Title:

Cost-effectiveness analysis of adalimumab for the treatment of uveitis associated with Juvenile Idiopathic Arthritis

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Conflict of interest:

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: University Hospitals Bristol NHS Foundation Trust, as Sponsor of Study has a data sharing agreement with AbbVie in support of regulatory purposes. AbbVie had no role in the funding, trial management or data analysis or writing of the manuscript but have licensed use of the data resulting from the study for regulatory purposes. AbbVie was given the opportunity to review the final draft of the manuscript, but the authors maintained complete control over the content of the paper.

Running head:

Cost-effectiveness of adalimumab for JIA associated uveitis

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Abstract

Objectives: To investigate the cost-effectiveness of adalimumab in combination with methotrexate, compared with methotrexate alone, for the management of uveitis associated with Juvenile Idiopathic Arthritis (JIA-U).

Design: A cost-utility analysis based on a clinical trial and decision analytic model.

Participants: Children and adolescents aged 2 to 18 years with persistently active JIA-U, despite optimized methotrexate treatment for at least 12 weeks.

Methods: The SYCAMORE trial [ISRCTN10065623] of methotrexate (up to 25mg per week) with or without fortnightly administered adalimumab (20mg or 40mg, according to body weight) provided data on resource use (based on patient self-report and electronic records) and health utilities (from the Health Utilities Index questionnaire). Surgical event rates and long-term outcomes were based on data from a 10-year longitudinal cohort. A Markov model was used to extrapolate the effects of treatment based on visual impairment.

Main outcome measures: Medical costs to the National Health Service in the UK, utility of defined health states, quality-adjusted life years (QALY), and incremental cost per QALY.

Results: Adalimumab in combination with methotrexate resulted in additional costs of £39,316 with a 0.30 QALY gain compared with methotrexate alone, resulting in an incremental cost-effectiveness ratio of £129,025 per QALY gained. The probability of cost-effectiveness at a threshold of £30,000 per QALY was less than 1%. Based on a threshold analysis, a price reduction of 84% would be necessary for adalimumab to be cost-effective.

Conclusions: Adalimumab is clinically effective in JIA-U, however its cost-effectiveness is not demonstrated compared with methotrexate alone in the UK setting.

Keywords: Anti-TNF, Juvenile Idiopathic Arthritis, uveitis, cost-effectiveness, economic evaluation

Introduction

Juvenile Idiopathic Arthritis (JIA) is the most common rheumatic disease in children, with a prevalence of 1-2 per 1,000 children in the UK. Between 12-38% of patients develop inflammation of the uvea (uveitis) which is associated with cataracts, glaucoma and macular oedema[1,2]. Treatment approaches to JIA-associated uveitis (JIA-U) include corticosteroids administered topically (first-line) and systemically (severe or sight-threatening JIA-U), and methotrexate (preferred second-line DMARD)[3]. However, 15-50% of children will develop refractory uveitis,[4–6] requiring further intervention. The efficacy of the anti-tumour necrosis factor α (TNF-α) monoclonal antibody, adalimumab, in JIA is well established,[7] and its use is recommended for children with active arthritis who have not responded adequately to DMARD[8]. The SYCAMORE trial (ISRCTN10065623) demonstrated the clinical effectiveness of adalimumab in combination with methotrexate for the treatment of JIA-U, with a hazard ratio of 0.25 (95% confidence interval, CI 0.12, 0.49; p <0.0001) compared with methotrexate alone[9].

Adalimumab remains on patent and costs around £350 per 40mg dose, administered fortnightly,[10] but a biosimilar will be marketed from October 2018. For its licensed indication in JIA, adalimumab was judged by the National Institute for Health and Care Excellence (NICE) to be cost-effective, with an incremental cost-effectiveness ratio (ICER) of £30,000 per quality-adjusted life year (QALY) gained[8]. There are no published economic evaluations in JIA-U; however a recent analysis of adalimumab and dexamethasone for treating active uveitis in adults showed that adalimumab was not cost-effective at £94,523 per QALY gained,[11] though these findings may not be generalizable to children with JIA-U.

Within the National Health Service (NHS) in England, the availability of adalimumab for the management of paediatric chronic non-infectious anterior uveitis is via an interim clinical commissioning policy[12]. It is also recommended for use within NHS Wales[13] but currently not in NHS Scotland[14]. We aimed to inform the cost-effective use of adalimumab for JIA-U in the NHS by conducting a model-based economic evaluation incorporating evidence from the SYCAMORE trial.

