 eyes gained one or more, two or three lines of vision respectively; third implant – 4/5 eyes (80%) gained three or more lines of vision	NR
Miserocchi 2012[79] retrospective study of DEX 700 for posterior uveitis, single centre, Italy	• 12 patients, 14 eyes • 11 months • 15 implants in 14 eyes	Mean BCVA was 20/80 (0.6 logMAR) before implant and 20/40 (0.3 logMAR) at the end of follow-up (6–11 months). Mean improvement in BCVA of 3.3 lines at the end of follow-up (range 0–6 lines)	NR	CRT was 496 (123) µm at baseline, improving to 226 (66) µm by the end of follow-up	NR	Concomitant systemic immunosuppressants or corticosteroids: all patients were on systemic immunosuppressants or corticosteroids; 3/12 patients reduced corticosteroid dose after receiving DEX 700

Study and design	Number of patients/eyes, follow-up and number of implants	BCVA	VH	CRT	Repeat implantations	Other
Nobre-Cardoso 2016[83] retrospective review of DEX 700 for non-infectious uveitic macular oedema, single centre, France	• 31 patients, 41 eyes • 12 months • 1: 18 eyes; 2: 10 eyes; 3: 2 eyes; 4: 1 eye	Significant improvement in mean BCVA at 1 month after first implant, from 0.84 ± 0.81 logMAR (Snellen 20/140) at baseline to 0.74 ± 0.84 logMAR (20/110) ($p < 0.01$). Mean BCVA remained improved from baseline at 12 months	Percentage with VH = 0 increased from 51.2% at baseline to 71.1% at month 1 ($p < 0.001$) and 75.6% at month 3 ($p < 0.01$). Percentage with VH = 0 at month 12 was higher than at baseline (64.7%)	After first implant, significant improvement in mean CRT, from 461 ± 158 µm at baseline to 308 ± 93 µm at 1 month ($p < 0.001$). Mean CRT was 340 ± 110 µm at 3 months ($p < 0.001$) and 442 ± 172 µm at 6 months. After one implant, 6 eyes were free of relapse in MO at 12 months	In 13 eyes with relapse after a positive response to first implant, mean time to second implant was 7.1 ± 2.9 months after the first implant. Repeat implantations improved BCVA (+0.08 logMAR) and CRT (–304 µm) at 1 month post implant. After repeat implant, mean time to relapse was 5.0 ± 1.6 months, similar to that for first implant ($p = 0.689$)	Mean time to relapse: after first implant (increase of ≥ 50 µm in CRT from month 1) was 6.7 ± 3.7 months; at 12 months the overall relapse rate was 83.3%
Palla 2015[80] retrospective review of DEX 700 for non-infectious uveitis, single centre, India	• 15 patients, 20 eyes • 12 months • NR	Mean BCVA improved from 0.666 logMAR (Snellen 20/93) at baseline to 0.479 logMAR (20/60) at 6 weeks (stated as statistically significant)	Proportion achieving VH = 0 was 60%, 45% and 30% at 6 weeks, 6 months and the last visit respectively	Mean CRT improved from 563.1 µm at baseline to 361.4 µm at 6 weeks. Trend continued at each follow-up. Two eyes with epiretinal membrane at baseline had minimal CRT improvement	NR	NR
Pelegrín 2015[51] retrospective review of DEX 700 for macular oedema secondary to non-infectious uveitis, single centre, Spain	• 32 patients, 42 eyes • 24 months • 1: 23 eyes; 2: 12 eyes; 3: 5 eyes; 4: 2 eyes	BCVA improved in vitrectomised and non-vitrectomised eyes. Maximum improvement at month 3 in both groups, maintained throughout follow-up. Difference between vitrectomised and non-vitrectomised eyes was statistically significant only at 24 months (favoured non-vitrectomised eyes; $p = 0.04$)	VH at baseline from +0.5 to +3.0 in 21 eyes (50%). Two-step improvement or change from +0.5 to 0 in 66.7% at 1 month, 62% at 3 months, 76.2% at 6 months and 80.1% at 12 months. Changes in maximum VH score were similar in non-vitrectomised and vitrectomised eyes at all follow-up points ($p = 0.706$)	Maximum decrease in CRT at month 1 in non-vitrectomised and vitrectomised eyes (251.2 and 229.9 µm respectively). Maintained throughout follow-up: at 24 months mean CRT improved by 189.1 and 273.8 µm in non-vitrectomised and vitrectomised eyes respectively (difference significant only at 24 months; $p = 0.02$)	Repeat implants required in 19 eyes (45.2%). No difference in frequency of repeat implants between non-vitrectomised and vitrectomised eyes. Median time to repeat implantation was 5 months (IQR 5–6 months). Twelve eyes (28.6%) required two implants, five (11.9%) required three implants and two (4.8%) received four implants	Concomitant systemic corticosteroid treatment: at baseline, 40.3% were receiving systemic prednisone and 53.1% second-line agents. Prednisone was reduced to < 10 mg/day in all patients at 1 month; dose reduction was maintained in 78% at 12 months. Prednisone was discontinued in 31.8% at 12 months

