Technology Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Clinical Excellence

Draft protocol 15/64/07 2016

1. Title of the project:

Adalimumab and dexamethasone for treating non-infectious uveitis

2. Name of TAR team and 'lead'

TAR team

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3. Plain English Summary

Uveitis is an inflammation of the uveal tract of the eye, which consists of the iris, the ciliary body and the choroid. It is usually caused by an underlying autoimmune disorder or trauma to the eye. In some people the cause is unknown. Uveitis is classified according to the main location of inflammation. Anterior uveitis is inflammation of the iris. 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 and the choroid. Panuveitis is inflammation of the whole of the uveal tract (front and back of the eye). Symptoms include pain and redness in the eye, blurred vision, sensitivity to light, loss of peripheral vision and headaches. One or both eyes may be affected.

Intermediate, posterior and panuveitis are less common than anterior uveitis (they account for around 1 in 4 uveitis diagnoses[1] but are more severe and more likely to cause vision loss. Consequences of uveitis include glaucoma (increased pressure inside the eye), cataracts (cloudiness of the lens) and cystoid macular oedema (swelling of the retina). Between 1500 and 5000 people are diagnosed with non-infectious intermediate or posterior uveitis each year in England.[2,3] There are no data on the incidence of panuveitis in England.

Non-infectious intermediate, posterior and panuveitis are initially treated with corticosteroids. Corticosteroids may be administered systemically (oral or parenteral), through periocular or intravitreal injections, or using intravitreal implants. Additionally, if the front of the eye is also affected, topical corticosteroids and dilating eye drops may be offered. People with severe or chronic non-infectious uveitis, whose disease has not adequately responded to corticosteroid treatment, or for whom corticosteroids are not appropriate, may also be given immunosuppressive drugs such as methotrexate, ciclosporin, mycophenolate mofetil and azathioprine (either systemically or with an intravitreal injection). Systemic corticosteroids carry significant morbidity (glaucoma, weight gain, raised blood pressure, diabetes, osteoporosis) and long-term use above 7.5mg per day is not recommended.[4,5] Immunosuppressive drugs can allow a reduction in the corticosteroid dose and associated complications. Immunosuppressive drugs may also be given when corticosteroids are contraindicated or not tolerated. If the disease does not respond to these treatments or if they are not tolerated, biological tumour necrosis factor (TNF)-alpha inhibitors may be used.

4. Decision problem

4.1 Purpose of the decision to be made

This review will assess the clinical and cost-effectiveness of adalimumab subcutaneous injection and dexamethasone intravitreal implant within their marketing authorisations for treating non-infectious, intermediate, posterior or pan uveitis.

4.2 Clear definition of interventions

Adalimumab (Humira, AbbVie) is a monoclonal antibody that inhibits the pro-inflammatory cytokine, TNF-alpha. Adalimumab does not currently have a marketing authorisation in the UK for treating uveitis, but EU regulatory submissions are expected this year. It has been compared with placebo in clinical trials in adults with active, non-infectious intermediate, posterior, or panuveitis despite conventional therapy (that is, corticosteroids with or without immunosuppressives). Adalimumab is administered as a subcutaneous injection containing 20 mg or 40 mg preparation of the active drug.

Dexamethasone intravitreal implant (Ozurdex, Actavis UK and Allergan) is a corticosteroid which suppresses inflammation by inhibiting the expression of pro-inflammatory mediators. Dexamethasone has a marketing authorisation in the UK for treating inflammation of the posterior segment of the eye presenting as non-infectious uveitis. Dexamethasone intravitreal implant is a biodegradable ophthalmic implant which contains 0.7 mg of the active drug. Each

implant is intravitreally administered using a single-use solid polymer drug delivery system or applicator.[6]