Methods

SYCAMORE trial data

SYCAMORE was a multicentre, double-blind, randomized, placebo-controlled trial to assess the clinical effectiveness of adalimumab in refractory uveitis associated with JIA[9,15]. The trial recruited children and adolescents aged 2 to 18 years with active JIA-associated uveitis, despite stable methotrexate treatment for at least 12 weeks, from 14 UK centres. Ninety participants aged between 2 and 18 years who were taking methotrexate without improvement in their uveitis were randomised in a 2:1 ratio to receive fortnightly subcutaneous injections of adalimumab (20mg for participants <30kg; 40mg for participants ≥30 kg) or placebo in a double-blind phase until treatment failure, or until 18-months had lapsed. They were then treated at their clinician's discretion, which could include adalimumab, and followed up for a further 6 months. Recruitment into the SYCAMORE trial was terminated early following an interim analysis which demonstrated a significantly lower risk of treatment failure in the adalimumab group[9]. All participants in the placebo group stopped the trial regimen and were followed up for 6 months as per protocol. All participants receiving adalimumab continued in an open-label follow-up in accordance with trial protocol.

Economics evaluation overview

The primary outcome of the economic evaluation was the incremental cost per QALY gained with adalimumab combined with methotrexate, versus methotrexate alone. In order to avoid time horizon bias, the primary analysis required a comparison of the long-term costs and consequences of adalimumab in JIA-U. A purposive search of the literature did not identify any relevant study to inform this extrapolation. We therefore used data from a longitudinal cohort of patients with idiopathic and JIA-U attending the Bristol Regional Tertiary Pediatric Uveitis clinic (the 'Bristol cohort'[16]). The economic analysis adopted the perspective of the NHS in the UK, and is reported according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS)[17].

Data sources

Health utilities

Utility was measured using an interviewer-administered and proxy-assessed version of the Health Utilities Index questionnaire,[18] administered at baseline and subsequently at 3, 6, 9, 12, 18 months and end of follow-up. Responses to the questionnaire were mapped onto the

HUI Mark 3 (HUI3) classification system which has validity in children[19]. It also includes vision among its health domains, along with hearing, speech, ambulation, dexterity, emotion, cognition and pain. Preference-based scoring algorithms were used to convert the descriptive health classifications into values for each health dimension, and a multi-attribute model was used to derive a utility score[18]. Although the EuroQol EQ-5D is the preferred generic, preference-based utility measure in the UK[20], it lacks validity in children[21] and is less sensitive to changes in vision[22].

Resource use

The use of trial and concomitant medicines was recorded by physicians at each study visit in dedicated sections of the trial case report form, and supplemented by patient diary records. Hospital admission and adverse event data were obtained from hospital electronic patient-level information costing systems or patient administration systems and were supplemented by baseline and 3-monthly resource use questionnaires. These questionnaires were completed by research nurses based on patient interviews and entries made in patient diaries, and included participants' use of hospital (outpatient clinic, hospital and A&E admissions), primary (e.g. GP consultations) and community (e.g. school nurse) care. Further details on the data collection methods are available from http://www.dirum.org/instruments/details/82.

Unit costs

All resource use was valued in monetary terms using appropriate UK unit costs estimated at the time of analysis (cost year 2016). The unit costs of medicines were obtained from standard NHS sources[10,23] (Table 1). Participants' use of hospital services were costed according to healthcare resource group (HRG) codes, using unit costs from the National Tariff 2016-17[24] or the National Schedule of Reference Costs 2015-16[25]. Unit costs for primary and community care services were sourced from the Personal Social Services Research Unit 2015[26]. The cost of surgery was assumed as the mean cost for paediatric ophthalmology, outpatient procedures[25].

Visual acuity

Data on the long-term consequences of using biologics in clinical practice could only be matched to trial outcomes by visual acuity. This was based on LogMAR scores in the worst eye, which was considered most clinically relevant, with a score <0.3 indicative of no visual

impairment, and ≥0.3 indicating a degree of visual impairment. Trial participants had their LogMAR scores recorded at every visit, including unscheduled visits.

Long-term outcomes and surgery

The Bristol cohort of 91 children with JIA-U[16], collected between 1997 and 2014, provided 10-year data on LogMAR scores, which were recorded at diagnosis, and at 1, 3, 5 and 10 years of follow-up, and the number and nature of surgeries performed. Some overlap existed between SYCAMORE and cohort patients, with the Bristol recruiting centre contributing 28 of 90 trial participants, of which 15 were included in the longitudinal dataset.

Analysis

Economic model

A trial-based analysis was conducted with an 18-month time horizon, corresponding with data from the double-blind phase of SYCAMORE, where available, and supplemented by post-trial treatment open-label and follow-up data, as necessary. A Markov model was constructed in Microsoft® Excel® 2013 to extrapolate the analysis by 10-years beyond the initial 18-month period of the trial-based analysis. A simulated cohort of patients entered a Markov model which consisted of three health states defined by visual impairment and survival (Figure 1). Patients were initially distributed according to the proportion of time spent in each state, by trial arm, over the preceding 18 months. The Bristol cohort was used to estimate the probabilities associated with transitions among health states, either with or without eye surgery (Table 2). A standardized mortality ratio of 3.9 (95%CI 0.8, 11.3) was applied to account for mortality[27,28]. The model had a cycle length of 1 year, and a half-cycle correction was applied.

