
Article:
Bermejo, I. orcid.org/0000-0001-9105-8088, Squires, H. orcid.org/0000-0002-2776-4014, Poku, E.N. et al. (7 more authors) (2019) Adalimumab for non-infectious uveitis: is it cost-effective? British Journal of Ophthalmology. ISSN 0007-1161

https://doi.org/10.1136/bjophthalmol-2018-312756

SYNOPSIS

Adalimumab is clinically effective for treating non-infectious posterior segment uveitis. Its cost-effectiveness is uncertain due to scarcity of evidence but appears to be more cost-effective in patients with active uveitis at high risk of blindness.

ABSTRACT

Background/Aims

Uveitis is inflammation inside the eye. Our objective was to assess the cost-effectiveness of adalimumab compared with current practice (immunosuppressants and systemic corticosteroids) in patients with non-infectious intermediate, posterior or panuveitis and to identify areas for future research.

Methods

A Markov model was built to estimate costs and benefits of the interventions. Systematic reviews were performed to identify the available relevant clinical and cost-effectiveness evidence. Data collected in two key randomised controlled trials (VISUAL I and VISUAL II) were used to estimate the interventions' effectiveness compared with the trials' comparator arms (placebo plus limited current practice (LCP)). The analysis was performed from the National Health Service (NHS) and Personal Social Services perspective. Costs were calculated based on standard UK sources.

Results

The estimated incremental cost-effectiveness ratios (ICERs) of adalimumab versus LCP for the base case are £92,600 and £318,075 per quality-adjusted life year (QALY) gained for active and inactive uveitis respectively. In sensitivity analyses, the ICER varied from £15,579 to £120,653 and £35,642 to £800,775 per QALY for active and inactive uveitis.

Conclusion

The estimated ICERs of adalimumab versus LCP are above generally accepted thresholds for cost-effectiveness in the UK. Adalimumab may be more cost-effective in patients with active uveitis at greater risk of blindness. However, there is an unmet need for additional primary data to provide more reliable estimates in several important areas, including: effectiveness of adalimumab versus current practice (instead of LCP); incidence of long term blindness; adalimumab effectiveness in avoiding blindness; and, rates and time to remission whilst on adalimumab.

Keywords

Drugs, inflammation, public health

INTRODUCTION

Uveitis describes a group of conditions characterised by inflammation inside the eye whose underlying cause may be broadly divided into infectious and non-infectious. In developed countries the cause is most commonly non-infectious, and appears to be autoimmune in origin, either idiopathic or associated with a systemic autoimmune disorder. The blindness causing forms of non-infectious uveitis are those that affect the posterior structures of the eye, namely intermediate uveitis, posterior uveitis and panuveitis. Consequences of uveitis, which may lead to vision loss, include early complications such as cystoid macular oedema and vitreous haze, and late complications such as cataracts, glaucoma, and irreversible damage to the retina. It has been estimated that uveitis accounts for 10% to 15% of all cases of total blindness in the United States, [1] and between three and ten out of 100,000 people in the European Union are estimated to have non-infectious posterior segment uveitis.[2]

Treatment for non-infectious uveitis depends upon whether systemic disease exists (and if so, whether it is controlled), and whether the inflammation affects one or both eyes. Initially, it is usually treated administering corticosteroids, systemically or locally via periocular or intravitreal injections or intravitreal implants. Systemic corticosteroids carry significant morbidity (e.g. cataract, glaucoma, diabetes, and osteoporosis) and long-term use is not recommended. Therefore, people with severe or chronic non-infectious uveitis, whose disease has not adequately responded to corticosteroids, 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, and cyclosporine) as second line treatment. Immunosuppressive drugs can allow a reduction in the corticosteroid dose and associated complications. If the disease is still active or if these treatments are not tolerated, especially in patients at high risk of losing their vision or those with systemic disease related to uveitis, biologics such as adalimumab (Humira®) may be used. However, healthcare providers need to know whether these treatments are cost-effective compared with usual care to inform recommendations about their use in practice. The objective of our study is to assess the cost-effectiveness of adalimumab compared with current practice (immunosuppressants and systemic corticosteroids) in patients with non-infectious intermediate, posterior or panuveitis and to identify areas for future research.