4.3 Place of the intervention in the treatment pathway(s)

Non-infectious intermediate, posterior and panuveitis are initially treated with corticosteroids. Corticosteroids may be administered systemically (oral or parenteral), through periocular or intravitreal injections, or using intravitreal implants. Additionally, if the front of the eye is also affected, topical corticosteroids and dilating eye drops may be offered. People with severe or chronic non-infectious uveitis, whose disease has not adequately responded to corticosteroid treatment, or for whom corticosteroids are not appropriate, may also be given immunosuppressive drugs such as methotrexate, ciclosporin, mycophenolate mofetil and azathioprine (either systemically or with an intravitreal injection). Immunosuppressive drugs can allow a reduction in the corticosteroid dose and associated complications. Immunosuppressive drugs may also be given when corticosteroids are contraindicated or not tolerated. If the disease does not respond to these treatments or if they are not tolerated, biological tumour necrosis factor (TNF)-alpha inhibitors may be used.

Intravitreal treatments such as dexamethasone implant are appropriate when a local treatment is required; for example, when disease affects only one eye, or to treat a temporary flare-up in one or both eyes. Systemic treatments such as adalimumab are most likely to be appropriate to treat uveitis affecting both eyes, particularly where it is associated with underlying autoimmune or inflammatory disease.

4.4 Relevant comparators

The interventions set out in Section 4.2 will be compared as appropriate with:

- 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).

Combinations of the above treatments may also be considered as comparators where appropriate and where evidence allows. Comparison with a sham procedure in combination with the above comparators may also be considered.

4.5 Population and relevant sub-groups

Population: People with non-infectious, intermediate, posterior or pan uveitis.

Subgroups: If appropriate, and where evidence allows, subgroups will be considered according to:

- Intermediate, posterior or pan uveitis
- Unilateral or bilateral uveitis
- Presence or absence of underlying autoimmune or inflammatory disease
- Existing treatment with long term systemic immunosuppressants
- Baseline visual acuity
- Patients for whom systemic or local corticosteroid treatments were not appropriate.

4.6 Key factors to be addressed

The review will aim to:

1) Evaluate the clinical effectiveness and safety of adalimumab subcutaneous injection and dexamethasone intravitreal implant within their marketing authorisations for treating non-infectious, intermediate, posterior or pan uveitis.
2) Estimate the incremental cost effectiveness of adalimumab subcutaneous injection and dexamethasone intravitreal implant within their marketing authorisations for treating non-infectious, intermediate, posterior or pan uveitis, compared with each other and current treatment.
3) Identify key areas for primary research.
4) Estimate the possible overall cost in England.

4.7 Factors that are outside the scope of the appraisal

Evaluation of dosages of Dexamethasone implant outside its licenced indication for the treatment of non-infectious posterior segment uveitis and panuveitis will not be considered in this review, e.g. 0.35 mg (Ozurdex, Actavis UK and Allergan), 0.60 mg Surodex Drug Delivery System (Oculex Pharmaceuticals, Inc., Sunnyvale, CA).

Uveitis in children will not be considered within this appraisal.

5. Methods for the synthesis of evidence of clinical effectiveness

A systematic review of the evidence for clinical effectiveness will be undertaken following the general principles outlined in 'Systematic Reviews: CRD's guidance for undertaking reviews in health care' and the principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[7]

5.1. Search strategy

5.1.1 Search scope

The scope of the search for clinical effectiveness evidence will take into account the following requirements:

- The need to take into consideration the sequencing of treatment
- The potential need to make indirect comparisons, including, if possible a network meta-analysis

Potentially relevant studies will be identified by:

- Searching of electronic databases
- Contact with experts in the field
- Examination of bibliographies of any relevant primary studies and systematic reviews.
- Sponsor submissions related to interventions within the scope of this review

A comprehensive literature search will be undertaken to systematically identify randomised controlled studies (RCTs) and systematic reviews (for the identification of additional trials) of clinical effectiveness of dexamethasone (intravitreal implant) and adalimumab (subcutaneous injection) in patients with active non-infectious intermediate uveitis, posterior uveitis and/or panuveitis. Additional searches for further evidence on comparators may be conducted if required.