Censored data

Any censoring of data on utility and time in visual impairment health state were imputed using the predictive mean matching approach[29]. Ten imputed datasets were created from a set of imputation models constructed from a range of potential prognostic factors (trial arm, age, gender, baseline visual impairment) and outcome variables (cost and exposure to adalimumab during the post-trial treatment open-label and follow-up phases).

Early trial closure cross-over

Intention-to-treat analyses may result in biased estimates of the causal treatment effect if participants are non-compliant to the treatment allocated. To account for cross-over effects resulting from early trial closure, we therefore applied an instrumental variable (IV) regression method with total costs and QALYs as outcome variables, adjusted for age and gender[30]. This method links the average causal effect for compliers to the average intention-to- treat effects. For the 10-year modelled extrapolation, costs and QALYs specific to each health state were calculated by applying the IV regression, and adjusting for treatment and time in state. All regression analyses were performed using STATA 13.

Key assumptions

Simulated patients were assumed to be fully adherent to adalimumab which, based on expert clinical opinion, was considered to continue for 3-years beyond the initial 18-month trial period. Progression of visual impairment after 18-months was assumed to be at the same rate for patients on either adalimumab or placebo.

Base-case analysis

Total costs were calculated for the 18-month trial-based analysis with an adjustment made to apportion drug costs if a medication administration spanned the period preceding randomisation, or extended beyond the 18-month time horizon. QALYs were calculated as the area under each patient's utility-time profile, based on the trapezium rule. The base-case analysis was defined as pertaining to a 7-year old girl, representative of the median demographics of SYCAMORE, and based on the 18-month trial period plus the 10-year modelled extrapolation, using the imputed data set to account for missing data, and adjusting for the cross-over of trial participants from the placebo arm. Costs and QALYs accruing in the model beyond the first year were discounted at an annual rate of 3.5%[20].

Uncertainty analyses

Parameter uncertainty in trial-based estimates of total costs and QALYs was assessed using 10,000 bootstrapped replications, and presented as 95% central ranges. Sensitivity analyses were conducted to assess the impact of varying: (i) the proportion of patients continuing adalimumab after end of study; (ii) the duration of post-study access to adalimumab; (iii) patient adherence to adalimumab and methotrexate; (iv) the time horizon of analysis; (v) the unit price of adalimumab; (vi) visual impairment rates, using the most and least favourable combinations; and (vii) the discount rate of future costs and benefits. Bivariate

sensitivity analysis were performed to assess the impact of varying the cost of adalimumab with either (i) the disutility associated with visual impairment or (ii) the proportion of adalimumab patients who develop visual impairment.

A probabilistic sensitivity analysis of the base-case analysis was performed using Monte Carlo simulation with 10,000 replications. All input parameters were sampled simultaneously within their distributions and Cholesky decomposition was used to generate probability distributions for regression-based analyses (Table 2). The joint uncertainty in costs and QALYs was assessed by considering the probability of adalimumab being cost-effective with reference to the NICE threshold range of £20,000 to £30,000 per QALY[20].

Patient and public involvement

The study was supported by a patient advisory group which were involved in the trial from the initial prioritisation, design stage and funding applications. They provided detailed input into all aspects of the trial protocol design and all subsequent amendments, patient information sheets, patient letters, consent forms and the content of the study website.

Ethical approval

The SYCAMORE trial was approved by the NHS National Research Ethics Service Committee (Hampstead, London) 11/LO/0425, and written, informed consent was given by a parent or guardian of each trial participant.

Results

Trial-based analysis

Utilities and QALYs

Baseline utility scores were 0.83 (95%CI 0.76, 0.89) and 0.87 (95%CI 0.78, 0.96) for the adalimumab and placebo groups, respectively. Based on a complete case analysis of 25 (42%) participants randomised to adalimumab and 3 (10%) participants randomised to placebo, the number of QALYs over the 18-month trial period was 1.40 (95% central range, CR 1.35, 1.45) and 1.45 (95%CR 1.41, 1.50), respectively. After imputation, the mean QALY scores were numerically higher for adalimumab at 1.35, (95%CI 1.30, 1.41) compared with the placebo group, at 1.28 (95%CI 1.15, 1.41).

Resource use and costs

Eighteen-month resource use data were available for all trial participants. The total costs over the 3-months preceding randomisation were £1,614 (95%CR 1,312, 1,946) and £1,526 (95%CR 1,072, 2,047) for the adalimumab and placebo groups, respectively (Table 3). During the 18-month trial-based analysis, total costs were £15,980 (95%CR 14,213, 17,943) and £6,248 (95%CR 3,922, 8,889) respectively, with the majority of the difference in costs (£8,579; 88%) attributable to the use of adalimumab. The cost of concomitant medications, GP and optician visits differed between groups, but were not major cost drivers, accounting for 3%, 0.4% and 0.2% of the difference in total costs, respectively.