Study and design	Number of patients/eyes, follow-up and number of implants	BCVA	VH	CRT	Repeat implantations	Other
Pleyer 2014[82] prospective case series, single DEX 700 implant for intermediate or posterior uveitis, two centres, Germany	• 84 patients, 84 eyes • 6 months • NR	Mean BCVA 0.68 ± 0.47 logMAR (Snellen 20/100) at baseline, improving to 0.53 ± 0.54 logMAR (20/63) by 4 weeks ($p = 0.001$) and 0.51 ± 0.49 logMAR (20/63) by 12 weeks ($p < 0.001$). BCVA improvement lost by week 24 ($p = 0.999$)	Percentage with VH = 0 increased from baseline to 4 weeks (19% vs. 61%; $p < 0.001$); percentage remained significantly above baseline throughout follow-up. Mean VH remained below baseline level ($p < 0.001$ at weeks 4, 12 and 24)	Mean CRT improved from 463 ± 165 µm at baseline to 300 ± 110 µm by week 4 ($p < 0.001$). Improvement remained significant throughout the follow-up period ($p < 0.001$ at 12 and 24 weeks)	NR	Concomitant systemic immunosuppressants or corticosteroids: 32 patients (38%) on systemic immunosuppressants (± corticosteroids) at baseline. Systemic corticosteroids discontinued in 8 (25%) and reduced (to < 10 mg) in a further 6 (19%)
Tomkins-Netzer 2014[18] retrospective review of treatment and retreatment with DEX 700 for non-infectious uveitis, two centres, UK	• 27 patients, 38 eyes • 24 months • 1: 14 eyes; 2: 14 eyes; 3: 7 eyes; 4: 2 eyes; 6: 1 eye	Mean BCVA improved significantly after first implantation, from 0.47 (SEM 0.05) logMAR (Snellen 20/60) at baseline to 0.27 (0.07) logMAR (20/37) at 2 months ($p < 0.001$); deteriorated to 0.43 (0.12) logMAR (20/54) by 6 months	Significant improvement in the percentage of eyes with VH = 0 after first implantation, from 58% at baseline to 83% at 1 month ($p = 0.03$); remained until month 6 (85%; $p = 0.02$) but decreased by 12 months (53%)	Mean (SEM) CRT decreased significantly from 453 (34) µm at baseline to 263 (44) µm at 1 month after first implantation ($p = 0.003$). Macular oedema persisted in 50% of eyes but remaining eyes had a decrease in CRT of 127 (52) µm at 6 months ($p = 0.01$); improvement was maintained up to 12 months	• BCVA: second implant – improved from 0.55 (0.1) logMAR (20/70) to 0.22 (0.07) logMAR (20/33) at 1 month ($p = 0.004$), decreased after 1 month; third implant – similar trend, not significant; fourth implant – BCVA improved from 0.83 (0.17) logMAR (20/135) at baseline to 0.32 (0.09) logMAR (20/42) at 1 month. One eye had six implants: BCVA improved within 1 month • CRT: second implant – decreased by 187 (SEM 52.9) µm at 2 months ($p = 0.043$); third implant – improved but not significantly; fourth implant – decrease of 225.67 (109.85) µm at 1 month	• Median time to relapse: 6 months (range 2–42 months) after first implant (relapse in 69% of eyes) and 6 months after second implant (1–12 months) (relapse in 48% of eyes) • Reducing other treatment: after first implant – systemic or local treatment reduced or stopped in 33 eyes of 21 patients (78%) • Implants in both eyes: 11 patients had implants in both eyes; second implant was administered 113 ± 32 days after the first. Three of 11 patients had a response in the second eye (reduced CRT, improved BCVA)

