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Abstract

Adalimumab in combination with methotrexate for refractory uveitis associated with juvenile idiopathic arthritis: a RCT

Athimalaipet V Ramanan,[1,2]* Andrew D Dick,[3,4,5] Ashley P Jones,[6] Dyfrig A Hughes,[7] Andrew McKay,[6] Anna Rosala-Hallas,[6] Paula R Williamson,[6] Ben Hardwick,[6] Helen Hickey,[6] Naomi Rainford,[6] Graeme Hickey,[6] Ruwanthi Kolamunnage-Dona,[6] Giovanna Culeddu,[7] Catrin Plumpton,[7] Eifiona Wood,[7] Sandrine Compeyrot-Lacassagne,[8] Patricia Woo,[8] Clive Edelsten[8] and Michael W Beresford[9,10] on behalf of the SYCAMORE Study Group

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Background: Children with juvenile idiopathic arthritis (JIA) are at risk of uveitis. The role of adalimumab (Humira®; AbbVie Inc., Ludwigshafen, Germany) in the management of uveitis in children needs to be determined.

Objective: To compare the efficacy, safety and cost-effectiveness of adalimumab in combination with methotrexate (MTX) versus placebo with MTX alone, with regard to controlling disease activity in refractory uveitis associated with JIA.

Design: This was a randomised (applying a ratio of 2 : 1 in favour of adalimumab), double-blind, placebo-controlled, multicentre parallel-group trial with an integrated economic evaluation. A central web-based system used computer-generated tables to allocate treatments. A cost–utility analysis based on visual acuity was conducted and a 10-year extrapolation by Markov modelling was also carried out.

Setting: The setting was tertiary care centres throughout the UK.

Participants: Patients aged 2–18 years inclusive, with persistently active JIA-associated uveitis (despite optimised MTX treatment for at least 12 weeks).

Interventions: All participants received a stable dose of MTX and either adalimumab (20 mg/0.8 ml for patients weighing < 30 kg or 40 mg/0.8 ml for patients weighing ≥ 30 kg by subcutaneous injection every 2 weeks based on body weight) or a placebo (0.8 ml as appropriate according to body weight by subcutaneous injection every 2 weeks) for up to 18 months. A follow-up appointment was arranged at 6 months.

Main outcome measures: Primary outcome – time to treatment failure [multicomponent score as defined by set criteria based on the Standardisation of Uveitis Nomenclature (SUN) criteria]. Economic outcome – incremental cost per quality-adjusted life-year (QALY) gained from the perspective of the NHS in England and Personal Social Services providers. Full details of secondary outcomes are provided in the study protocol.

Results: A total of 90 participants were randomised (adalimumab, $n = 60$; placebo, $n = 30$). There were 14 (23%) treatment failures in the adalimumab group and 17 (57%) in the placebo group. The analysis of the data from the double-blind phase of the trial showed that the hazard risk (HR) of treatment failure was significantly reduced, by 75%, for participants in the adalimumab group (HR 0.25, 95% confidence interval 0.12 to 0.51; $p < 0.0001$ from log-rank test). The cost-effectiveness of adalimumab plus MTX was £129,025 per QALY gained. Adalimumab-treated participants had a much higher incidence of adverse and serious adverse events.

Conclusions: Adalimumab in combination with MTX is safe and effective in the management of JIA-associated uveitis. However, the likelihood of cost-effectiveness is < 1% at the £30,000-per-QALY threshold.

Future work: A clinical trial is required to define the most effective time to stop therapy. Prognostic biomarkers of early and complete response should also be identified.

Trial registration: Current Controlled Trials ISRCTN10065623 and European Clinical Trials Database number 2010-021141-41.

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List of abbreviations

AC	anterior chamber
ACR	American College of Rheumatology
A&E	accident and emergency
AE	adverse event
AIC	Akaike information criterion
CHAQ	Childhood Health Assessment Questionnaire
CHQ	Childhood Health Questionnaire
CI	confidence interval
CR	credible range
CRF	case report form
CTRC	Clinical Trials Research Centre
DIC	deviance information criterion
DMARD	disease-modifying antirheumatic drugs
GFR	glomerular filtration rate
GP	general practitioner
HR	hazard ratio
HRG	Healthcare Resource Group
HUI	Health Utilities Index
HUI2	Health Utility Index Mark 2
HUI3	Health Utility Index Mark 3
ICER	incremental cost-effectiveness ratio
IDSMC	Independent Data and Safety Monitoring Committee
IMP	investigational medicinal product
IOP	intraocular pressure
ITT	intention to treat
JADAS	Juvenile Arthritis Disease Activity Score
JIA	juvenile idiopathic arthritis
LMM	linear missed model
logMAR	logarithm of the minimum angle of resolution
MTX	methotrexate
PAS	patient administration systems
PhS	physical subscale
PLICS	patient-level information and costing systems
PsS	psychosocial subscale
QALY	quality-adjusted life-year
RF	rheumatoid factor
RR	relative risk
SAE	serious adverse event
SAP	statistical analysis plan
SAS PROC	Statistical Analysis Systems Procedure
SD	standard deviation
SE	standard error
SUN	Standardisation of Uveitis Nomenclature
SYCAMORE	a randomised controlled trial of the clinical effectiveness, SafetY and Cost-effectiveness of Adalimumab in Combination with MethOtRExate for the treatment of juvenile idiopathic arthritis associated uveitis
TMG	Trial Management Group
TNF-α	tumour necrosis factor alpha
TSC	Trial Steering Committee
VI	visual impairment

Plain English summary

Juvenile idiopathic arthritis (JIA) is one of the most common rheumatic diseases in children and young people, who are at risk of developing inflammation in an area of the eye called the uvea (called uveitis).

The purpose of the study was to look at how effective the use of adalimumab in combination with methotrexate (MTX) is compared with using MTX alone to treat JIA-associated uveitis.

A total of 90 children (aged 2–18 years) taking MTX with JIA-associated uveitis took part in the study.

If the inflammation in a patient's eye or eyes was not getting better during the 18 months, the patient was told to stop taking the study drug.

It was found that those patients who were taking placebo and MTX in the trial stopped taking the study drug sooner than those who were taking adalimumab and MTX. This means that adalimumab and MTX was better at treating uveitis than MTX alone.

It was found that more patients taking adalimumab and MTX together either reduced or stopped taking topical steroids than the patients taking placebo and MTX.

It was found that patients taking adalimumab and MTX together experienced more side effects than those taking placebo with MTX. However, these were expected based on what was already known about adalimumab's side effects.

An economic evaluation was conducted to estimate whether or not adalimumab would represent value for money for the NHS for this condition. This included long-term effects based on information about patients' clarity of vision. The analysis showed that adalimumab may not be cost-effective, as the additional costs of treatment may not be justified by the benefits.

The final results show that although adalimumab used in combination with MTX does help to treat patients with JIA and uveitis, it may not represent good value for the NHS.

Scientific summary

Background

Juvenile idiopathic arthritis (JIA) is the most common paediatric rheumatic disease. Children with JIA are at significant risk of inflammation of the uvea (uveitis). Approximately 12–38% of patients with JIA develop uveitis within 7 years following the onset of arthritis. Despite current screening and therapeutic options, up to 15% of children with JIA-associated uveitis may develop bilateral visual impairment and be certified legally blind.

Experimental models of autoimmune uveitis demonstrate that tumour necrosis factor alpha (TNF-α) plays a pivotal role in pathogenesis, which is borne out in the treatment of adult uveitis and paediatric case series. Adalimumab (Humira®; AbbVie Inc., Ludwigshafen, Germany) is a fully human anti-TNF-α monoclonal antibody. A multicentre randomised, double-blind, parallel-group trial has shown significant benefit in children with active rheumatoid arthritis.

The randomised controlled trial of the clinical effectiveness, SafetY and Cost-effectiveness of Adalimumab in Combination with MethOtRExate for the treatment of juvenile idiopathic arthritis associated uveitis (SYCAMORE) was conducted to assess the role of adalimumab in the treatment of methotrexate (MTX)-refractory JIA-associated uveitis.

Aims and objectives

The primary objective of the trial was to compare the clinical effectiveness of adalimumab in combination with MTX versus placebo with MTX alone, with regard to controlling disease activity in refractory uveitis associated with JIA.