Visual outcomes

Seven (11.7%) participants randomised to adalimumab, and 2 (6.7%) participants randomised to placebo had visual impairment at baseline. At 18-months, complete data were available for 43 and 9 participants in each group, respectively, of which 1 (2.3%) and 0 (0.0%) reported visual impairment. On average, adalimumab participants spent 3.4% (95%CI 0.5, 6.3) of their time in the visual impairment state compared with 2.1% (95%CI -2.8, 7.0) on placebo. Following imputation, participants randomised to adalimumab spent 5.3% (95%CI 2.2, 8.4) of time in visual impairment during the 18-month analysis, compared with 11.2% of time (95%CI 5.6, 16.7) for those randomised to placebo.

Bristol longitudinal cohort

The characteristics of patients included in the Bristol cohort are presented in Table 4. Thirty-seven surgeries in 25 patients were recorded, corresponding to 7.87 per 100 patient-years of follow-up.

Base-case results

In the base-case analysis, adalimumab in combination with methotrexate generated more QALYs but at a higher cost than methotrexate alone. The total costs for each group were £70,719 and £31,403, with corresponding QALYs of 8.60 and 8.29, respectively. The incremental costs and QALYs were £39,316 and 0.30, resulting in an ICER of £129,025 per QALY gained.

Sensitivity analyses

Univariate sensitivity analyses

The ICER was comparatively stable to a range of sensitivity analyses concerning parameter uncertainty and modelling assumptions (Table 5). Alternative assumptions relating to the duration and proportion of patients being prescribed adalimumab beyond 18-months, as well as adherence to treatment, all resulted in ICERs of at least £115,708 per QALY gained. The ICER was stable to varying the distribution of patients across visual impairment states on entry to the Markov model. Taking the lower 95%CI for the proportion from the adalimumab arm of the trial, and upper 95%CI for the placebo arm, the ICER remained in excess of £127,000 per QALY gained. A shortened time horizon of analysis increased the ICER to £136,751 per QALY gained. Plausible alternative rates of visual impairment had no demonstrable impact on the ICER. However under the extreme condition of all placebo group patients transitioning to the state of being visually impaired for the duration of the model, the ICER reduced to £78,524 per QALY gained; and in a scenario where, in addition to this, all adalimumab patients transition to (and remain) in the state of no visual impairment, the ICER reduced further to £53,072 per QALY gained. The ICER also decreased with a discounted price of adalimumab, reflecting the future prospect of a biosimilar, but a price reduction of 84% would be necessary for adalimumab to be cost-effective at the £30,000 per QALY thresholds, respectively. An alternative analytical approach which did not account for cross-over resulted in an ICER of £158,259 per QALY gained.

Two-way sensitivity analyses

These support our finding that the ICER is sensitive to the cost of adalimumab, but not to either the disutility associated with VI or the proportion of adalimumab patients who develop VI (Table 5).

Probabilistic Sensitivity Analyses

Results from the probabilistic sensitivity analysis indicated that adalimumab is very unlikely to be cost-effective, with less than 1% of simulations falling below the £30,000 per QALY threshold. These results are illustrated as cost-effectiveness planes in Figure 2. Whilst these are presented for 10,000 iterations, the ICER was stable by 2,500 iterations.

Discussion

Principal findings

This analysis suggests that adalimumab in combination with methotrexate for JIA-U is associated with appreciably higher healthcare costs than methotrexate alone, and exceeds the threshold for cost-effectiveness operated by the NHS in the UK, by a significant margin. The results are robust to changes in parameter estimates and some alternative modelling assumptions (although we had limited scope for assessing structural uncertainty), and are consistent with the cost-effectiveness of adalimumab used in the management of active uveitis in adults[11].

Comparison with other studies

There are important differences when making comparisons with existing economic evaluations of biologic treatments for JIA[30]. Our estimated incremental QALY gain (0.30 over the time horizon of the analysis), for instance, is considerably less than 2.0 QALYs (over a 30 year period) reported by Shepherd et al.[30]. While their analysis was also based on HUI3 utilities, these were derived from a 27-month cohort study of etanercept-treated patients whose measured utility at baseline (0.53) was assigned as the annual health-state utility of patients treated with methotrexate, and at 15-months (0.74) was assigned to adalimumab-treated patients. This difference was maintained for the duration of the analysis, and treatment continued for much longer than our assumed 4½ years.

Strengths and limitations of study

Our analysis had strengths in being based on least biased data (having controlled for cross-over effects), and estimating cost-effectiveness up until adulthood, but there were also many limitations. Principally was the incomplete data on health utilities (QALYs could only be calculated for 28 (31%) trial participants) and visual acuity which required a strong assumption of data being missing at random. Visual acuity data were censored in 70% and 28% of patients randomised to placebo and adalimumab, respectively. This was because some entered the trial late (in relation to the date of early trial closure) and resulted in incomplete follow up. However, adalimumab remained non-cost-effective in a sensitivity analysis in which all placebo and no adalimumab patients had visual impairment.