METHODS

Systematic reviews (described elsewhere [3]) were undertaken to assess the clinical effectiveness and safety of adalimumab and to identify the evidence relevant to our economic evaluation. Two randomised controlled trials were identified in the clinical effectiveness review that reported outcomes for adalimumab in the target population: VISUAL I [4] and VISUAL II,[5] which recruited patients with active and inactive non-infectious uveitis, respectively (see Table 1 for a summary of these trials'

characteristics). These trials provided most of the outcomes used in the model. The use of a network meta-analysis (NMA) was explored to compare the effectiveness of treatments. Unfortunately, it was considered infeasible and inappropriate to conduct an NMA because the systematic review did not identify any sources of evidence for the target population that reported comparable effectiveness measures that formed a connected network of evidence.

Table 1: Summary of study characteristics of VISUAL I and VISUAL II

	VISUAL I [4]	**VISUAL II [5]**
Population (n)	223	229
Age (mean)	42.7 years	42.5 years
% of females	57%	62%
Type of uveitis	Active	Inactive
% of bilateral	91%	96%
Intervention	Adalimumab (40 mg dose every other week)	Adalimumab (40 mg dose every other week)
Comparator	Placebo	Placebo
Concomitant treatments (% of patients)	Oral prednisone 60 mg/d tapered to 0 mg by week 15 (100%) Immunosuppresant (32%*)	Oral prednisone 10 to 35mg/d tapered to 0 mg by week 19 or earlier (100%) Immunosuppresant (47%*)
Primary outcome	Time to treatment failure	Time to treatment failure
Secondary outcomes	BCVA, change in VH or AC grade, % change in CRT, time to MO, change in VFQ-25, adverse events	BCVA, change in VH or AC grade, % change in CRT, time to MO, change in VFQ-25, adverse events

*Balanced across both arms. AC, anterior chamber; BCVA: best-corrected visual acuity; CRT, central retinal thickness; MO, macular oedema; VFQ, Visual Functioning Questionnaire; VH, vitreous haze

Model design

To estimate and analyse the cost effectiveness of adalimumab for non-infectious uveitis, compared with current practice, we built a Markov model. The model simulates a cohort of patients, which is followed over a lifetime. The analysis is performed from a National Health Service (NHS) and Personal Social Services (PSS) perspective. Costs and quality-adjusted life years (QALYs) are discounted at a rate of 3.5% per year. The modelled population consists of people with active or inactive non-infectious intermediate, posterior or pan uveitis, with more than 90% having bilateral uveitis. A corticosteroid burst was given to all patients at the start of VISUAL I whilst patients in VISUAL II were already receiving high-dose corticosteroids at randomisation. Corticosteroids were tapered to zero by week 15 in VISUAL I and week 19 in VISUAL II. Given the evidence available, the intervention considered in the analysis is a subcutaneous injection of 40mg of adalimumab every two weeks plus an initial oral corticosteroid burst (instead of adalimumab alone) whilst the comparator is current practice, which includes corticosteroids and a range of immunosuppressants (such as methotrexate, mycophenolate

mofetil, and cyclosporine). Current practice is assumed to be equivalent to the control arm (placebo) in VISUAL I and VISUAL II, in which 32% of patients were receiving at least one immunosuppressant at baseline (across arms). Given that a greater proportion of patients in current practice are likely to receive immunosuppressants, the comparator is denoted throughout as limited current practice (LCP).

The model structure, presented in

Figure 1, includes five health states: (i) on treatment; (ii) post treatment failure; (iii) blindness; (iv) remission; and, (v) death. Patients start in the "on treatment" state and may discontinue treatment due to either treatment failure as defined in the VISUAL I and II trials[4, 5], in which case they transition to "post treatment failure", or after two years on treatment, due to achieving remission, in which case they transition to the "remission" state. Patients in the "post treatment failure" state are at risk of experiencing permanent damage to the eye and may transition to "blindness". Upon entering remission, patients do not receive further adalimumab treatment but they maintain the benefit of the previous treatment. Given the lack of data, the probability of remission was assumed to be zero in the base case and its impact explored in sensitivity analyses. Patients can transition to the "death" state at any time. Treatment benefit is represented by higher health-related quality of life (HRQoL) and lower rates of adverse events and treatment failure, resulting in turn in a reduced risk of permanent blindness. For more details on the model, please refer to the corresponding HTA report.[3]

Figure 1: State transition diagram of the decision model

[INTRODUCE FIGURE 1 HERE]

Model inputs

Model input parameters were taken from a variety of sources. A summary of these parameters are included in Table 2.