The secondary objectives of the trial were to:

- evaluate short-term safety and tolerability of adalimumab in combination with MTX versus MTX alone, with regard to ocular complications of treatment, adverse events (AEs) and laboratory assessments
- determine quality of life and cost-effectiveness of adalimumab in combination with MTX versus MTX alone in severe uveitis associated with JIA
- determine the clinical effectiveness of adalimumab in combination with MTX versus MTX alone, with regard to underlying JIA disease activity
- determine the durability and magnitude of adalimumab efficacy response in sustaining inactive disease and achieving complete clinical remission
- determine the long-term safety of adalimumab in combination with MTX versus MTX alone
- assess the efficacy of treatment with adalimumab to permit concomitant medication reduction, in particular regional and parenteral steroids
- develop a fully consented, trial-related tissue bank for subsequent investigation.

Methods

Study design

This was a randomised, parallel-group, double-blind, placebo-controlled, multicentre clinical trial that compared the effects of adalimumab in combination with MTX with placebo in combination with MTX in participants with active uveitis in association with JIA refractory to MTX monotherapy.

Participants were randomised in a ratio of 2 : 1 (in favour of adalimumab) to receive up to 18 months of the randomised treatment. Once treatment had stopped, participants were followed up for a further 6 months. The primary outcome (treatment failure) was assessed by a blinded assessor at each scheduled or unscheduled visit.

The trial also included an economic evaluation to estimate the incremental cost per quality-adjusted life-year (QALY) with adalimumab in addition to MTX, versus MTX alone.

Eligibility criteria

Children and adolescents aged 2–18 years with active JIA-associated uveitis, despite stable MTX treatment for at least 12 weeks, were eligible for randomisation.

Exclusion criteria were previous exposure to adalimumab, previous exposure to another biologic (within five half-lives), receipt of more than six topical glucocorticoid drops per eye per day and receipt of prednisone (or equivalent) at a dose exceeding 0.2 mg/kg of body weight per day.

Recruitment

The trial took place in 17 centres throughout the UK, 14 of which randomised at least one participant.

Randomisation and blinding

Participants were randomised in a 2 : 1 ratio (in favour of adalimumab); randomisation sequences were computer-generated, stratified by centre.

Participants, investigators and study personnel were all blinded to the study medication that the participant received. Pharmacy department staff were not blinded to the study medication that the participant received.

Outcome measures

Primary outcome

The primary end point of the study was ‘time to treatment failure’. ‘Treatment failure’ was defined by the presence of one or more of the following factors:

- Anterior segment inflammatory score grade [Standardisation of Uveitis Nomenclature (SUN) criteria] –
  - two-step increase from baseline in SUN cell activity score (anterior chamber cells) over two consecutive readings
  - sustained non-improvement with entry grade of ≥ 3 for two consecutive readings
  - only partial improvement (1+ grade) or no improvement from baseline, with development of other ocular comorbidities (defined below) that are sustained
  - worsening of existing (on enrolment) ocular comorbidities (defined below) after 3 months
  - sustained scores recorded at entry grade, measured over two consecutive readings (grade 1 or 2) and still present after 6 months of therapy.

In addition, following at least 3 months of therapy, treatment failure was met if any of the following factors were met:

- Use of concomitant medications – at any time, requirement for concomitant medications in a manner outside the predefined acceptable criteria or for any of the concomitant medications not allowed.
- Intermittent or continuous suspension of study treatment (adalimumab or placebo) for a cumulative period of longer than 4 weeks.
- Ocular comorbidities, defined as:

  i. disc swelling and/or cystoid macular oedema (as gauged clinically and when possible by optical coherence tomography evidence)
  ii. raised intraocular pressure (IOP) (> 25 mmHg) sustained over two consecutive visits (not responding to a single ocular hypotensive agent)
  iii. hypotony (< 6 mmHg) sustained over two consecutive visits
  iv. development of an unexplained reduction in vision over two consecutive visits of 0.3 logarithm of the minimum angle of resolution (logMAR) units (in the event of cataracts, participants will remain in the trial; if cataract surgery is required, failure will still remain as described in end points above)

Please note that an IOP of ≥ 25 mmHg or < 6 mmHg was an exclusion criterion at baseline. Ocular comorbidities (i)–(iv) could be developed during follow-up only; (i) may worsen based on the existing (on enrolment) ocular comorbidity.

Secondary outcomes

- Number of participants failing treatment.
- Incremental cost-effectiveness of adalimumab added to MTX, compared with MTX alone.
- Health status according to the multiattribute Health Utility Index Mark 3 (HUI3).
- Safety, tolerability and compliance defined as follows:

  - AEs and serious adverse events (SAEs)
  - laboratory parameters (haematological and biochemical analysis and urinalysis)
  - participant diaries and dosing records determined tolerability and compliance throughout the trial treatment period.

- Use of corticosteroids over the duration of the study period and throughout follow-up, including the following:

  - total oral corticosteroid dose
  - reduction and reduction rate of systemic corticosteroid dose from entry dose
  - topical corticosteroid use (frequency) compared with use at time of entry
  - need for pulsed corticosteroid.

- Optic and ocular outcomes, defined as follows:

  - number of participants with disease flares (defined by worsening based on SUN criteria) following a minimum of 3 months of disease control
  - number of participants with disease flares within the first 3 months of the study
  - visual acuity as measured by age-appropriate logMAR assessment
  - number of participants with resolution of associated optic nerve or macular oedema [as assessed by slit lamp biomicroscopy or optical coherence tomography (when available)]
  - number of participants with disease control (defined as zero cells with topical treatment for 3 and 6 months)
  - number of participants entering disease remission (defined as zero cells without topical treatment for 3 and 6 months)
  - duration of sustaining inactive disease (zero cells with or without topical treatment).

- Quality-of-life assessments [as assessed via the Childhood Health Questionnaire (CHQ) and Childhood Health Assessment Questionnaire (CHAQ)].
- American College of Rheumatology (ACR) Pedi core set criteria at ACR 30, 50, 70, 90 and 100 levels.
- Number of participants with disease flares, in remission on and/or off medication, related to their JIA and with minimum disease activity.
- Number of participants requiring change in biological and/or disease-modifying antirheumatic drug therapy for arthritis due to failure to respond.
- Juvenile Arthritis Disease Activity Score.

Sample size

The total target number of participants was 114 (adalimumab, $n = 76$; placebo with MTX, $n = 38$).

Statistical methods

Primary and secondary outcome data were analysed following the intention-to-treat (ITT) principle. Safety analyses included participants' data if they had received at least one dose of the randomised treatment.

The statistical analysis plans were developed prior to the analyses being conducted.

The primary outcome was 'time to treatment failure' and was analysed at two planned interim analyses; the final analysis used Kaplan–Meier curves and the log-rank test. Nine predefined sensitivity analyses were conducted to test the robustness of the primary analyses to different assumptions.

The secondary outcomes were analysed using the following methods: binary outcomes were analysed using the chi-squared test, time-to-event data and longitudinal data were analysed using joint modelling, time-to-event data with competing risks were analysed using a competing risk model, continuous data were analysed using *t*-tests or random intercept models and count data were analysed using Poisson regression.

Economic analysis

The economic analysis adopted the perspective of the NHS in England and Personal Social Services providers. Resource use was estimated using questionnaires and via medical records, and utilities were estimated via the HUI3 multiattribute utility scoring system. Costs were based on 2016 prices, and both costs and QALYs were discounted at 3.5% after the first year. Missing utility data were handled using multiple imputation. Costs and QALYs were analysed using an instrumental variable regression approach to account for patients having access to adalimumab during the open-label phase of the trial. A trial-based evaluation, based on the ITT population, was extrapolated by 10 years using a Markov model in order to assess the long-term costs and consequences of adalimumab treatment. The primary outcome of the economic evaluation was the incremental cost per QALY with adalimumab in addition to MTX versus MTX alone. Probabilistic sensitivity analyses assessed the impact of parameter uncertainty, and scenario analyses were conducted to assess the impact of varying (1) the proportion of patients continuing adalimumab after the end of the study; (2) the duration of post-study access to adalimumab; (3) patient adherence to adalimumab and MTX; (4) the time horizon of analysis; (5) the unit price of adalimumab; (6) visual impairment rates, using the most and least favourable combinations; and (7) the discount rate of future costs and benefits.

Results

Recruitment to the trial was halted based on the results of the second interim analysis of the trial data. These data showed that there was significant evidence that adalimumab was more effective than placebo. The Independent Data and Safety Monitoring Committee (IDSMC) made the recommendation to stop recruitment and unblind the participants who were on trial treatment at that time. Participants who were on placebo stopped taking their randomised treatment and entered the follow-up period of the trial; participants who were on adalimumab continued with their treatment as per the protocol.