5.1.2 Electronic searches

The following electronic databases will be searched from inception: Medline (Ovid); Medline in Process; CINAHL; EMBASE; the Cochrane Library including the Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register (CENTRAL), DARE, and HTA databases; Web of Science (Science Citation Index (SCI) and Conference Proceedings Citation Index (CPCI).

To identify on-going or recently completed studies, trial registers will be searched using the World Health Organisation's International Clinical Trials Registry Portal (WHO ICTRP) which regularly compiles and updates data from more than 15 clinical trial registers.[8] Relevant professional and research organisations will be contacted for relevant studies. Citation searches of key included studies will be undertaken using the Web of Science database. In addition TOXLINE will be searched for evidence on safety and adverse events.

5.1.2 Search strategy

Searches will not be limited by language or publication date. Search terms will include Medical Subject Heading (MesH) terms and free text synonyms for 'uveitis', 'dexamethasone' and 'adalimumab'. The proposed draft of the MEDLINE search strategy is presented in Appendix 1. Search filters designed to retrieve clinical trials, systematic reviews and economic evaluations will be used on MEDLINE and other databases, where appropriate. The search will be adapted for other databases. Subsequent searches for observational studies will be undertaken if required, in the event that identified RCTs do not provide sufficient evidence for long-term outcomes such as adverse events.

5.1.3 Supplementary searches

To identify additional studies, examination of reference lists of relevant studies, systematic reviews and clinical guidelines will be undertaken. In addition to reviewing sponsors' submissions related to interventions within the scope of this review, experts in the field will also be contacted.

5.1.4 Data management

A comprehensive database of relevant published and unpublished articles will be constructed using *EndNote* software.

5.2 Inclusion and exclusion criteria

5.2.1 Inclusion criteria

Inclusion criteria are based on the scope provided by NICE, outlined below:

5.2.1.1 Populations

Studies reporting on participants with non-infectious, intermediate, posterior or pan uveitis, aged 18 years or more. Studies with populations broader than non-infectious posterior segment uveitis and pan-uveitis will only be considered if data for the relevant study population (those with uveitis) is available. Studies including patients under 18 years will be included if data for adult patients is reported separately or if at least 80% of patients are aged 18 years or older.

5.2.1.2 Interventions

- Adalimumab subcutaneous injection
- Dexamethasone intravitreal implant

5.2.1.3 Comparators

Interventions compared with each other or compared with the following:

- 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).

Combinations of the above treatments may also be considered as comparators where appropriate and where evidence allows. Comparison with a sham procedure in combination with the above comparators may also be considered.

5.2.1.4 Outcomes

The following outcomes, if ascertained objectively, will be considered. Choice of outcomes will be finalised based on availability of outcomes in relevant trials and clinical advice on relevance.

- visual acuity (the affected eye)
- visual acuity (both eyes)

    - measured as mean difference in best corrected visual acuity (BCVA) according to a validated measure such as the Early Treatment Diabetic Retinopathy Study (ETDRS) chart, Snellen chart or a similar tool.
    - other measures of visual acuity will be considered if outcomes can be justified and validated in relation to accepted relevant standard measures
- improvement in disease activity (e.g. vitreous haze score)
- uveitis-related tissue damage or complication (e.g. cataract, macular oedema, retinal vascular occlusion)
- reduction in systemic steroid use
- mortality
- adverse effects of treatment
- health-related quality of life.
    - including generic measures and functional measures such as the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25)
- A combined endpoint which includes BCVA and NEI VFQ-25.

Where data are available, outcomes will be reported and presented for different time-frames: short-term, medium-term and long-term.

5.2.1.5 Study design

Randomised controlled trials (RCTs) will be included in the clinical effectiveness systematic review. If no relevant RCTs are identified for an intervention, non-randomised comparative studies may be considered for inclusion. Non-randomised comparative studies may also be included, where necessary, as a source of additional evidence (e.g., regarding adverse events) related with the interventions.