We were also reliant on a secondary outcome (visual impairment) for matching to the external dataset. SYCAMORE was not powered to detect differences in visual impairment,

and while the effect of adalimumab on the time to treatment failure (primary endpoint) was profound, there was no significant improvement in visual acuity, with a treatment effect on worst-eye LogMAR of -0.02 (95% CI -0.07, 0.02)[9].

The extrapolated model also had limitations. There was no consideration of severe visual impairment (LogMAR ≥1) or blindness, which is associated with high lifetime costs, and significant impacts on quality of life, education and employment. While modelling based on the association between anterior chamber (AC) cell count and blindness might have offered an alternative approach, this would not have reduced the need for considerable assumptions relating to magnitude of long term treatment benefits. In mitigation, expected rates of blindness may be low as trial participants had mild or moderate uveitis, with 91% having AC cell counts of 1+ or 2+ at baseline[9].

A further limitation was our reliance on data from the Bristol cohort, which included patients that may not be comparable to, or managed differently from those recruited to the SYCAMORE trial, such as in respect of DMARD treatment or thresholds for prescribing biologics[16]. Moreover, the care offered at Bristol may not be representative of wider practice across the NHS. Bristol pioneered combined (ophthalmology and rheumatology) clinics from 2006 (70% of the cohort had a diagnosis since 2006), representing the best model for service delivery in UK, and were early adopters of biologics for this indication. This became a key factor in SYCAMORE, where combined services needed to be developed during the trial in many centres, or optimised in others. The Bristol data were limited in patient numbers and lack of collection of some important long-term outcome data (e.g. disutilities associated with surgery), which may otherwise have added to our interpretation of progression of uveitis within the model. Transition probabilities were also independent of treatment received since in the Bristol dataset, it appeared that adalimumab was only prescribed to those patients in a worse health state, and this would bias the results.

Notwithstanding these limitations, our analysis was robust to multiple assumptions. In order to demonstrate cost-effectiveness, patients receiving adalimumab would need to gain 1.00 additional QALY over the 10-year time frame, which is unlikely given the QALY gain over the course of the trial was only 0.11. Significant price reductions through the introduction of

biosimilars would be expected to reduce the ICER, but there would need to be a discount of 84% to meet the £30,000 per QALY threshold.

Conclusions and policy implications

In conclusion, and based on the first and only randomised double-blind, placebo-controlled trial in JIA-U, adalimumab is unlikely, at present, to represent a cost-effective treatment option in the UK. Our findings have important implications for the routine availability of adalimumab for this indication across the NHS in the UK.

Footnotes

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Contributors:

DAH, GC, CP, EW, ADD, MWB and AVR conceived and designed the study. DAH, GC, CP and EW conducted the analysis. APJ, AM and PRW provided statistical expertise. All authors contributed to data collection. DAH, GC, CP and EW drafted the manuscript. All authors contributed to the interpretation of the results and critical revision of the manuscript for important intellectual content and approved the final version of the manuscript. DAH is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Data sharing:

No additional data available.

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Table 1. Unit costs of trial medications, outpatient attendances, inpatient attendances (including day case and surgical procedures)

HRG code	Health care resource	Unit cost	Reference
Trial medications			
	Adalimumab Humira 40mg or 80mg pre-filled syringe	£352.14	[10]
	Methotrexate Metoject Pen (different volumes)	£14.85 - £18.48	[23]
	Methotrexate Tablet 2.5mg	£0.06	[23]
	Methotrexate Oral Solution 2mg/ml sugar-free	£2.65	[23]
Outpatient procedures			
BZ22Z	Intermediate Vitreous Retinal Procedures	£142	[24]
BZ23Z	Minor Vitreous Retinal Procedures	£109	[24]
WF01B	Ophthalmology First Attendance - Single Professional	£113	[24]
WF02B	Ophthalmology First Attendance – Multi Professional	£125	[24]
WF01A	Ophthalmology Follow Up Attendance - Single Professional	£64	[24]
WF02A	Ophthalmology Follow Up Attendance- Multi Professional	£94	[24]
WF01B	Paediatric Ophthalmology First Attendance - Single Professional	£136	[24]
WF01A	Paediatric Ophthalmology Follow Up Attendance - Single Professional	£82	[24]
	Paediatric Rheumatology attendance	£203	[25]
WF01A	Rheumatology Follow Up Attendance - Single Professional	£103	[24]
WF01B	Rheumatology First Attendance - Single Professional	£225	[24]
WF02B	Rheumatology First Attendance - Multi Professional	£246	[24]
WF02A	Rheumatology Follow Up Attendance- Multi Professional	£165	[24]
WF01B	Paediatrics First Attendance - Single Professional	£222	[24]
WF01A	Paediatrics Follow Up Attendance - Single Professional	£135	[24]
WF02A	Paediatrics Follow Up Attendance- Multi Professional	£156	[24]
	Physiotherapy attendance	£48	[25]
Day case			
	Rheumatology	£246	[24]
HB29Z	Minimal Knee Procedures for Non-Trauma, with length of stay ≤1 day	£356	[24]
PA64A	Non-Surgical Ophthalmology with length of stay 0 days	£552	[24]
PH34D	Paediatric, Musculoskeletal or Connective Tissue Disorders, with CC Score 0	£590	[25]
HB39Z	Minimal Foot Procedures for Non-Trauma, with length of stay ≤1 day	£672	[24]
PA34B	Musculoskeletal or Connective Tissue Disorders, without CC	£688	[24]
PH34C	Paediatric, Musculoskeletal or Connective Tissue Disorders, with CC Score 1-2	£696	[25]
PA34A	Musculoskeletal or Connective Tissue Disorders, with CC	£988	[24]
Surgeries			
BZ32B	Intermediate, Cataract or Lens Procedures, with CC Score 0-1	£208	[25]
BZ85Z	Very Major or Major, Vitreous Retinal Procedures, ≤18 years	£334	[25]
BZ94B	Intermediate, Glaucoma or Iris Procedures, with CC Score 0	£401	[25]
BZ33Z	Minor, Cataract or Lens Procedures	£140	[25]