The trial had three distinct phases: the double-blind phase of the trial refers to the period of time that participants were on treatment prior to the IDSMC recommending that unblinding of allocations should take place; the open-label phase of the trial refers to the period of time that participants were on treatment following the IDSMC recommendation to unblind treatment allocations (this phase of the trial only contained participants who were on adalimumab); and the follow-up phase of the trial is the period of time that followed discontinuation of treatment.

The total number of participants analysed was 90 (adalimumab, $n = 60$; placebo, $n = 30$).

The analysis of the data from the double-blind phase of the trial showed that the hazard of treatment failure was significantly reduced by 75% for participants in the adalimumab group [hazard ratio (HR) 0.25, 95% confidence intervals (CI) 0.12 to 0.51; $p < 0.0001$ from log-rank test]. Additional data collected during the open-label phase of the trial continued to support this conclusion for the integrated analysis of the double-blind and open-label data. The results of the sensitivity analyses showed that the conclusions of the primary analysis were robust to changes that were made. These results all remained highly statistically significant.

The results of the analysis of the secondary outcomes strengthen the evidence to support the effectiveness of adalimumab over placebo.

Adalimumab-treated patients had a much higher incidence of AEs and SAEs. However, this difference was not deemed to be clinically significant and the differences observed between the adalimumab and placebo groups in terms of the frequency of AEs and SAEs, or for the laboratory parameters, were as expected for this population. Data collected during the follow-up period for laboratory parameters continued to show no clinically significant differences between the two treatment groups.

The total costs associated with adalimumab treatment over the time horizon of the 18-month trial plus 10-year extrapolation were £70,951 [95% credible range (CR) £45,204 to £123,764] The corresponding costs of the placebo arm were £31,587 (95% CR £5308 to £83,320). Total mean QALYs were 8.60 (95% CR 8.00 to 9.19) and 8.29 (95% CR 7.42 to 9.17) for the adalimumab and placebo arms, respectively. The incremental cost-effectiveness ratio (ICER) was £129,025 per QALY gained. In 96% of simulations, adalimumab was both more costly and more effective; however, the probability of cost-effectiveness at the £30,000 per QALY threshold was < 1%.

Conclusions

Adalimumab significantly controlled inflammation and reduced the rate of treatment failure in patients with active uveitis on a stable dose of MTX. Adalimumab-treated patients had a much higher incidence of AEs and SAEs, and the treatment is not cost-effective at the £30,000-per-QALY threshold.

Recommendations for future research

This trial demonstrated effective achievement of inactive disease using a combination of adalimumab and MTX. A clinical trial is now needed to determine which treatment regimen (continuing or stopping adalimumab) will result in shorter time to recurrence of ocular inflammation in patients with quiescent JIA-associated uveitis.

There is also a need to identify effective clinical biomarkers of early and complete response.

Trial registration

This trial is registered as ISRCTN10065623 and European Clinical Trials Database EudraCT number 2010-021141-41.

Funding

Funding for this study was provided by the National Institute for Health Research Health Technology Assessment programme and Arthritis Research UK (grant reference 19612). Two strengths of adalimumab (20 mg/0.8 ml and 40 mg/0.8 ml) and a matching placebo were manufactured by AbbVie Inc. (the Marketing Authorisation holder) and supplied in bulk to the contracted distributor (Sharp Clinical Services, Crickhowell, UK) for distribution to trial centres.

Chapter 1 Introduction

Scientific background

Children with juvenile idiopathic arthritis (JIA), the most common rheumatic disease in children, are at risk of inflammation of the uvea in the eye (uveitis). Overall, 20–25% of all paediatric uveitis is associated with JIA.[1,2] Several major risk factors are known for the development of uveitis in JIA, including oligoarticular pattern of arthritis, onset of arthritis at < 7 years of age and antinuclear antibody positivity.[3] Generally, in the initial stages of mild to moderate inflammation, the uveitis is entirely asymptomatic; therefore, current practice is to screen all children with JIA regularly for uveitis. Between 12% and 38% of patients with JIA will develop uveitis in the initial 7 years following the onset of arthritis.[4,5] Structural complications are present in 30–50% of children with JIA-associated uveitis at diagnosis.[6] Importantly, 50–75% of those children with severe uveitis will eventually develop visual impairment secondary to ocular complications including cataracts, glaucoma, band keratopathy and macular pathology.[7–9] Defining the severity of inflammation and structural complications in uveitis patients can now be more consistently described following Standardisation of Uveitis Nomenclature (SUN) guidelines.[10] These guidelines allow incorporation into randomised controlled trials and cohort studies.[10]

Poor prognosticators of poor visual acuity include structural changes at presentation, need for intraocular surgery, posterior segment inflammation, abnormal intraocular pressure (IOP) and the failure to maintain long-term disease control as marked by persistent anterior chamber (AC) cell scores of ≥ 1+.[6–8,11] Despite current screening and therapeutic options (pre biologics), some 10–15% of children with JIA-associated uveitis may eventually develop bilateral visual impairment and will be certified legally blind.[12,13] It is, therefore, critical to find more effective therapeutic interventions.

Rationale for research

Methotrexate (MTX) is well established as the first-line disease-modifying agent in the management of JIA.[14,15] Topical corticosteroids are among the current approaches to treatment of mild JIA-associated uveitis. In children with moderate to severe JIA-associated uveitis, MTX is also effective.[16–18] However, there have been no prospective randomised placebo-controlled trials of MTX or corticosteroid regimens for JIA-associated uveitis.

A systematic review of the evidence of the use of MTX in JIA is restricted to joint involvement[14] and does not include paediatric uveitis. Despite the scarce evidence, MTX has become the mainstay of treatment for JIA-uveitis.[19] However, up to 15–50% of children will have refractory uveitis in spite of optimal therapy with MTX.[16–18] In a small study,[20] some 30% of patients started on MTX for JIA-associated uveitis did not achieve disease control during the first year of therapy and, even when remission was achieved with MTX, nearly 70% of patients will later relapse, suggesting that only 4 out of 22 (18%) patients achieved total remission.[13] In a Dutch study, only 12% were found to be in total remission 5 years after starting MTX.[20] In small, retrospective case series, other agents including ciclosporin and mycophenolate mofetil have been shown to be of partial benefit in controlling JIA-uveitis.[21,22] However, there is little evidence that they rescue MTX-refractory patients and their use is restricted because of intolerability and adverse reactions. Neither ciclosporin nor mycophenolate mofetil is very effective in controlling joint manifestations of JIA in children.[19]

More recently, animal models and corroborative human evidence[23] support the role of tumour necrosis factor alpha (TNF-α) in the aetiopathogenesis of uveitis and, moreover, the potential value of its inhibition as a therapeutic intervention.[24] Studies on experimental models of autoimmune uveitis have demonstrated

that TNF-α plays a pivotal role in pathogenesis of intraocular inflammation,[23] which has been borne out in treatment of adult uveitis.[24] In mouse models of anterior uveitis, deleting the TNF p55 receptor alone is as effective as combined tumour necrosis factor p55 and p75 knockout animal in demonstrating reduced ocular inflammation,[25] equivalent to the effect of tumour necrosis factor p55 fusion protein.[26] In an animal model of uveitis, infliximab reduced disease severity,[27] albeit at doses of 20 mg/kg.