Utilities

EQ-5D scores, where one is equivalent to full health and zero is equivalent to death, were used in the analysis to derive utility values representing HRQoL. For each treatment arm, average EQ-5D scores measured at each time point in the relevant arms of VISUAL I and VISUAL II were used. These scores were taken from confidential Clinical Study Reports of the respective trials and therefore are not included in Table 2. Patients in the "post treatment failure" state were assigned the average EQ-5D at baseline whilst patients in remission were assigned the average EQ-5D score measured at the end of the VISUAL I trial. For the "blindness" state, we considered two studies of utilities associated with blindness based in the UK: Czoski-Murray et al.,[6] which led to an estimated EQ-5D score of 0.38, and Brown,[7] who reports a score of 0.57. Both estimates were used in sensitivity analyses.

Treatment failure

Treatment failure was defined in the VISUAL I and II trials[4, 5] as fulfilling at least one of these four criteria: (i) development of new inflammatory lesions; (ii) worsening of anterior chamber cell grade; (iii) worsening of vitreous haze grade; or (iv) worsening of visual acuity. Time to treatment failure was modelled using parametric survival functions fitted to Kaplan-Meier survival functions from the trials. Amongst the parametric survival functions fitted, the log normal was deemed the most appropriate in terms of statistical goodness-of-fit and clinical plausibility. After treatment failure, patients were assumed to continue on LCP.

Permanent blindness

The VISUAL I and II trials did not report any occurrence of permanent blindness, probably because of their short duration [4, 5, 8]. However, we assume that adalimumab, by preventing permanent damage to the eye, could prevent future blindness. We identified three relevant sources to estimate the blindness rate associated with current practice: Dick et al.,[9] a retrospective analysis of insurance claims data of patients with posterior segment, non-infectious uveitis; Tomkins-Netzer et al.,[10] which included a wider population than our target population (including patients with infectious and anterior uveitis); and, Durrani et al.,[11] based on a tertiary referral centre. Dick et al. was used in the base case analysis, as it was deemed the most appropriate source because of its large sample size (n=1769) and because it only included patients with posterior segment non-infectious uveitis; Tomkins-Netzer et al. and Durrani et al. were used in sensitivity analyses. We assumed that patients could not go blind before treatment failure.

Adverse events

Given that EQ-5D data were used to model treatment effectiveness, the impact on quality of life associated with adverse events (AEs) was already captured. Only the additional costs associated with the AEs whose treatment cost is substantial were modelled: cataract, raised intraocular pressure, glaucoma, serious infections, hypertension, fractures, and diabetes. The probabilities for AEs per cycle were calculated based on the incidence in the trials.

Costs

We included treatment costs, administration costs and monitoring costs as well as adverse event costs and the cost of permanent blindness. Adalimumab is assumed to be mostly self-administered with only 10% of patients needing help from a district nurse. We assumed that patients would receive monitoring every six weeks irrespective of treatment, consisting of outpatient visits to assess the efficacy of the treatments and to monitor the risk of AEs. It is also assumed that patients receiving immunosuppressants would receive six additional blood monitoring visits annually. The costs of treatment for AEs were on NHS Reference Costs 2014-15,[12] except raised intraocular pressure, which was assumed to be treated

with two doses of bimatoprost, and the treatment for hypertension, which was based on Breeze et al.[13] The cost of blindness, which includes NHS costs as well as PSS costs, was based on the cost estimated by Colquitt et al.[14] for age-related macular degeneration and was updated with the most recent cost data.