5.2.2 Exclusion criteria

Studies conducted in paediatric populations will be excluded. Pre-clinical or biologic studies as well as studies of animal models will be excluded. The following publication types will not be considered for inclusion: narrative reviews, systematic reviews, clinical guidelines, editorials, letters, opinion pieces, abstracts with insufficient details to assess study quality or results, as well as non-English articles. Study selection will be presented in a PRISMA flow diagram. A list of all excluded full-text articles, with reasons for exclusion, will be provided in an appendix to the submitted report.

5.2.3 Study selection

Study selection will be conducted in two stages according to the specified inclusion and exclusion criteria in Sections 5.2.1 and 5.2.2. Retrieved records will be assessed for relevance by examination of title/abstract first, followed by a detailed examination of the full text version, excluding at each step studies which do not satisfy the eligibility criteria. All records will be selected by one reviewer followed by a 10% check of selected studies by a second reviewer. Disagreements will be resolved by discussion, and involvement of a third researcher if needed.

5.3 Data extraction strategy

Data will be extracted by one reviewer using a standardised piloted data extraction form, and checked by a second reviewer. Disagreements will be resolved by discussion. Data will be extracted with no blinding to authors or journal. A draft data extraction form is presented in Appendix 2. Data abstracted will include information relating to the author and publication year of study, study population, interventions, comparators and outcomes. Where multiple publications of the same study are identified, data will be extracted and reported as a single study.

5.4 Quality assessment strategy

The methodological quality of each included study will be assessed by one reviewer and checked by a second reviewer, using the Cochrane Risk of Bias tool or (adapted) criteria based on those proposed by the NHS Centre for Reviews and Dissemination for randomised controlled trials (RCTs).

5.5. Methods of analysis/synthesis

Characteristics of included RCTs including population characteristics, intervention details, comparator details and outcomes will be tabulated and discussed in a narrative review.

Where appropriate (i.e. depending on the number of studies that report data on specific outcome measures), RCTs that meet the inclusion criteria for the target patient population for the decision may be subjected to evidence synthesis. Primary outcome measures of interest, including those used to inform the economic model, will be analysed using random effects models to account for heterogeneity between RCTs in estimates of treatment effect arising from differences in study protocol. Other outcome measures will either be analysed using random effects models or fixed effect models when there is interest in estimating the treatment effect conditional on the studies satisfying the inclusion criteria for the target

patient population. For outcome measures about which there is interest in simultaneously comparing all treatments, and where data allow, a network meta-analysis (NMA) will be undertaken. Where possible, explanations for heterogeneity between RCTs in treatment effects will be explored using meta-regression, including factors such as clinical presentation of uveitis, prior treatment(s) and underlying conditions.

Random effects models will be implemented using a Bayesian framework using the freely available software packages WinBUGS and R. Results will be summarised using point estimates and 95% credible intervals (CrIs) of the effect of each treatment relative to the reference treatment. Other summary measures may also be presented such as 95% CrIs for all pairwise comparisons and probabilities of treatment rankings. Evidence required to inform parameters in the economic model will be generated by taking draws from the posterior predictive distribution of a new study. Absolute goodness-of fit will be assessed using residual deviance. Where possible, consistency between direct and indirect estimates of treatment effect in NMAs will be assessed using the node splitting approach.

5.6 Methods for estimating quality of life

Health-related quality of life (HRQoL) data reported by studies included in the clinical effectiveness systematic review will be extracted. In the absence of such evidence, the mathematical model may use evidence on HRQoL drawn from alternative sources.

6. Methods for synthesising evidence of cost-effectiveness

6.1 Identifying and systematically reviewing published cost-effectiveness studies

Studies relating to the cost-effectiveness of interventions for treating non-infectious intermediate, posterior, or panuveitis will be identified using an economic search filter which will be integrated into the search strategy detailed in Section 5.1; this economic search filter is presented in Appendix 1. The inclusion criterion is any economic evaluation which meets the inclusion criteria outlined in Section 5.2 with regards to the population, intervention and comparator. Included studies will be synthesised within a qualitative analysis. The quality of economic literature will be assessed using a combination of key components of the British Medical Journal checklist for economic evaluations[9] together with the Eddy checklist on mathematical models[8] (see Appendix 3).