Translating this to humans, several case series have been published demonstrating the efficacy of infliximab and adalimumab (Humira®; AbbVie Inc., Ludwigshafen, Germany) in the treatment of severe refractory uveitis in adults and children.[28–33] In contrast, etanercept has been reported not to halt the onset of uveitis or be more effective than placebo,[34,35] and is less effective than infliximab in treating JIA-uveitis.[31,36,37] There are a number of reports of new-onset uveitis associated with etanercept use in JIA.[38] An adverse events (AEs) register-based study examining these cases determined that, although the frequency was greater for etanercept than for infliximab or adalimumab ($n = 20$, 4 and 2 cases, respectively), causality could not be established.[39] Etanercept is not considered to be effective in treating intraocular inflammation.[31]

Intervention

Adalimumab is a fully human monoclonal antibody, engineered by gene technology that uses site-directed mutagenesis to enhance its binding efficiency to TNF-α. It does not contain non-human or artificial protein sequences. Adalimumab binds only to TNF-α and has an elimination half-life of approximately 2 weeks. The antibody has been studied extensively in vitro as well as in vivo and in animal toxicology experiments. A clinical trial of adalimumab as monotherapy or in combination with MTX in adult subjects with rheumatoid arthritis showed a significant clinical response.[40] In children with JIA, a multicentre randomised, double-blind stratified parallel-group trial has shown a significant benefit in children with active arthritis: disease flares (the primary end point) occurred in a significantly lower percentage of those receiving adalimumab than of those receiving placebo [13 of 30 (43%) vs. 20 of 28 (71%); $p = 0.03$].[41]

Studies in paediatric non-infectious uveitis have shown very promising results with adalimumab, with 21 out of 26 eyes from 14 children with JIA- or idiopathic-uveitis showing improvement in inflammation.[42] In another retrospective case series of 18 paediatric patients with uveitis, 88% had a substantial decrease in ocular inflammation and adalimumab showed corticosteroid-sparing potential.[28]

At the time of starting the randomised controlled trial of the clinical effectiveness, SafetY and Cost-effectiveness of Adalimumab in Combination with MethOtRExate for the treatment of juvenile idiopathic arthritis associated uveitis (SYCAMORE), there were no prospective studies of efficacy and safety of anti-TNF-α agents in JIA-associated uveitis, or of their cost-effectiveness. In the randomised controlled trial of adalimumab in JIA that demonstrated efficacy and supported its safety, the most commonly reported AEs were infections and injection-site reactions.[41] Serious adverse events (SAEs) that were considered to be possibly related to the study drug by the investigator occurred in 14 patients. Seven of these included one case of bronchopneumonia, one of herpes simplex infection, one of pharyngitis and one of pneumonia, and two cases of herpes zoster infection. In this trial, there were no deaths, malignant conditions, opportunistic infections, cases of tuberculosis, demyelinating diseases or lupus-like reactions.[41] The fixed-dose model of fortnightly 20 mg of adalimumab (for 16 weeks) for children weighing < 30 kg and 40 mg for children weighing ≥ 30 kg selected for this trial is based on the data generated in the previously mentioned trial using the same dosing regimen.[41]

Although there are no published economic evaluations of JIA-associated uveitis, there are a number of economic evaluations of anti-TNF-α agents (including adalimumab) in JIA. These are of interest but limited applicability, because they are not directly transferable for estimating the cost-effectiveness of treatment in the context of uveitis management. The only study to adopt a costing perspective of the NHS in the UK is Shepherd *et al.*,[43] who constructed a cost–utility Markov model to compare abatacept, adalimumab, etanercept and tocilizumab[44–47] in JIA using disease flare as the measure of efficacy. The analysis was based on four economic evaluations of biological disease-modifying antirheumatic drugs (DMARDs) in JIA.

Utility values were sourced from the Prince *et al.* study.[47] The incremental cost-effectiveness ratios (ICERs) for adalimumab, etanercept, tocilizumab and abatacept, versus MTX, were £38,127, £32,256, £38,656 and £39,536 per quality-adjusted life-year (QALY), respectively. The model results were found to be most sensitive to changes in utility values and the differences in cost-effectiveness of the biological DMARDs were primarily due to differences in drug acquisition cost. A limitation common to economic analyses in JIA is the challenge of obtaining valid utility scores and extrapolation of effects over a longer time period, both of which can significantly influence cost-effectiveness. A recent economic evaluation of adalimumab and dexamethasone intravitreal implant (Ozurdex®; Allergan Ltd, Marlow, UK) for treating non-infectious intermediate uveitis, posterior uveitis or panuveitis in adults indicated that adalimumab was not cost-effective at £94,523 per QALY gained in active uveitis,[48] but these findings may not be generalisable to children with active JIA-associated uveitis. The aim of the economic evaluation as part of the SYCAMORE trial was to assess the cost-effectiveness of adalimumab, based on utility and cost data acquired directly within the trial, and extrapolated using data on representative patients from routine care.

Objectives

The primary objective of the trial was to compare the clinical effectiveness of adalimumab in combination with MTX versus placebo with MTX alone, with regard to controlling disease activity in refractory uveitis associated with JIA.

The secondary objectives of the trial were to:

- evaluate short-term safety and tolerability of adalimumab in combination with MTX versus MTX alone, with regard to ocular complications of treatment, AEs and laboratory assessments
- determine quality of life and cost-effectiveness of adalimumab in combination with MTX versus MTX alone in severe uveitis associated with JIA
- determine the clinical effectiveness of adalimumab in combination with MTX versus MTX alone, with regard to underlying JIA disease activity
- determine the durability and magnitude of adalimumab efficacy response in sustaining inactive disease and achieving complete clinical remission
- determine the long-term safety of adalimumab in combination with MTX versus MTX alone
- assess the efficacy of treatment with adalimumab to permit concomitant medication reduction, in particular regional and parenteral steroids
- develop a fully consented, trial-related tissue bank for subsequent investigation.

Chapter 2 Trial design and methods

Study design

This was a randomised, parallel-group, double-blind, placebo-controlled, multicentre clinical trial that compared the effects of adalimumab in combination with MTX versus placebo in combination with MTX in participants with active uveitis in association with JIA refractory to MTX monotherapy. Participants were randomised applying a ratio of 2 : 1 (in favour of adalimumab), stratified by centre.

Patients with persistently active JIA-associated uveitis (despite optimised MTX treatment for at least 12 weeks) were recruited from tertiary care centres throughout the UK.

A schematic of the study design can be seen in *Figure 1*.

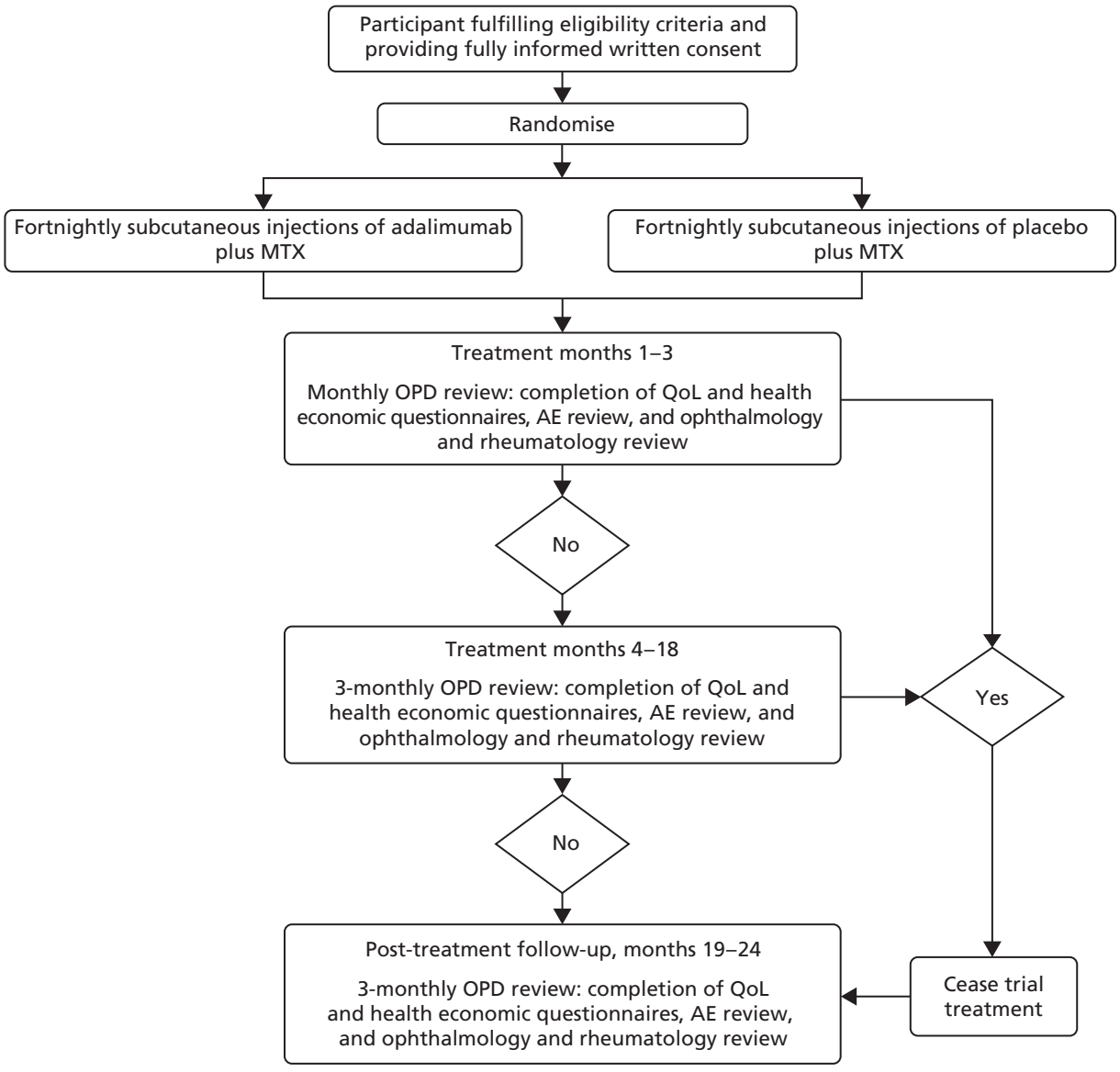


FIGURE 1 The SYCAMORE study design. OPD, outpatient department; QoL, quality of life.