BZ93B	Major, Glaucoma or Iris Procedures, with CC Score 0-1	£106	[25]

CC – complication or co-morbidity

Table 2. Parameter estimates for the modelled extrapolation

Parameter	Point estimate	Distribution	Source
18-month data (trial-based)			
Cost coefficient: Adalimumab	14,374.01	Cholesky decomposition	Trial data
Cost coefficient: Age	-257.72		
Cost coefficient: Gender	-445.89		
Cost coefficient: Constant	3,765.78		
QALY coefficient: Adalimumab	0.11	Cholesky decomposition	Trial data
QALY coefficient: Age	-0.00		
QALY coefficient: Gender	-0.02		
QALY coefficient: Constant	1.26		
Month 19-138 (Markov model): Base case model assumptions			
Costs			
Cost coefficient: Adalimumab arm (excluding trial drug costs)	1,437.13	Cholesky decomposition	Trial data
Cost coefficient: Time in visual impairment	2,662.57		
Cost coefficient: Constant	1,603.05		
Drug cost: Adalimumab	£7,411.73	Gamma~(8.11, 1,370.33)	Trial data
Drug cost: Methotrexate	£1,598.17	Gamma~(0.56, 4,315.70)	Trial data
Surgery cost (per surgery transition)	£418.71	Gamma~(2.66,157.27)	[16]
Discount rate: Cost (per annum)	0.035	None (fixed)	[20]
QALYs			
QALY coefficient: Adalimumab arm	0.07	Cholesky decomposition	Trial data
QALY coefficient: Time in visual impairment	-0.00		
QALY coefficient: Constant	0.83		
Discount rate: QALY (per annum)	0.035	None (fixed)	[20]
Probabilities			
Proportion VI: Adalimumab arm	0.05	Beta~(4.75, 85.25)	Trial data
Proportion VI: Placebo arm	0.11	Beta~(10.04, 79.96)	Trial data
No VI -> no VI (no surgery)	0.95	Dirichlet~(162, 4, 14, 2) approximated by standardised series of gamma distributions	[16]
No VI -> no VI (surgery)	0.01		

No VI -> VI (no surgery)	0.04		
No VI -> VI (surgery)	0.01		
VI -> no VI (no surgery)	0.33	Dirichlet~(29, 6, 38, 13) approximated by standardised series of gamma distributions	[16]
VI -> no VI (surgery)	0.06		
VI -> VI (no surgery)	0.47		
VI -> VI (surgery)	0.14		
Mortality rate* (per annum)	0.000071	None (fixed)	[28]
Standardised mortality ratio	3.9	Lognormal~(3.9,2.6785)	[27]

VI – visual impairment

*Age based, figure indicated is for 8-year old.