Table 2: Model input parameters for the base case analysis

Parameters	**Mean**	**Distribution used in PSA**	**Source**
Starting age (active/inactive)	42.7/42.5	Fixed	VISUAL I/VISUAL II[4, 5]
Discount rate (costs and utilities)	3.5%	Fixed	NICE Reference Case[15]
Gender (% males)	43%/39%	Fixed	VISUAL I/VISUAL II[4, 5]
Cycle length	2 weeks	Fixed	
Utilities			
Baseline EQ-5D (active/inactive)	0.83/0.85	Beta	VISUAL I/VISUAL II[4, 5]
EQ-5D at different time points	Confidential	Beta	VISUAL I/VISUAL II*
Blindness utility	0.38	Multivariate normal	Czoski-Murray et al.[6]
Proportion of bilateral uveitis (active/inactive)	90.8/95.6%	Beta	VISUAL I/VISUAL II[4, 5]
Probability of blindness (annual)	0.0068	Beta	Dick et al.[9]
Drug costs			
Adalimumab 40mg	£352.14	Fixed	BNF[16]
Prednisolone	£1.24	Fixed	BNF[16]
Mycophenolate mophetil	£9.31	Fixed	BNF[16]
Methotrexate	£2.40	Fixed	BNF[16]
Cyclosporine	£48.50	Fixed	BNF[16]
Azathioprine	£3.24	Fixed	BNF[16]
Bimatoprost	£11.71	Fixed	BNF[16]
Adcal D3	£7.49	Fixed	BNF[16]
Omeprazole	£1.17	Fixed	BNF[16]
Administration and monitoring			
Monitoring visit frequency	6 weeks		Jabs et al.[17]
Monitoring visit cost	£96.11	Gamma	NHS Reference costs 2014-15[12]
% of patients needing nurse help for adalimumab injection	10%	Beta	NICE TA375[18]
Adalimumab administration help cost	£44	Gamma	PSSRU 2015[19]
Costs of adverse events			
Cataract surgery	£852.40	Gamma	NHS Reference costs 2014-15[12]
Raised intraocular pressure	£23.42	Gamma	BNF[16]
Glaucoma procedure	£581.25	Gamma	NHS Reference costs 2014-15[12]
Serious infection	£5,940.50	Gamma	NHS Reference costs 2014-15[12], VISUAL I and II
Hypertension	£7.04	Gamma	Breeze et al.[13]

Parameters	Mean	Distribution used in PSA	Source
Blindness (onset)	£237	Gamma	Colquitt et al.[14]
Blindness (annual)	£7,659	Gamma	Colquitt et al.[14]
Fracture	£2,116.17-£6,022.62	Gamma	Davis et al.[20]
Diabetes	£1,521.46	Gamma	Alva et al.[21], Breeze et al.[13]

*From the confidential Clinical Study Report of VISUAL I and VISUAL II.
BNF: British National Formulary; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; PSA: probabilistic sensitivity analysis; PSSRU: Personal Social Services Research Unit; TA: Technology Assessment.

Model analysis

We estimated the incremental cost-effectiveness ratios (ICERs), in terms of incremental cost (in pounds sterling) per QALY gained, of adalimumab plus LCP compared with LCP, in patients with active and inactive uveitis. For the base case analysis we ran probabilistic sensitivity analyses (PSA) by specifying input parameters as probability distributions and propagating the uncertainty through the model using Monte Carlo simulation (5,000 samples), hence allowing for non-linearity and producing an estimate of the decision uncertainty. Given the scarcity of relevant evidence on key model parameters, we supplemented the base case analysis with a range of exploratory analyses using alternative evidence sources and assumptions. In one such exploratory analysis, we used evidence from the Multicenter Uveitis Steroid Treatment (MUST) trial,[22] where fluocinolone corticosteroid implant was compared with systemic corticosteroids and immunosuppressants, the primary outcome being change in best-corrected visual acuity (BCVA), in patients with active non-infectious posterior segment uveitis. In the MUST trial, a greater proportion of patients in the comparator arm were treated with a mix of systemic steroids and immunosuppressant (86%), which reflects current practice better. We also conducted exploratory analyses combining different blindness rates and utility estimates associated with blindness, based on alternative sources, as well as alternative remission rates. Finally, we conducted exploratory analyses using alternative parametric survival functions (Weibull and Gompertz distributions) to the log normal distribution used in the base case to extrapolate time to treatment.