The trial protocol has previously been published in an open access journal.[49]

Trial registration and ethics

The trial was registered on EudraCT on 1 June 2010 (EudraCT number 2010-021141-41) and received Clinical Trials Authorisation from The Medicines and Healthcare products Regulatory Agency on 9 May 2011 (Clinical Trials Authorisation reference number 12893/0228/001). The trial, and all subsequent protocol amendments, were reviewed and authorised by the Medicines and Healthcare products Regulatory Agency.

The trial protocol was not initiated until it had received the favourable opinion of the Main Research Ethics Committee (London – Hampstead Research Ethics Committee 11/LO/0425) on 24 June 2011. It was then reviewed at the research and development offices at participating sites.

The trial and any subsequent amendments were reviewed and approved by the National Research Ethics Service Committee London – Hampstead.

The trial was listed on the International Standard Randomised Controlled Trials Number (ISRCTN) register on the 2 September 2011 (ISRCTN10065623) and adopted onto the Medicines for Children Research Network and co-adopted onto the Ophthalmology portfolio on the 10 May 2011.

Participant inclusion and exclusion criteria

Patients who met the following eligibility criteria were considered for the trial.

Inclusion criteria

- Children and young people aged ≥ 2 and < 18 years who fulfilled the International League of Associations for Rheumatology (ILAR) diagnostic criteria for JIA (all subgroups that had uveitis).
- At the time of trial screening, the participant must have had active anterior uveitis, defined as a 'sustained grade of cellular infiltrate in AC of the SUN criteria[10] grade > 1+ during the preceding 12 weeks of therapy despite MTX and corticosteroid (both systemic and topical) therapy'.[10] The latest date of SUN grade score must have been the date of the screening visit.
- Participants must have failed MTX (minimum dose of 10–20 mg/m^2 once per week, with a maximum dose of 25 mg per participant). The participant must have been on MTX for at least 12 weeks and have been on a stable dose for 4 weeks prior to screening visit. (Omission of a maximum of 2 weeks' MTX treatment within the 12 weeks was acceptable and did not render the patient ineligible, unless they were missed in the 4 weeks prior to the screening visit.)
- No disease-modifying immunosuppressive drugs, other than MTX, in the 4 weeks prior to screening were allowed.
- Written informed consent of adult participant or parent/legal guardian of minor, and assent, when appropriate, must have been received.
- Participant and parent/legal guardian must have been willing and able to comply with protocol requirements.
- Participants of reproductive potential (males and females) must have been willing to use a reliable means of contraception throughout their trial participation. Post-pubertal females must have had a negative serum pregnancy test within 10 days before the first dose of the trial drug.
- Participant must have been able to be randomised and commence trial treatment within 2 weeks of the screening visit.

Exclusion criteria

- Uveitis without a diagnosis of JIA.

- Currently on adalimumab or had previously received adalimumab.
- Have been on other biological agent within previous five half-lives of agent.
- More than six topical steroid drops per eye per day prior to screening (this dose must have been stable for at least 4 weeks prior to screening visit).
- For patients on prednisone or prednisone equivalent, change of dose within 30 days prior to screening.
- For patients on prednisone or prednisone equivalent with a dose > 0.2 mg/kg per day.
- Intra-articular joint injections within 4 weeks prior to screening.
- Any ongoing chronic or active infection (including infective uveitis) or any major episode of infection requiring hospitalisation or treatment with intravenous antibiotics within 30 days or oral antibiotics within 14 days prior to the screening evaluation.
- History of active tuberculosis of < 6 months treatment or untreated latent tuberculosis.
- Participant has history of central nervous system neoplasm, active infection, demyelinating disease, or any progressive or degenerative neurological disease.
- Poorly controlled diabetes or persistently poorly controlled severe hypertension (> 95th percentile for height/age), as deemed by the treating physician.
- Previous history of malignancy.
- Intraocular surgery within the 3 months prior to screening (cataract/glaucoma/vitrectomy).
- Intraocular or periocular corticosteroids within 30 days prior to screening.
- History of ocular herpetic disease.
- Pregnant or nursing female.
- Demonstrations of clinically significant deviations in any of the following laboratory parameters:
    - a platelet count of < 100,000/mm^3
    - a total white cell count of < 4000 cells/mm^3
    - a neutrophil count of < 1000 cells/mm^3
    - aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels of > 2× the upper limit of normal or serum bilirubin > 2× the upper limit of normal
    - a glomerular filtration rate (GFR) of < 90 ml/minute/1.73 m^2 [GFR (ml.minimum/1.73 m^2 body surface area)] = 0.55 × height (cm)/plasma creatinine (mg/dl)
    - a haematocrit of < 24%.
- Having been administered a live or attenuated vaccine within 3 months prior to screening.
- Previous randomisation into SYCAMORE to either arm of the trial.
- An intraocular pressure of < 6 mmHg or > 25 mmHg.
- Intraocular pressure control requiring more than one topical pressure-lowering therapy or requiring systemic acetazolamide.

Recruitment

Recruitment took place in 14 tertiary care centres throughout the UK. Participants were identified through rheumatology and ophthalmology outpatient clinics. Most tertiary care centres also set up referral links with local district general hospitals.

Informed consent

This trial recruited minors and young people aged < 16 years. Informed consent procedures reflected the legal and ethics requirements to obtain valid informed consent for this population. Prior written informed consent was required for all trial participants. In obtaining and documenting informed consent, the investigator complied with applicable regulatory requirements and adhered to good clinical practice and to the ethics principles that have their origin in the Declaration of Helsinki.[50]

Information was provided to potential participants and their families verbally and in writing. All participants had the opportunity to discuss the project with the responsible investigator at site and/or a designated member of the research team. Discussions were supported with detailed written, ethics-approved patient information sheets and consent forms, provided directly to young people able to consent for themselves (defined in statutory instrument 2004 number 1031 as aged ≥ 16 years[51]) and parents/legal guardian of minors (aged < 16 years). Information leaflets appropriate to age and stage of development were provided to minors and their assent was obtained, when appropriate. Careful presentation was made of the known risks of the disease and trial medications and the possible benefits, as well as a detailed explanation of the trial procedures and protocol.

All participants were given the opportunity to ask any questions that may arise and to discuss the study with their surrogates and were given the time to consider the information prior to agreeing to participate.

All of the recruiting investigators were experienced rheumatologists and/or ophthalmologists familiar with imparting information to families and young people. All investigators obtaining consent had attended good clinical practice courses. When potentially eligible minors and young people were identified, they/their parent/the person with parental responsibility were approached by the investigator, or a designated member of the investigating team, and an opportunity was given to understand the objectives of the trial. The treatment schedule and trial visits were in line with standard clinical care, although they were made aware that additional travel may be needed if the trial assessments required they be reviewed at their tertiary centre rather than their local hospital. The potential risks and benefits of the anti-TNF-α agent were discussed, as were treatment failure criteria and what would happen if they chose not to enter the trial or had to withdraw from the trial for any reason. In addition, the rationale for the use of a placebo and the applied randomisation ratio was explained.

The right of the patient (non-minors) or parent/legal guardian (for minors) to refuse consent to participate in the trial without giving reasons was respected. After the patient had entered the trial, the clinician remained free to give alternative treatment to that specified in the protocol, at any stage, if they felt that it was in the best interest of the patient. However, the reason for doing so was recorded and the patient remained within the trial for the purpose of follow-up and data analysis in accordance with the treatment option to which they had been allocated. Similarly, the patient remained free to withdraw at any time from the protocol treatment and trial follow-up without giving reasons and without prejudicing their further treatment.