Table 3. Disaggregated healthcare resource use and costs, from randomisation to 18-months, by intervention group

Item of resource use	**Adalimumab mean count (95%CR)**	**Placebo mean count (95%CR)**	**Difference in means (95% CR)**
GP visits	2.1 (1.4, 2.7)	1.1 (0.5, 1.7)	1.0 (0.1, 1.8)
Nurse visits	1.2 (0.6, 1.9)	0.4 (0.3, 1.2)	0.7 (-0.2, 1.6)
Physiotherapist	0.5 (0.2, 0.8)	0.4 (0, 0.8)	0.1 (0.4, 0.6)
Psychologist	0.1 (0.0, 0.2)	0.2 (0.0, 0.5)	-0.1 (-0.4, 0.1)
OP - HRG - WF01A	2.6 (1.6, 3.8)	1.9 (0.7, 3.3)	0.7 (-1.0, 2.4)
OP - HRG - WF01B	0.2 (0.1, 0.4)	0.2 (0.1, 0.4)	0 (-0.2, 0.2)
OP - HRG - WF02A	0.3 (0.0, 0.7)	0.3 (0.0, 0.7)	0 (-0.5, 0.5)
IP - HRG - PA34A	1.5 (0.4, 3.0)	1.4 (0.2, 3.0)	0.1 (-1.8, 2.1)
IP - HRG - PA34B	0.5 (0.0, 1.0)	0.2 (0.0, 0.4)	0.3 (-0.3, 1.0)
IP - HRG - PA34C	0.1 (0.0, 0.2)	0.4 (0.0, 0.9)	-0.3 (-0.8, 0.1)
IP - HRG - PA34D	0.3 (0.0, 0.6)	0.2 (0.0, 0.5)	0.1 (-0.3, 0.4)
Item of resource use	**Adalimumab mean £ (95%CR)**	**Placebo mean £ (95%CR)**	**Difference in means (95% CR)**
Adalimumab	10340 (9392, 11245)	1761 (722, 2951)	8579 (7065, 9978)
Methotrexate	778 (638, 910)	637 (462, 816)	141 (-80, 364)
Concomitant medications	540 (379, 743)	249 (92, 471)	291 (11, 549)
In-patient HRGs	2522 (1195, 4135)	2549 (1166, 4267)	-27 (-2198, 2158)
Out-patient HRGs	700 (434, 1011)	692 (294, 1191)	8 (-559, 510)
GP visits	91 (64, 122)	48 (23, 79)	43 (2, 84)
Optician	21 (8, 37)	0	21 (8, 37)
Nurse visits	18 (9, 27)	7 (0, 18)	11 (-3, 23)
Physiotherapist	12 (4, 21)	9 (0, 20)	3 (-10, 15)
Psychologist	3 (0, 6)	6 (1, 14)	-3 (-12, 4)
Total cost	15980 (14213, 17943)	6248 (3922, 8889)	9732 (6562, 12793)

Table 4. Characteristics of patients included in the Bristol cohort[16].

Age at diagnosis	
Mean (SD) [range]	7.9 (3.8) [1-15]
Sex N(%)	
Male	60 (38.2)
Ethnicity N(%)	
Caucasian	122 (78.2)
Asian	6 (3.9)
African	1 (0.6)
Other	6 (3.9)
Unknown	22 (14.1)
Aetiology N(%)	
JIA	91 (58.3)
Idiopathic	66 (42.3)
Type of uveitis	
Anterior	120
Intermediate	28
Panuveitis	8
Posterior	1
Year of diagnosis N(%)	
1997-2000	10 (6.4)
2001-2005	37 (23.6)
2005-2010	61 (38.9)
2011-2015	48 (30.6)
Biologics received N(%) (abatacept, adalimumab, etanercept, infliximab, tocilizumab)	
None	104 (66.2)
One	41 (26.1)
Two	9 (5.7)
Three	2 (1.3)
Five	1 (0.6)
Adalimumab	47 (30.0)
LogMAR > 0.3 at diagnosis N(%)*	
Best eye	12 (9.5)
Worst eye	47 (37.3)
Surgical procedures N **	
Capsulotomy	3
Cataract	15
Glaucoma tube	1
Iridectomy	2
Trabeculotomy	10
Vitrectomy	6

* LogMAR data at diagnosis were available for 126 patients

**A total of 37 procedures out of 268 observations

Table 5. Sensitivity analysis results

	Costs			QALYs			ICER
Univariate sensitivity analysis	ADA + MTX	MTX	Incre-mental	ADA + MTX	MTX	Incre-mental	
Base-case*	£70,719	£31,403	£39,316	8.60	8.29	0.30	£129,025
(i) Proportion administered adalimumab beyond 18-months							
Reduced to 0.23, reflecting the observed value	£51,304	£31,403	£19,900	8.44	8.29	0.15	£131,511
(ii) Duration of adalimumab treatment							
Adalimumab treatment for 18-months only	£45,504	£31,403	£14,101	8.40	8.29	0.11	£133,656
Adalimumab treatment for 18-months + 10 years	£120,262	£31,403	£88,858	8.99	8.29	0.70	£127,646
(iii) Adherence to treatment							
Adalimumab adherence based on vials issued (111%)	£74,011	£31,175	£42,835	8.60	8.29	0.30	£140,576
Adalimumab adherence based on accountability logs (94%)	£68,800	£31,536	£37,264	8.60	8.29	0.30	£122,291
Adherence based on patient diaries: Adalimumab (83%), MTX (adalimumab group) (61%), MTX (placebo group) (50%)	£59,896	£24,638	£36,258	8.60	8.29	0.30	£115,708
(iv) Time horizon of analysis							
18-months	£16,336	£1,962	£14,374	1.36	1.25	0.11	£136,751
(v) Price of adalimumab							
25% reduction in the price of adalimumab	£56,665	£27,821	£28,844	8.60	8.29	0.30	£94,661
50% reduction in the price of adalimumab	£48,865	£28,361	£20,504	8.60	8.29	0.30	£67,288
(vi) Visual impairment rates							
Adalimumab:Placebo VI proportions High:Low	£70,864	£31,147	£39,716	8.60	8.29	0.30	£130,586
Adalimumab:Placebo VI proportions Low:High	£70,574	£31,659	£38,915	8.60	8.29	0.31	£127,471
All placebo-group participants transition to VI state	£70,719	£45,224	£25,495	8.60	8.27	0.32	£78,524
All adalimumab patients transition to no VI and all placebo patients transition to VI and remain in those states	£68,722	£50,902	£17,820	8.60	8.26	0.34	£53,072
(vii) Discount rate							