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Study and design	Number of patients/eyes, follow-up and number of implants	BCVA	VH	CRT	Repeat implantations	Other
					• VH: improvement in percentage with VH = 0 after second implant not significant (72.7% at baseline, 91.7% at 1 month); similar trend after third implant	
Tsang 2016[84] retrospective review of DEX 700 for uveitic macular oedema, Canada	• 15 patients, 25 eyes • 12 months • Single: 18 eyes; repeat: 7 eyes	BCVA improved in 20/25 eyes (80%). Significant improvement in mean BCVA at 3 months, from 0.614 ± 0.089 logMAR (Snellen 20/82) at baseline to 0.35 ± 0.10 logMAR (20/45) at month 3. Five of 25 eyes (20%) had worsening of VA during follow-up	NR	CRT improved in 32/35 eyes (91.4%), from 590 ± 28 µm at baseline to 380 ± 28 µm at 1 month and 370 ± 3 µm at 3 months ($p < 0.001$); maintained throughout follow-up	For 7 eyes with repeat implant: BCVA improvement at 1 month after first implant 0.069 ± 0.179 logMAR; improvement after second implant 0.184 ± 0.171 logMAR (difference not significant). CRT reduced by 268 ± 76 µm at 1 month after first implant and by 291 ± 74 µm at 1 month after repeat implant (difference not significant). Median time to treatment failure (increase in CRT > 10% and ≥ 50 µm or need for repeat implant) was 6 months	NR

Study and design	Number of patients/eyes, follow-up and number of implants	BCVA	VH	CRT	Repeat implantations	Other
Zarranz-Ventura 2014[50] retrospective review of DEX 700 for non-infectious uveitis, multicentre, UK and Spain	• 63 patients, 82 eyes • Mean 15.4 months • 1: 43 eyes; 2: 24 eyes; ≥ 3: 15 eyes	Mean VA was 0.68 (SD 0.4) logMAR (Snellen 20/90) at baseline, improving to 0.59 (0.4) logMAR (20/78) after 2 weeks, 0.49 (0.4) logMAR (20/62) at 1 month, 0.49 (0.5) logMAR (20/62) at 3 months, 0.60 (0.5) logMAR (20/80) at 6 months and 0.52 (0.5) logMAR (20/66) at 12 months (all $p < 0.01$)	VH analysed in only 39 eyes with vitritis at baseline (VH ≥ +0.5). Probability of VH improvement (two-step improvement or change from +0.5 to 0) was 41% at 2 weeks, 63% at 1 month, 73% at 3 months, 79% at 6 months and 88% at 12 months. The median time to improvement in VH was 1 month (95% CI 0.6 to 1.3 months)	CRT analysed in only 59 eyes with CMO. Mean (SD) CRT at baseline was 469 (193) µm, improving to 326 (81) µm at 2 weeks, 267 (74) µm at 1 month, 318 (149) µm at 3 months, 366 (140) µm at 6 months and 355 (160) µm at 12 months (all $p < 0.01$)	Median time to second implant: 10 months (95% CI 6.3 to 13.6 months)	Concomitant systemic immunosuppressants or corticosteroids: probability of dose reduction (≥ 5 mg of steroids or any reduction in immunosuppressants) was 36% at 1 month, 42% at 3 months, 46% at 6 months and 62% at 12 months. Probability of steroid discontinuation: 8% at 1 and 3 months, 11% at 6 months and 36% at 12 months

CMO, cystoid macular oedema; CRT, central retinal thickness; IQR, interquartile range; MO, macular oedema; NR, not reported; SE, standard error; SEM, standard error of the mean; VA, visual acuity.

Appendix 6 Safety data from non-randomised studies of the dexamethasone implant

Study	Design	Number of patients/eyes	Follow-up	Number of implants	Increased IOP	Cataracts	Other AEs
Adán 2013[85]	Retrospective study of DEX 700 after vitrectomy for uveitic macular oedema, Spain	13 patients, 17 eyes	12 months	Single: 9 eyes; repeat: 8 eyes	• IOP 22–30 mmHg: 41% • IOP 30–40 mmHg: 1 (6%) • IOP > 40 mmHg: 0 • All treated with topical medication and normalised within 8 weeks • Surgery for IOP: 1 patient	• Cataract surgery for pre-existing cataract: 1 (6%)	• Hypotony (transient, resolved without treatment): 2 (12%) • Retinal detachment: 1 (6%), 5 months post implant • No cases of endophthalmitis or vitreous haemorrhage
Khurana 2015[86]	Retrospective review of DEX 700 for cystoid macular oedema secondary to non-infectious uveitis, single centre, USA	13 patients, 18 eyes	3 months	1: 8 eyes; 2–4: 10 eyes	• IOP ≥ 25 mmHg: 2 (11%) over 3 months • IOP ≥ 35 mmHg: 0 • All managed with topical medications • None required surgery	• Progression of pre-existing cataract: 1/10 phakic eyes	• No cases of retinal detachment, hypotony or migration of implant to AC • No SAEs
Lam 2015[81]	Retrospective chart review of DEX 700 for macular oedema, multicentre, Canada	101 patients, 120 eyes	1–6 months	Mean implants: 1.7	• Raised IOP in 2/20 (10%) • Of eyes with a history of steroid response, 37.5% had an IOP ≥ 25 mmHg and 12.5% had an IOP ≥ 35 mmHg • Topical IOP-lowering medications required for 62.5% of eyes with a history of steroid response	• Cataract: 1/11 (9%) phakic eyes • Cataract surgery: 5/11 (45%) phakic eyes	• Retinal detachment: 1/20 (5%) • Serious uveitis flare: 1/20 (5%)
Miserocchi 2012[79]	Retrospective study of DEX 700 for chronic posterior non-infectious uveitis, single centre, Italy	12 patients, 14 eyes	11 months	15 implants in 14 eyes	• Raised IOP in 3/14 eyes (21%) within 2 weeks, all transient, all controlled with topical IOP-lowering medication	• No cataracts or cataract surgery reported	• Subconjunctival haemorrhage: one case • Vitreous haemorrhage: one case in patient on anticoagulants