RESULTS

Base case analysis

In patients with active uveitis, adalimumab in combination with LCP was estimated to produce 0.200 incremental QALYs compared with LCP alone at an additional cost of £18,541, resulting in an ICER of £92,600 per QALY gained as shown in Table 3. The ICER generated using the deterministic version of the model (£94,262) was similar to that from the probabilistic model. In patients with inactive uveitis,

adalimumab plus LCP was estimated to produce 0.119 incremental QALYs compared with LCP alone at an extra cost of £37,784, resulting in an ICER of £318,075 per QALY gained.

Table 3: Results of the base case analysis comparing adalimumab + LCP(VI) vs LCP(VI) in patients with active uveitis and adalimumab + LCP(VII) vs LCP(VII) in patients with inactive uveitis (probabilistic)

	Total QALYs	Total costs	Inc. QALYs	Inc. costs	ICER	Probability of cost-effectiveness at WTP threshold	
						£20,000	£30,000
Active uveitis							
LCP(VI)	15.221	£49,036				1.00	1.00
Adalimumab + LCP(VI)	15.421	£67,577	0.200	£18,541	£92,600	0.00	0.00
Inactive uveitis							
LCP(VII)	15.549	£50,230				1.00	1.00
Adalimumab + LCP(VII)*	15.668	£88,014	0.119	£37,784	£318,075	0.00	0.00

*LCP(VI)= Limited current practice, as provided in the VISUAL I trial: initial systemic steroid burst tapered by week 15 and around 30% of patients on systemic immunosuppressants; LCP(VII)= Limited current practice, as provided in the VISUAL II trial: on systemic steroids at baseline tapered by week 19 and around 47% of patients on systemic immunosuppressants; WTP: willingness to pay.

Sensitivity analyses

In the exploratory analysis we conducted based on the MUST trial, the ICER for adalimumab versus current practice in patients with active uveitis is £110,068 per QALY compared with £94,262 per QALY in the base case. The results of the exploratory analyses combining different blindness rates and utilities are shown in Table 4. In patients with active uveitis, the ICER for adalimumab versus LCP using the blindness rate from Durrani et al.[11] is reduced from the base case £94,262 to £32,544 per QALY but increases to £120,650 per QALY using the lower blindness rate based on Tomkins-Netzer et al.[10] Using the utility estimates associated with blindness reported by Brown[7] instead of Czoski-Murray et al.,[6] the ICER for adalimumab versus LCP increased to £117,571 per QALY. Assuming that after two years of successful treatment, some patients would achieve remission and no longer require adalimumab, led to a considerable reduction of the ICER for adalimumab versus LCP: in patients with active uveitis; it decreased to £66,176 and £55,161 per QALY assuming annual remission rates of 0.1 and 0.2 respectively. The lowest estimated ICER for adalimumab versus LCP is £15,579 per QALY when using the utility score for blindness from Czoski-Murray et al.,[6] the blindness rate calculated from Durrani et al.[11] and assuming an annual remission rate of 0.2 after the second year of successful treatment. Exploratory analyses using alternative parametric survival functions to extrapolate time to treatment failure showed that the ICER for adalimumab versus LCP was slightly higher when using a

Gompertz distribution (£100,225 per QALY) and a Weibull distribution (£102,218 per QALY) compared with the log normal distribution used in the base case.

Table 4: Exploratory analyses using different sources for the rate of blindness, utility score for blindness and different rates of remission after two years in patients with active uveitis. (deterministic)

Blindness utility	**Czoski-Murray**[6]			**Brown**[7]		
Remission rate	**0***	**0.1**	**0.2**	**0**	**0.1**	**0.2**
Blindness rate						
Tomkins-Netzer et al. [10]	£120,650	£85,785	£72,111	£141,099	£100,324	£84,332
Dick et al. [9]*	£94,262*	£66,176	£55,161	£117,571	£82,540	£68,801
Durrani et al. [11]	£32,544	£20,358	£15,579	£48,094	£30,086	£23,024

*base case

The same sensitivity analyses were undertaken for inactive patients (except from the analysis based on the MUST trial, given that it only included active patients) and all analyses resulted in an ICER greater than £35,000 per QALY gained.