No discounting	£77,634	£36,743	£40,621	9.88	9.57	0.32	£128,886

Two-way sensitivity analyses	**Incremental cost-effectiveness ratio (per QALY gained)**			
Cost of adalimumab (% of base-case)	100%	75%	50%	25%
(i) Disutility in VI (% of base-case)				
Base-case disutility*	£129,025	£94,661	£67,288	£39,916
200%	£128,860	£94,540	£67,202	£39,864
300%	£128,695	£94,419	£67,116	£39,813
400%	£128,531	£94,298	£67,030	£39,763
500%	£128,367	£94,178	£66,945	£39,712
(ii) Progression of adalimumab patients to VI (% of base-case)				
Base-case progression*	£129,025	£94,661	£67,288	£39,916
10%	£128,366	£94,029	£66,678	£39,327
25%	£127,362	£93,067	£65,749	£38,431
50%	£125,645	£91,422	£64,161	£36,900
75%	£123,874	£89,724	£62,521	£35,319
100%	£122,044	£87,970	£60,829	£33,687

*In the base-case analysis, with a 18-month plus 10 year time horizon, all patients in the adalimumab group received treatment according to protocol (full adherence) for a total of 18-months plus 3 years (54 months). ADA – adalimumab; MTX – methotrexate; VI – visual impairment

Figure 1: Model structure

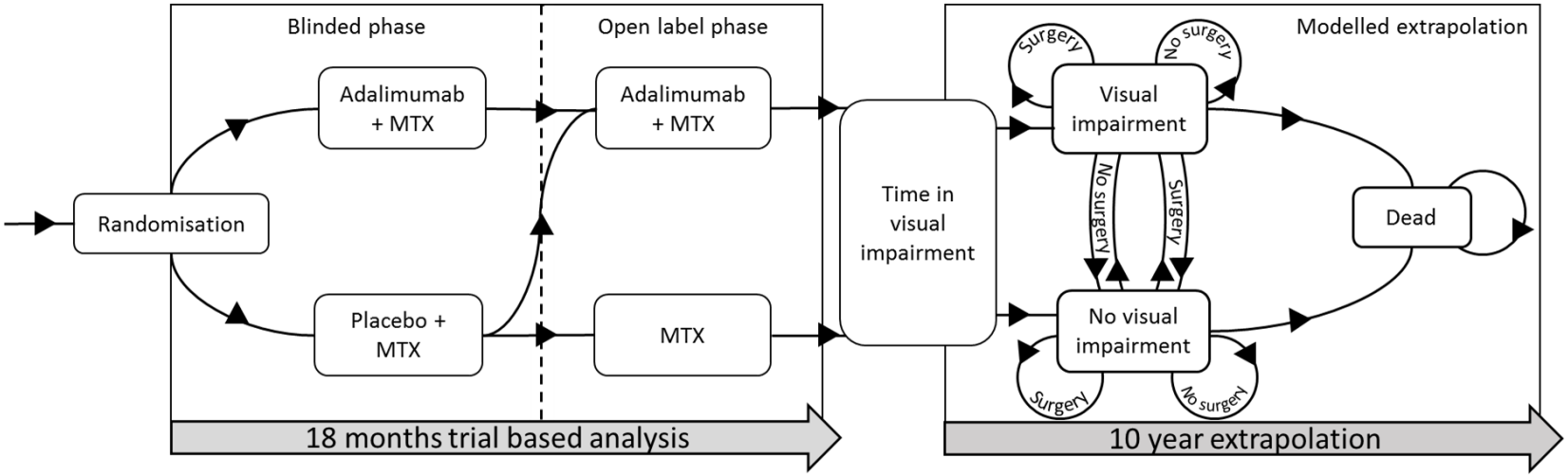

Figure 2: Cost-effectiveness plane