Study	Design	Number of patients/eyes	Follow-up	Number of implants	Increased IOP	Cataracts	Other AEs
Nobre-Cardoso 2016[83]	Retrospective review of DEX 700 for non-infectious uveitic macular oedema, single centre, France	31 patients, 41 eyes	12 months	1: 18 patients; 2: 10 patients; 3: 2 patients; 4: 1 patient	• IOP > 21 mmHg: 36% • IOP > 25 mmHg: 31% • IOP > 30 mmHg: 6.9% • All cases responded to topical IOP-lowering medication • Ocular hypertension: 15 eyes; 10 had a history of steroid response	• Cataract surgery: 3 eyes (all with repeat implants)	• Vitreous haemorrhage: one case, patient on antiplatelet medication
Palla 2015[80]	Retrospective review of DEX 700 for non-infectious uveitis, single centre, India	15 patients, 20 eyes	12 months	NR	• IOP > 21 mmHg in 3 eyes (15%) and IOP ≥ 25 mmHg in 2 eyes (10%) by week 6 • All manageable with medication	• Cataract surgery: 2 (10%) within 6 months, 5 (25%) within 1 year	• Pars planitis: 1 (5%)
Pelegrín 2015[51]	Retrospective review of DEX 700 for macular oedema secondary to non-infectious uveitis, single centre, Spain	32 patients, 42 eyes	NR	1: 23 eyes; 2: 12 eyes; 3: 5 eyes; 4: 2 eyes	• IOP > 21 mmHg: 20 (48%) – 8 non-vitrectomised eyes (36.4%) and 12 vitrectomised eyes (60%) • New hypotensive treatment required in 9 eyes	• Pre-existing cataracts progressed in 4/4; 3 required surgery	• Implant migration to AC: 2 (4.7%; one aphakic, one with iris claw intraocular lens) • Hypotony (transient, resolved without treatment): 3 (7.1%) • Vitreous haemorrhage: 3 (7.1%)
Pleyer 2014[82]	Prospective case series of single DEX 700 implants for non-infectious intermediate or posterior uveitis, two centres, Germany	84 patients, 84 eyes	6 months	NR	• IOP ≥ 25 mmHg: 13 (16%) • IOP ≥ 35 mmHg: 3 (4%) • IOP-lowering medication: 21% at baseline, 42% at 12 weeks, 28% at 24 weeks • Larger IOP increase in intermediate than in posterior uveitis ($p = 0.003$)	• Cataract: 7 phakic eyes • Pre-existing cataracts progressed in 2/3 • No surgery required	• Conjunctival haemorrhage in 'few patients' (*n* NR), cleared rapidly • No cases of endophthalmitis or uveitis flare-up