Adequate time to consider trial entry (generally 24 hours, although it was acknowledged that some patients/families came to a decision sooner) was allowed before written consent of the participant/parent/legal representative was obtained by the responsible clinician or other designated team member (recorded on the signature and delegation log).

Randomisation

Randomisation was undertaken during normal working hours (Monday to Friday, 09.00 to 17.00) by the pharmacy departments of participating centres on receipt of a randomisation request form and prescription from authorised clinicians. Pharmacy personnel verified that these documents were appropriately completed before proceeding.

It was the responsibility of the principal investigator or delegated research staff to:

- notify the pharmacy of potential randomisations so that the pharmacy could ensure that adequate drug supplies were at site
- complete the appropriate trial documents and deliver these to the pharmacy department at their centre in order that the pharmacy could proceed with a randomisation.

Participants were randomised using a secure (24-hour) web-based randomisation system, which was controlled centrally by the Clinical Trials Research Centre (CTRC). Randomisation lists were generated in a 2 : 1 ratio in favour of the active therapy. The lists were produced by an independent statistician (based at CTRC, but otherwise not involved in the trial) in Stata® version 9.2 (StataCorp LP, College Station, TX, USA) using the ralloc command. The randomisation lists were stratified by centre but in order to reduce the predictability of the randomisation sequence, the randomisation numbers were sequential across all sites (rather than within each site) to make it appear that there was no stratification by centre. For smaller sites (i.e. expected recruitment of < 10), a block size of three was used. For larger sites (i.e. expected recruitment of at least 10), random block sizes of three and six were used.

Participant treatment allocation was displayed on a secure webpage and an automated e-mail confirmation was sent to the authorised randomiser.

Description of interventions

All participants received a stable dose of MTX and either adalimumab (20 mg/0.8 ml for participants weighing < 30 kg or 40 mg/0.8 ml for participants weighing ≥ 30 kg) or placebo (0.8 ml, based on body weight) via a subcutaneous injection every 2 weeks for a maximum period of 18 months.

All participants in both arms continued to receive a stable dose of MTX at a minimum dose of 10–20 mg/m^2 and a maximum dose of 25 mg as a non-IMP throughout the 18-month treatment period.

Clinical trial supplies were to be delivered to an investigator site only once the site had been initiated by the CTRC, acting on behalf of the sponsor to ensure full ethics and regulatory approvals had been granted. The size of the shipments to each site were predetermined, based on the participant recruitment target for that individual site. Recruitment was monitored centrally and drug shipment dates tailored accordingly, to ensure that pharmacies held adequate supplies of trial treatment. Pharmacies documented all shipment receipts and provided copies of this documentation to the CTRC. IMP stock was to be received by a designated member of the pharmacy department and stored at 2–8 °C, with temperature monitoring and in accordance with IMP regulations. Records of all shipments were to be kept in the pharmacy site file. All temperature excursions or damage to stock was reported to CTRC, which liaised with AbbVie Inc. for assessment.

The dose of adalimumab or placebo remained the same as at trial entry, regardless of minor fluctuations in weight that may cause a participant to cross the 30-kg threshold for the upper and lower doses.

The first dose was administered by the research/clinical team looking after the participant. Participants, or a family member, were invited to self-administer the study treatment after the first dose and taught how to do this, following the procedures in place within each participating centre. The first self-administered dose was carried out under the supervision of the clinical team, which would ensure that the participant was confident and able to carry out all parts of the procedure appropriately and accurately. The trial provided validated cooler bags for participants to transport their trial medication home. If participants did not want to self-administer the trial medication, then arrangements were put in place, on an individual basis, to ensure that trial medication was administered as prescribed.

Investigational medicinal products were labelled in accordance with regulation 46 SI2004/1031 and the detailed guidance provided in annex 13 of the EU Good Manufacturing Practice (GMP) guide.[51]

Blinding

Participants, investigators, study personnel, the trial co-ordinator, statisticians and data management personnel were all blinded to the trial medication that the participant received. Pharmacy department staff were not blinded to the trial medication that the participant received.

This trial was placebo controlled and all trial assessments were carried out by health professionals, parents/carers and participants without knowledge of treatment allocation. The placebo solution for subcutaneous injection was a clear, colourless solution (matching the adalimumab vial) presented in a single-use vial for subcutaneous injection in volumes of 0.8 ml.

The packaging of the kit for adalimumab and placebo was identical. Each kit consisted of two vials of adalimumab or placebo in an outer carton. The vials of adalimumab and placebo were also identical in appearance.

Treatment allocation was concealed unless knowledge was essential for the ongoing care of the participant. If knowledge of treatment allocation was required by the responsible investigator, the process was to obtain it via the pharmacy department at the respective hospital, which would then complete an unblinding case report form (CRF) and submit this to the CTRC.

All children participating in this study during the active treatment phase of the study were immunosuppressed, in view of their concomitant MTX therapy and/or potential corticosteroid therapy, irrespective of whether they were on adalimumab or placebo. In addition, for the purpose of out-of-hours management of the patient, all participants were presumed to be on anti-TNF-α therapy and managed as such. In this way, in the event of an AE or SAE, such as an intercurrent infection, the treating clinician managed patients presuming them to be on anti-TNF-α therapy. For this reason, if unblinding was deemed necessary, this was carried out via the local pharmacy department following the procedure described below. If out-of-hours unblinding was required, this was accessed via the local pharmacy department's on-call service.

Unblinding of individual participants during trial conduct

Procedures regarding potential unblinding were available for a number of relevant clinical scenarios.

On completion of 18 months of treatment

Although discouraged, it was acceptable to unblind participants on completion of their trial treatment (at 18 months) if this was necessary to enable appropriate ongoing treatment decisions by the participant's clinician.

Early withdrawal from treatment

On early withdrawal from trial therapy, breaking the statistical blind was considered only when knowledge of the treatment assignment was deemed essential for the participant's care by the participant's physician, or a regulatory body. It was considered that it may not always be necessary to know the allocation of these participants.

Investigators were instructed that if simply ceasing trial treatment was a viable option for the participant's care, then it was not necessary for unblinding to occur.

The procedure for unblinding during the course of the trial is set out below. The decision to unblind a single case was made when knowledge of an individual's allocated treatment was essential to enable:

- treatment of SAEs
- administration of another therapy that is contraindicated by the trial treatment
- appropriate ongoing care on cessation of allocated trial therapy.

When possible (during office hours), consent for individual unblinding was made via the trial co-ordinator at CTRC who would seek agreement of one of the lead co-chief investigators (Athimalaipet V Ramanan and Michael W Beresford).

Pharmacy departments were unblinded to the treatment allocations of participants within their centre. It was the principal investigator's responsibility to ensure that all research personnel were aware of contact details for obtaining details of treatment allocation, if this was necessary.

The request for the allocated treatment was made to the local pharmacy department. Only the individual participant was to be unblinded and the following was documented by the pharmacy on the unblinding CRF:

- date the information was needed
- detailed reason for unblinding
- identity of recipients of the unblinding information.

The local investigator ensured that all necessary CRFs to time of unblinding were completed and submitted to CTRC (if possible, completed before unblinding was performed).

All instances of unblinding were recorded and reported in writing to the CTRC by the local investigator, including the identities of all recipients of the unblinding information.

Allocation was not routinely revealed to CTRC personnel.

All instances of inadvertent unblinding were recorded and reported in writing to the CTRC by the local investigator. Reports included:

- date of unblinding
- detailed explanation of circumstances
- recipients of the unblinding information
- action to prevent further occurrence.

Data collection and management

For SYCAMORE, a paper CRF was used to collect participant data at each study visit. The paper CRF was designed by the Trial Management Group (TMG) and CTRC specifically for the study, in line with the trial protocol. Completed paper CRFs were transferred from the trial sites to the CTRC; data were then entered in to a Good Clinical Practice-compliant database (MACRO; Elsevier, Amsterdam, the Netherlands) by trial staff.

The configuration of the database was specific to SYCAMORE: there were built-in validations on certain aspects of the trial data. Any missing or inconsistent data were queried with the site using paper data query forms: query responses were completed by site staff and returned to the CTRC for entry into the database. A full audit trail of changes to the data was maintained.