6.2 Development of a *de novo* economic model

It is expected that a de novo mathematical model may need to be developed to estimate the incremental cost-effectiveness associated with adalimumab subcutaneous injection and dexamethasone intravitreal implant for treating non-infectious intermediate, posterior, or

panuveitis compared with current practice (see Section 4.4). The exact comparisons undertaken will depend upon the intended usage of these interventions since the interventions being assessed may be used within different patient groups (underlying systemic disease versus unilateral uveitis). The model structure will be determined in consultation with clinical experts. It will use efficacy data from the key RCTs identified through the systematic searches. Cost data for the economic model will be extracted from a variety of published sources. Costs will include the direct costs of the interventions and their administration, as well as costs of adverse events. Direct savings due to the avoidance of the consequences of uveitis, including glaucoma (increased pressure inside the eye), cataracts (cloudiness of the lens) and cystoid macular oedema (swelling of the retina), will be incorporated.

The final outcome measures estimated within the model will depend on the available evidence, but are likely to include cost per life year gained (LYG) and cost per quality-adjusted life year (QALY) gained. It is hoped that suitable quality of life data will be identified from the effectiveness evidence. In the absence of this, the model may use indirect evidence on quality of life from alternative sources. Quality of life data on the effect of AEs related to treatment and the consequences of uveitis (including glaucoma, cataracts and cystoid macular oedema) will be extracted from the key RCTs and a variety of published sources. Searches for additional information regarding model parameters, patient preferences and other topics not covered within the clinical effectiveness and cost-effectiveness reviews will be informed by NICE DSU Guidance.[10]

The time horizon of our analysis will be a patient's lifetime in order to reflect the chronic nature of the disease. The perspective will be that of the National Health Services and Personal Social Services. Both costs and QALYs will be discounted at 3.5%. Univariate sensitivity analysis and probabilistic sensitivity analysis (PSA) will be undertaken to assess the impact of uncertain parameters upon the model results. Results of the PSA will be shown graphically within cost-effectiveness acceptability curves. Expected value of perfect information (EVPI) will also be estimated. If resources allow, expected value of partial perfect information (EVPPI) may also be considered.

7. Handling the company submission(s)

The TAR team will be happy to consider any evidence submitted by the manufacturers/ sponsors if received by 31st August 2016. It may not be possible to consider data arriving after this date. If the data meet the inclusion criteria for the review they will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any economic evaluation included in the company submission, provided it complies with NICE's advice on

presentation, will be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used. If the TAR team judge that the existing economic evidence is not robust, then further work will be undertaken, either by adapting what already exists or developing de-novo modelling.

Any ‘commercial in confidence’ data taken from a company submission will be underlined and highlighted in turquoise in the assessment report (followed by an indication of the relevant company name, e.g. in brackets). Any academic in confidence data will be underlined and highlighted in yellow.