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Study	Design	Number of patients/eyes	Follow-up	Number of implants	Increased IOP	Cataracts	Other AEs
Tomkins-Netzer 2014[18]	Retrospective review of treatment and retreatment with DEX 700 in non-infectious uveitis, two centres, UK	27 patients, 38 eyes	24 months	1: 14 eyes; 2: 14 eyes; 3: 7 eyes; 4: 2 eyes; 6: 1 eye	• First implant: 3 eyes had IOP of > 21 mmHg within 2 months • Second implant: 4 eyes had IOP of > 25 mmHg within 2 months • Third implant: no eyes with increased IOP • Frequency of increased IOP: 0.13 per eye-year	• First implant: cataract in 1/21 phakic eyes • Second implant: no new cataracts • Third implant: one further cataract	Implant migration in 1 eye that had undergone cataract extraction
Tsang 2016[84]	Retrospective review of DEX 700 for uveitic macular oedema, Canada	15 patients, 25 eyes	12 months	Single: 18 eyes; repeat: 7 eyes	• No patients had IOP > 21 mmHg or an increase of > 10 mmHg (patients with IOP of > 21 mmHg were excluded)	• No new cataracts • Pre-existing cataracts progressed in 2/15	• Implant injected into lens in 1 eye • Macular hole: 1 • Epiretinal membrane: 3 • No cases of endophthalmitis or retinal detachment
Zarranz-Ventura 2014[50]	Retrospective review of DEX 700 for non-infectious uveitis, multicentre, UK and Spain	63 patients, 82 eyes	12 months	1: 43 eyes; 2: 24 eyes; ≥ 3: 15 eyes	• IOP ≥ 21 mmHg in 33/82 eyes (40.2%) • IOP ≥ 35 mmHg in 7% at months 1 and 3 • IOP-lowering medication required in 32 eyes (39%)	• Cataract surgery in 4/40 (10%) phakic eyes during follow-up	• Implant migration to AC: 2/142 implant injections (1.4%), 1 aphakic eye, 1 pseudophakic eye • Vitreous haemorrhage: 3 (2.1%) • Hypotony: 3 (2.1%) • Endophthalmitis: 1 (0.7%)

NR, not reported.

Appendix 7 Breakdown of the cost-effectiveness analysis results for the base case

TABLE 66 Breakdown of the results of the base-case analysis for DEX vs. limited clinical practice: deterministic model

Outcome	Sham	DEX	Increment
Life-years			
On treatment	18.669	18.703	0.034
Blind	1.859	1.826	–0.034
Total	20.529	20.529	0.000
QALYs			
On treatment	13.904	13.946	0.042
Blind	0.709	0.696	–0.013
Total	14.613	14.641	0.029
Costs (£)			
Drugs	2449.61	3324.03	874.42
Administration and monitoring	17,452.41	17,597.44	145.04
AEs	5186.39	5255.04	68.64
Rescue therapy	285.26	35.25	–250.01
Blindness	14,281.54	14,023.09	–258.46
Total	39,655.21	40,234.85	579.64
ICER (£/QALY)			20,057.73

TABLE 67 Breakdown of the results of the base-case analysis for ADA vs. limited clinical practice in patients with active uveitis: deterministic model

Outcome	Placebo	ADA	Increment
Life-years			
On treatment	0.620	2.081	1.460
Failed treatment	17.565	16.323	–1.242
Remission	0.000	0.000	0.000
Blind	2.343	2.125	–0.218
Total	20.529	20.529	0.000
QALYs			
On treatment	0.524	1.799	1.274
Failed treatment	13.603	12.595	–1.008
Remission	0.000	0.000	0.000
Blind	0.792	0.716	–0.076
Total	14.919	15.110	0.191

continued

TABLE 67 Breakdown of the results of the base-case analysis for ADA vs. limited clinical practice in patients with active uveitis: deterministic model (*continued*)

Outcome	Placebo	ADA	Increment
Costs (£)			
Drugs	2813.59	21,961.73	19,148.14
Administration and monitoring	18,352.07	18,811.80	459.73
AEs	8037.18	8338.60	301.43
Blindness	17,983.53	16,289.21	–1694.32
Total	47,186.36	65,401.34	18,214.98
ICER (£/QALY)			95,505.74

TABLE 68 Breakdown of the results of the base-case analysis for ADA vs. limited clinical practice in patients with inactive uveitis: deterministic model

Outcome	Placebo	ADA	Increment
Life-years			
On treatment	2.937	4.223	1.286
Failed treatment	15.137	14.104	–1.034
Remission	0.000	0.000	0.000
Blind	2.454	2.202	–0.252
Total	20.529	20.529	0.000
QALYs			
On treatment	2.458	3.519	1.061
Failed treatment	11.957	11.100	–0.856
Remission	0.000	0.000	0.000
Blind	0.830	0.742	–0.088
Total	15.244	15.361	0.116
Costs (£)			
Drugs	4990.76	43,855.57	38,864.81
Administration and monitoring	19,944.05	20,708.76	764.71
AEs	4345.10	4002.68	–342.42
Blindness	18,830.87	16,894.93	–1935.94
Total	48,110.78	85,461.94	37,351.16
ICER (£/QALY)			321,405.45

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