Outcome measures

Primary outcome

The primary outcome for the trial was 'treatment failure'. This was assessed at each scheduled or unscheduled visit and was defined by one or more of the following:

- Anterior segment inflammatory score grade (SUN criteria[10]). Following at least 3 months of therapy –
    - two-step increase from baseline in SUN cell activity score (AC cells) over two consecutive readings
    - sustained non-improvement with entry grade of ≥ 3 for two consecutive readings

  - only partial improvement (1 grade) or no improvement, from baseline, with development of other ocular comorbidity that is sustained
  - worsening of existing (on enrolment) ocular comorbidity after 3 months
  - sustained scores, as recorded at entry grade, measured over two consecutive readings (grades 1 or 2) still present after 6 months of therapy.

- Use of ineligible concomitant medications: these include medications that are not listed in the prespecified acceptable criteria or those that were not allowed.
- Intermittent or continuous suspension of study treatment (adalimumab/placebo) for a cumulative period of no longer than 4 weeks.

Ocular comorbidities were defined as:

i. disc swelling and/or cystoid macular oedema as gauged clinically, and when possible, by optical coherence tomography evidence
ii. a raised IOP (of > 25 mmHg) sustained over two consecutive visits, not responding to single ocular hypotensive agent
iii. hypotony (of < 6 mmHg) sustained over two consecutive visits
iv. development of unexplained reduction in vision [logarithm of the minimum angle of resolution (logMAR)] over two consecutive visits of 0.3 logMAR units (in the event of cataracts, participants remained in the trial, also if cataract surgery is required. Failure will still remain as described in end points above).

Note that an IOP of $\geq$ 25 mmHg or < 6 mmHg was an exclusion criterion at baseline and ocular comorbidities (i)–(iv) could be developed during follow-up only; (i) may worsen based on the existing (on enrolment) ocular comorbidity.

When a reading was required to be sustained over two consecutive visits to define treatment failure, the time of treatment failure was taken as the second of these readings.

Secondary outcomes

The following secondary outcomes were also recorded during the course of the trial:

- Number of participants failing treatment.
- Incremental cost-effectiveness of adalimumab added to MTX compared with MTX alone, based on:
  - health status according to the multiattribute Health Utility Index Mark 3 (HUI3)
  - resource use, estimated from participant diaries, questionnaires and routine data from patient-level information and costing systems (PLICS).
- Safety, tolerability and compliance, defined as follows:
  - AEs and SAEs
  - laboratory parameters (haematological and biochemical analysis and urinalysis)
  - participant diaries and dosing records determined tolerability and compliance throughout the trial treatment period.
- Use of corticosteroids over the duration of the study period and throughout follow-up, including the following:
  - total oral corticosteroid dose
  - reduction and reduction rate of systemic corticosteroid dose from entry dose
  - topical corticosteroid use (frequency) compared with use at time of entry
  - need for pulsed corticosteroid.

- Optic and ocular outcomes, defined as follows:
  - number of participants with disease flares (defined by worsening based on SUN criteria) following a minimum of 3 months of disease control
  - number of participants with disease flares within the first 3 months of the study
  - visual acuity as measured by age-appropriate logMAR assessment
  - number of participants with resolution of associated optic nerve or macular oedema (as assessed by slit-lamp biomicroscopy or optical coherence tomography, where available)
  - number of participants with disease control (defined as zero cells with topical treatment for 3 and 6 months)
  - number of participants entering disease remission (defined as zero cells without topical treatment for 3 and 6 months)
  - duration of sustaining inactive disease (zero cells with or without topical treatment).
- Quality-of-life assessments [as assessed by the Childhood Health Questionnaire (CHQ)[52] and Childhood Health Assessment Questionnaire (CHAQ)[53]].
- American College of Rheumatology (ACR) Pedi core set criteria[54] at ACR 30, 50, 70, 90 and 100 levels
- Number of participants with disease flares,[55] in remission on and/or off medication,[56] related to their JIA and with minimum disease activity.[57]
- Number of participants requiring change in biological and/or DMARD therapy for arthritis because of failure to respond.
- Participants' score on the Juvenile Arthritis Disease Activity Score (JADAS).[58] The JADAS comprises four components: a physician's global assessment of disease activity, parent/patient global assessment of well-being, active joint count (in 27, 71 or 10 joints) and erythrocyte sedimentation rate.

The outcome 'development of human antihuman antibody to adalimumab determined with samples collected at 1, 6 and 18 months' was removed in version 4.0 of the trial protocol (in substantial amendment 10), because during the trial it was not possible to collect human antihuman antibody samples.

Data collection tools

Quality of life

Quality of life was measured by the use of CHQ[52] and CHAQ.[53] Data collection took place on a monthly basis for the first 3 months, and then 3-monthly until withdrawal from the active phase of trial treatment.

Child Health Assessment Questionnaire

The CHAQ[53] is the most widely used functional measure of disability in JIA, both in routine clinical practice throughout the UK and in clinical trials. Translated into many languages and validated in respective cultures and countries, it is easily completed and scored. It consists of eight domains, enquiring about the child/young person's ability to manage a range of activities of daily living on a 5-point scale. Completion of the questionnaire was checked by staff.

Childhood Health Questionnaire

The CHQ[52] is a generic measure of quality of life used in JIA. It explores a number of important domains including self-esteem, emotional and behavioural difficulties, and family impact. Completion of the questionnaire was checked by staff.

Sample size

Sample size calculations were undertaken using nQuery Advisor software version 4.0 (Statistical Solutions, Saugus, MA, USA).

Details of the original and revised sample size calculations are given below. Sample size revisions were necessary as a result of lower patient availability than expected.

Original trial sample size calculation

The original sample size calculation was based on data on failure rates from 62 patients on MTX in a comparable population provided by Clive Edelsten from Great Ormond Street Hospital for Children NHS Trust (2008). After 3 months, 11 patients had disease control based on grade 0 SUN criteria (18%) and, therefore, based on the trial inclusion criteria, would not be eligible for the trial. At 15 months following the start of treatment with MTX, 23 out of the 51 patients who had failed at 3 months had achieved disease control (45%), leaving 28 patients (55%) who had not. A total of 140 participants (adalimumab, $n = 93$; placebo, $n = 47$) were required to detect a relative reduction of 50% between a failure rate of 60% and 30% with 90% power (to optimise the detection of a significant difference between treatment regimens if one truly exists) at a 5% significance level, using a 2 : 1 randomisation.

The advent of biological therapies in JIA has led international investigators to a paradigm shift in the treatment of JIA and related complications, leading to significantly more ambitious outcomes in clinical trials, including elimination of inflammation and normalisation of short- and long-term function.[15,59] To this end, in JIA, instead of previously accepted clinical outcomes of 30% absolute difference in outcome between active agent and placebo,[60] increasingly significant differences are being expected, with new definitions of response being established for use in clinical trials, such as clinical remission and minimal disease activity.[56,57] Indeed, 40% of patients in the adalimumab-JIA trial were reported as showing an ACR Pedi 100% response (100% response rate) at 2 years.[41]

The clinically relevant outcomes of JIA-uveitis may take years to develop and the relationship between isolated measures of clinical activity and long-term outcomes remains ill-defined. Recent studies do suggest that the length of continuously controlled activity is likely to be of more clinical relevance than short-term improvements in levels of activity.

In view of these factors, as well as the expectation expressed unanimously through consultation with parent representatives in the development of the trial protocol, a minimum of 50% relative difference in failure rate between interventions was set. Based on the nature of the disease (potentially resulting in loss of vision) and a meeting of investigators representing participating centres as well as consumer representatives, and their experience of compliance from current usage of biological therapies in JIA-uveitis, it was estimated that loss to follow-up would be approximately 10%. Therefore, the sample size was increased by approximately 10% to allow for this, giving a total number of 154 participants (adalimumab, $n = 102$; placebo, $n = 52$).

The null hypothesis underlying this trial was that there is no significant difference between adalimumab and placebo in controlling disease activity of JIA-associated uveitis that is unresponsive to MTX therapy.

Revised sample size calculation for the primary outcome

The original sample size calculation had a power of 90%, but given a series of challenges arising, including those that were faced during recruitment, it was proposed by the TMG, and agreed on by the Trial Steering Committee (TSC) and Independent Data and Safety Monitoring Committee (IDSMC), as well as the sponsor and trial funders, to revise this. Reducing power to what is a universally accepted convention of 80% power maintained the status of this trial as an internationally relevant and robust contribution to the evidence base for the safety of this intervention, and was felt to be clinically acceptable. This was both acceptable to patients/families and clinicians, and would enable the sample size to be markedly reduced, and, therefore, more feasible within a reasonable period.