DISCUSSION

Adalimumab combined with LCP has shown significant benefit over placebo combined with LCP in patients with active and inactive non-infectious posterior segment uveitis.

Adalimumab has been shown to be clinically effective for treating non-infectious uveitis. We have conducted a cost-effectiveness analysis of adalimumab in patients with non-infectious posterior segment uveitis from the NHS and PSS perspective. However, the estimated ICERs for adalimumab versus LCP in most of our analyses are above the range of £20,000 to £30,000 per QALY gained that the National Institute for Health and Care Excellence (NICE) considers as a cost-effective use of NHS resources. [15] Our analyses suggest that it is more cost-effective in patients with active uveitis at greater risk of blindness, but that it is unlikely to be considered cost-effective for most patients with inactive uveitis from a healthcare provider's perspective. We recognise however that there is very significant uncertainty in these estimates as highlighted by our sensitivity analyses. In addition, this perspective does not consider a number of indirect costs and outcomes (such as productivity losses of patients and/or carers) and.

Our analyses, alongside other evidence, informed the decision of where adalimumab should sit within the treatment pathway for adults with non-infectious posterior segment uveitis. Within the United Kingdom (UK), until recently it was only available on a named patient basis through exceptional funding routes dependent on local decision-makers. In this context it was usually used only after at least two, and often many more, standard immunosuppressants. From 2017 onwards, expert

review by NHS England,[23] publication of the VISUAL trials[4, 5] and assessment by NICE[24] has resulted in adalimumab becoming a standard part of treatment pathways in the UK, being used in refractory disease according to criteria which includes 'inadequate response to steroids' and 'inadequate response or intolerance to immunosuppressants'. Its place in this stage of the pathway aligns with its relatively high cost compared to standard second-line immunosuppressants; however, it could be argued that the VISUAL trials provide more robust clinical effectiveness and safety data for adalimumab than is currently available for any other non-corticosteroid therapy, and that if cost were not a factor it could be used earlier in the treatment pathway.

ACKNOWLEDGEMENTS

The authors received financial support for this research from the National Institute of Health Research (NIHR) Health Technology Assessment (HTA) Program (project number 15/64/07). Any views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health.

CONFLICTS OF INTEREST

The authors have no potential conflicts of interest that are directly relevant to the content of this article.

CONTRIBUTIONS OF AUTHORS

Inigo Bermejo undertook the cost-effectiveness review and developed the cost-effectiveness model. Hazel Squires coordinated the project and advised on the cost-effectiveness modelling. Edith Poku and Katy Cooper undertook the clinical effectiveness review. John Stevens and Jean Hamilton commented on statistical issues and feasibility of NMAs and Ruth Wong performed the literature searches. Alastair Denniston, Ian Pearce and Fahd Quhill provided clinical advice. All authors were involved in drafting and commenting on the manuscript.

REFERENCES

1. Rothova, A., M.S. Suttorp-van Schulten, W. Frits Treffers, et al., Causes and frequency of blindness in patients with intraocular inflammatory disease. Br J Ophthalmol, 1996. **80**.
2. European Medicines Agency. Public summary of opinion on orphan designation. Dexamethasone (intravitreal implant) for the treatment of non-infectious uveitis affecting the posterior segment of the eye. 2010 20/10/16]; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Orphan_designation/2010/08/WC500095728.pdf.