8. Competing interests of authors

None

9. Appendices

Appendix 1: Search strategy

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present> Search Strategy:
Terms for Uveitis
1 exp Uveitis/ (27152)
2 uveitis/ or panuveitis/ or ophthalmia, sympathetic/ or behcet syndrome/ or iridocyclitis/ or iritis/ or uveitis, posterior/ or choroiditis/ or chorioretinitis/ or pars planitis/ or uveitis, intermediate/ or panophthalmitis/ or uveomeningoencephalitic syndrome/ (24745)
3 panuveitis.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (1090)
4 uveiti*.ti,ab. (14510)
5 Retinochoroidopathy.mp. (120)
6 chorioretinopathy.mp. (1704)
7 iridocyclitis.mp. or Iridocyclitis/ (1571)
8 (uveitic macular oedema or uveitic macular edema or UMO or UME).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (326)
9 (retinochorioditis or chorioditis or retinitis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (14647)
10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (46477)
Terms for interventions
11 exp Dexamethasone/ or dexamethasone.mp. (62092)
12 (Decadron or Dexasone or Diodex or Hexadrol or Maxidex).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (170)
13 11 or 12 (62139)
14 adalimumab.mp. or Adalimumab/ (4996)
15 humira.mp. (145)
16 14 or 15 (5014)
17 13 or 16 (67148)
Uveitis & interventions
18 10 and 17 (720)
RCT filter
19 Randomized Controlled Trials as Topic/ (103348)
20 randomized controlled trial/ (415888)
21 Random Allocation/ (86724)
22 Double Blind Method/ (135325)
23 Single Blind Method/ (21817)
24 clinical trial/ (499924)
25 clinical trial, phase i.pt. (16087)
26 clinical trial, phase ii.pt. (25985)

27	clinical trial, phase iii.pt. (11120)
28	clinical trial, phase iv.pt. (1166)
29	controlled clinical trial.pt. (90678)
30	randomized controlled trial.pt. (415888)
31	multicenter study.pt. (201093)
32	clinical trial.pt. (499924)
33	exp Clinical Trials as topic/ (292178)
34	or/19-33 (1125467)
35	(clinical adj trial$).tw. (255731)
36	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw. (141491)
37	PLACEBOS/ (33268)
38	placebo$.tw. (175246)
39	randomly allocated.tw. (20177)
40	(allocated adj2 random$).tw. (22949)
41	or/35-40 (479120)
42	34 or 41 (1304012)
43	case report.tw. (233685)
44	letter/ (914603)
45	historical article/ (330361)
46	or/43-45 (1465750)
47	42 not 46 (1272741)
	Filter to identify systematic reviews
48	Meta-Analysis as Topic/ (14861)
49	meta analy$.tw. (89748)
50	metaanaly$.tw. (1603)
51	Meta-Analysis/ (65435)
52	(systematic adj (review$1 or overview$1)).tw. (79718)
53	exp Review Literature as Topic/ (8597)
54	or/48-53 (167068)
55	cochrane.ab. (42890)
56	embase.ab. (43575)
57	(psychlit or psyclit).ab. (886)
58	(psychinfo or psycinfo).ab. (11633)
59	(cinahl or cinhal).ab. (14392)
60	science citation index.ab. (2371)
61	bids.ab. (387)
62	cancerlit.ab. (603)
63	or/55-62 (69298)
64	reference list$.ab. (12234)
65	bibliograph$.ab. (13380)
66	hand-search$.ab. (4839)
67	relevant journals.ab. (883)
68	manual search$.ab. (2955)
69	or/64-68 (30720)
70	selection criteria.ab. (23107)
71	data extraction.ab. (12391)

72	70 or 71 (33658)
73	Review/ (2109777)
74	72 and 73 (22525)
75	Comment/ (663052)
76	Letter/ (914603)
77	Editorial/ (401729)
78	animal/ (5856173)
79	human/ (15919769)
80	78 not (78 and 79) (4206952)
81	or/75-77,80 (5628140)
82	54 or 63 or 69 or 74 (200701)
83	82 not 81 (189113)
	Economic studies filter
84	Economics/ (26705)
85	"costs and cost analysis"/ (44050)
86	Cost-benefit analysis/ (65817)
87	Cost control/ (20846)
88	Cost savings/ (9746)
89	Cost of illness/ (20459)
90	Cost sharing/ (2108)
91	"deductibles and coinsurance"/ (1521)
92	Medical savings accounts/ (497)
93	Health care costs/ (30742)
94	Direct service costs/ (1090)
95	Drug costs/ (13252)
96	Employer health costs/ (1077)
97	Hospital costs/ (8792)
98	Health expenditures/ (15261)
99	Capital expenditures/ (1971)
100	Value of life/ (5493)
101	exp economics, hospital/ (21402)
102	exp economics, medical/ (13859)
103	Economics, nursing/ (3937)
104	Economics, pharmaceutical/ (2617)
105	exp "fees and charges"/ (28170)
106	exp budgets/ (12813)
107	(low adj cost).mp. (32793)
108	(high adj cost).mp. (9666)
109	(health?care adj cost$).mp. (6214)
110	(fiscal or funding or financial or finance).tw. (99631)
111	(cost adj estimate$).mp. (1681)
112	(cost adj variable).mp. (37)
113	(unit adj cost$).mp. (1835)
114	(economic$ or pharmacoeconomic$ or price$ or pricing).tw. (208528)
115	or/84-114 (540923)