3. Squires, H., E. Poku, I. Bermejo, et al., A systematic review and economic evaluation of adalimumab and dexamethasone for treating non-infectious intermediate uveitis, posterior uveitis or panuveitis in adults. Health Technol Assess, 2017. **21**(68).
4. Jaffe, G.J., A.D. Dick, A.P. Brézin, et al., Adalimumab in Patients with Active Noninfectious Uveitis. New England Journal of Medicine, 2016. **375**(10): p. 932-943.
5. Nguyen, Q.D., P.T. Merrill, G.J. Jaffe, et al., Adalimumab for prevention of uveitic flare in patients with inactive non-infectious uveitis controlled by corticosteroids (VISUAL II): a multicentre, double-masked, randomised, placebo-controlled phase 3 trial. Lancet, 2016. **388**(10050): p. 1183-92.
6. Czoski-Murray, C., J. Carlton, J. Brazier, et al., Valuing Condition-Specific Health States Using Simulation Contact Lenses. Value in Health, 2009. **12**(5): p. 793-799.
7. Brown, G.C., Vision and quality-of-life. Transactions of the American Ophthalmological Society, 1999. **97**: p. 473-511.
8. Lowder, C., R. Belfort, Jr., S. Lightman, et al., Dexamethasone intravitreal implant for noninfectious intermediate or posterior uveitis. Archives of Ophthalmology, 2011. **129**(5): p. 545-53.
9. Dick, A.D., N. Tundia, R. Sorg, et al., Risk of Ocular Complications in Patients with Noninfectious Intermediate Uveitis, Posterior Uveitis, or Panuveitis. Ophthalmology, 2016. **123**(3): p. 655-662.
10. Tomkins-Netzer, O., L. Talat, A. Bar, et al., Long-term clinical outcome and causes of vision loss in patients with uveitis. Ophthalmology, 2014. **121**(12): p. 2387-92.
11. Durrani, O.M., N.N. Tehrani, J.E. Marr, et al., Degree, duration, and causes of visual loss in uveitis. British Journal of Ophthalmology, 2004. **88**(9): p. 1159-1162.
12. Department of Health. NHS Reference Costs 2014-15. 2015; Available from: https://www.gov.uk/government/publications/nhs-reference-costs-2014-to-2015.
13. Breeze, P.R., C. Thomas, H. Squires, et al., School for Public Health Research (SPHR) Diabetes Prevention Model: Detailed Description of Model Background, Methods, Assumptions and Parameters. The University of Sheffield, School of Health and Related Research, Health Economics & Decision Science (HEDS). **Discussion Paper Series**(15.01).
14. Colquitt, J.L., J. Jones, S.C. Tan, et al., Ranibizumab and pegaptanib for the treatment of age-related macular degeneration: A systematic review and economic evaluation. Health Technology Assessment, 2008. **12**(16): p. iii-107.
15. NICE. Guide to the methods of technology appraisal. 2013 20/10/16]; Available from: https://www.nice.org.uk/process/pmg9/chapter/the-reference-case.
16. British Medical Association. British National Formulary (BNF). 2016 01/09/16]; Available from: https://www.evidence.nhs.uk/formulary/bnf/current.
17. Jabs, D.A., J.T. Rosenbaum, C.S. Foster, et al., Guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders: recommendations of an expert panel. American Journal of Ophthalmology, 2000. **130**(4): p. 492-513.
18. National Institute for Health and Care Excellence (NICE), Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed. 2016.
19. Curtis, L.,A. Burns, PSSRU Unit Costs of Health and Social Care 2015. 2016.
20. Davis, S., M. Martyn-St James, J. Sanderson, et al., A systematic review and economic evaluation of bisphosphonates for the prevention of fragility fractures. Health Technol Assess, 2016. **20**(78): p. 1-406.
21. Alva, M.L., A. Gray, B. Mihaylova, et al., The impact of diabetes-related complications on healthcare costs: new results from the UKPDS (UKPDS 84). Diabetic Medicine, 2015. **32**(4): p. 459-466.
22. Multicenter Uveitis Steroid Treatment Trial Research, G., J.H. Kempen, M.M. Altaweel, et al., Randomized comparison of systemic anti-inflammatory therapy versus fluocinolone acetonide implant for intermediate, posterior, and panuveitis: the multicenter uveitis steroid treatment trial.[Erratum appears in Ophthalmology. 2012 Feb;119(2):212]. Ophthalmology, 2011. **118**(10): p. 1916-26.

23. NHS England, Interim Clinical Commissioning Policy Proposition: Adalimumab for Adults with Severe Refractory Uveitis. 2017. Available from https://www.rcophth.ac.uk/wp-content/uploads/2017/01/21_Interim-Policy-Proposition-for-Adalimumab-for-Adults-PWG-updated-100117-for-stakeholder-testing.pdf.
24. National Institute for Health and Care Excellence (NICE). Adalimumab and dexamethasone for treating non-infectious uveitis. 2017; Available from: https://www.nice.org.uk/guidance/ta460.