Uveitis + interventions + RCTs:	
116	18 and 47 (119)
Uveitis + interventions + reviews	
117	18 and 83 (17)
Uveitis + interventions + economic studies	
118	18 and 115 (9)

Appendix 2. Draft data extraction form

Date	
Name of reviewer:	
Study ID	Author/ year
Study ID of multiple reports (if any):	
Study characteristics:	Study design
	Trial name (if any)
	Setting
	Length of follow-up
	Funding
Study population:	Sample size
	Selection/Eligibility criteria
	Participants' characteristics (mean age/ gender/ underlying condition(s), previous treatment, concomitant treatment, baseline best corrected visual acuity)
	Type of uveitis (intermediate, posterior, pan-uveitis)
Interventions and comparators:	Pharmacologic agent (dose, route of administration, treatment schedule) according to number of participants in each treatment group
Outcomes (for intervention and comparator groups):	Reported outcomes, method and time of assessment, according to number of participants in each treatment group

Appendix 3: Critical appraisal checklist for economic evaluations using key components of the British Medical Journal checklist for economic evaluations[9] together with the Eddy checklist on mathematical models employed in technology assessments.[8]

Reference ID		
Title		
Authors		
Year		
Modelling assessments should include:		Yes/No
1	A statement of the problem.	
2	A discussion of the need for modelling vs. alternative methodologies.	
3	A description of the relevant factors and outcomes.	
4	A description of the model including reasons for this type of model and a specification of the scope including; time frame, perspective, comparators and setting. *Note: n=number of health states within sub-model*	
5	A description of data sources (including subjective estimates), with a description of the strengths and weaknesses of each source, with reference to a specific classification or hierarchy of evidence.	
6	A list of assumptions pertaining to: the structure of the model (e.g. factors included, relationships, and distributions) and the data.	
7	A list of parameter values that will be used for a base case analysis, and a list of the ranges in those values that represent appropriate confidence limits and that will be used in a sensitivity analysis.	
8	The results derived from applying the model for the base case.	
9	The results of the sensitivity analyses; unidimensional; best/worst case; multidimensional (Monte Carlo/parametric); threshold.	
10	A discussion of how the modelling assumptions might affect the results, indicating both the direction of the bias	

	and the approximate magnitude of the effect.	
11	A description of the validation undertaken including; concurrence of experts; internal consistency; external consistency; predictive validity.	
12	A description of the settings to which the results of the analysis can be applied and a list of factors that could limit the applicability of the results.	
13	A description of research in progress that could yield new data that could alter the results of the analysis.	

Appendix 4. Timetable/milestones

Milestone	**Date**
Draft protocol	28/01/16
Final protocol	19/05/16
Progress report	16/09/16
Draft assessment report	02/11/16
Final Assessment report	30/11/16

10. References

1. NHS Choices: Uveitis - overview. http://www.nhs.uk/Conditions/Uveitis/Pages/Introduction.aspx, 2015.

2. *North East Treatment Advisory Group. Ozurdex dexamethasone ocular implant for uveitis*2012.

3. *Committee for Orphan Medicinal Products. Public summary of opinion on orphan designation: Dexamethasone (intrvitrael implant) for the treatment of non-infectious uveitis affecting the posterior segment of the eye*2010.

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