Furthermore, as of September 2013, there had only been one participant who had withdrawn and refused to provide primary outcome data. Therefore, it was reasonable to assume that the original assumption of adding 10% to the sample size calculation to account for missing data could be reduced to 5%.

The total sample size (including 5% drop out) that was required to detect the difference between a placebo proportion of 60% and treatment group proportion of 30% (with 0.05 two-sided significance level) was 114 participants.

Tissue bank

A blood sample collection system was developed, in accordance with Arthritis Research UK's guidelines[61] on detailed clinical and related material banks.

Written information was provided to families for this part of the study and written informed consent (with assent when appropriate) obtained for those who wished to provide blood samples. Participants who did not give consent to provide samples were eligible to take part in the main part of the trial.

Samples have been collected for future analysis and could be used as a resource to investigate the pharmacogenetics, aetiopathogenesis and identification of biomarkers of JIA-associated uveitis, for example. Understanding the genetic basis of age-specific disease processes allows consideration of the unique and rapid period of human development through to adulthood. Pharmacologic modulation of developing gene networks may have unintended and unanticipated consequences that do not become apparent or relevant until later in life. Early predictors of response allow future personalised treatment prescription in children.

Blood samples were collected pre treatment (0 months) and at two time points post treatment (at 3 months and 18 months).

Patient and public involvement

Patient and public involvement (PPI) representatives have been an integral part of SYCAMORE since the initial prioritisation, design stage and funding applications. PPI representatives provided detailed input into all aspects of the protocol design and all subsequent amendments and patient information sheets and consent forms and amendments. The patient information sheets, consent forms and assent forms were reviewed and feedback was given by the Medicine for Children Research Network young person's advisory group. PPI representatives also provided input into any information sent to patients, such as letters to explain the closure of recruitment and the frequently asked questions section on the SYCAMORE website.

Changes to the protocol

Over the course of the whole trial, eight amendments were made to the protocol. These consisted of six non-substantial and 15 substantial amendments. A summary of amendments follows and the full list is reported in the trial protocol.

Version 1.0 (25 February 2011) amended to version 1.1 (8 September 2011)

The first amendment to the protocol made corrections to typographical errors in the original protocol.

Version 1.1 (8 September 2011) amended to version 2.0 (30 September 2011)

The second amendment added clarification to the tissue bank section; added clarification to the primary end point section and introduced an end point for the intermittent or continuous suspension of adalimumab/placebo; added clarification that patients cannot have previously received adalimumab; added two further exclusion criteria points relating to IOP; removed the limit on how many times patients can be screened; added a window for adalimumab/placebo injections; added clarification of topical treatment after 3 months of trial treatment; changed the dose range of allowed MTX to 10–20 mg/m^2; and added clarification of treatment timelines and visit windows.

Version 2.0 (30 September 2011) amended to version 3.0 (25 April 2013)

The third amendment to the protocol made changes to the monthly visit windows to allow a window of 7 days; clarified in the table of assessments that the Clinical Service Receipt Inventory (CSRI) questionnaire is completed at baseline only; changed the timeline for tuberculosis assessment from 4 weeks to 12 weeks prior to baseline; and clarified that haematological and biochemical samples taken at screening can be used for the baseline visit.

Version 3.0 (25 April 2013) amended to version 4.0 (25 September 2013)

The fourth amendment to the protocol reduced the sample size from 154 to 114 participants and the duration of follow-up post treatment from 18 months to 6 months; changed the assessment of reduction of vision from number of letters to logMAR units; added clarification to inclusion and exclusion criteria; added systemic acetazolamide to the list of medication not permitted; removed the requirement for collection of human antihuman antibody samples; window for MTX administration added change to the collection of routine PLICS data; and added clarification on the definition of 'end of trial'.

Version 4.0 (25 September 2013) amended to version 4.1 (11 August 2014)

The fifth amendment to the protocol added text to say that the IDSMC may request an interim analysis of the primary outcome.

Version 4.1 (11 August 2014) amended to version 5.0 (11 August 2014)

The sixth change to the protocol clarified that patients are classed as withdrawals and not treatment failures if they miss > 4 weeks of MTX treatment; added further clarification that haematological and biochemical blood results can be used for baseline (if taken at screening) only if assessment was completed within the previous 15 days; added clarification to tissue bank samples to state that the 3-month samples should be taken at the very next opportunity if not taken at 3 months and that the 18-month samples should be taken if patient ends treatment early.

Version 5.0 (11 August 2014) amended to version 6.0 (17 April 2015)

The seventh change to the protocol stated that the blinded phase of the trial had been stopped and that all patients on adalimumab would continue to be treated but that patients on placebo would stop treatment and proceed to follow-up.

Version 6.0 (17 April 2015) amended to version 6.1 (14 July 2016)

The eighth change to the protocol clarified that JADAS was a secondary outcome and clarified SAE reporting procedures.

Compliance with intervention

Participant diaries and dosing records determined tolerability and compliance throughout the trial period. The parent/guardian of a participant maintained a diary for all trial and other medications that were administered outside the trial visit (i.e. at home). In the diary, the date and time that the drug was administered were recorded. The dosing records were reviewed and verified for compliance at each visit by the research personnel at the trial centre.

Trial management and oversight

Trial Management Group

The TMG was a multidisciplinary team comprising the co-chief investigators, several co-investigators, PPI representatives, a sponsor representative, health economists and members of the CTRC (see *Appendix 1*). The TMG was responsible for the day-to-day clinical and practical aspects of the trial.

Independent Data and Safety Monitoring Committee

The IDSMC comprised two independent ophthalmologists, a statistician and a paediatric rheumatologist (see *Appendix 1*). The main responsibilities of the IDSMC were to safeguard the interests of the SYCAMORE participants, assess the safety and efficacy of the interventions during the course of the trial and monitor the overall progress and conduct of the trial. The IDSMC met at least annually during the course of the trial and provided recommendations to the TSC. The statistical team at the CTRC produced reports for the IDSMC.

Trial Steering Committee

The membership of the TSC included an independent rheumatologist, an independent ophthalmologist and an independent statistician, as well as representatives from the TMG (see *Appendix 1*). An observer from the sponsor and from the funder(s) were also invited to meetings. The TSC met at least annually, shortly after the IDSMC meeting. Its main role was to provide overall oversight of the trial.

Chapter 3 Statistical methods

Interim analysis

Interim monitoring reports of the accumulating data were performed at regular intervals (at least annually) for review by the IDSMC. In addition to the interim monitoring reports, the IDSMC requested that an interim analysis of the primary outcome was to be undertaken. The Peto–Heybittle stopping rule was applied to both interim analyses of the primary outcome. This required an extreme *p*-value of $p < 0.001$ as evidence to indicate potentially stopping for benefit. This approach was used to allow the IDSMC flexibility with the number and timing of further analyses, based on current safety and efficacy data, as it has the added benefit of preserving an overall two-sided type I error of 0.05 for the final analysis[62] (see *Chapter 4*).

Final analysis

The results of this report are based on the data collected during three phases of the trial. *Chapter 5* presents the results from the double-blind phase of the trial, *Chapter 6* presents the results from the integrated analysis of the double-blind phase and the open-label phase, and *Chapter 7* presents the results of the integrated analysis of the double-blind phase, open-label phase and the follow-up phase of the trial.

The data presented in this report are based on data at the final database lock that occurred on 2 August 2017.

The results from the blinded phase of the trial that were presented in the published manuscript of SYCAMORE were based on data snapshots taken on 11 September 2015 (primary outcome and AE data) and 24 May 2016 (secondary outcomes).

Because data were still being received from sites during this period, there were minor ongoing updates and changes to the database. The differences between the results in the *New England Journal of Medicine* manuscript[63] and *Chapter 5* in this report are documented in *Appendix 2*.

There were three statistical analysis plans (SAPs) written for the final analysis of study results. The first SAP was written by the trial statistician and contained detail only of the analyses for the primary outcome and the safety data of the blinded phase of the trial. The second and third SAPs were written after the completion of the primary analysis (after the blind had been broken to treatment allocation) and, therefore, written by independent statisticians who were blinded to the allocation of the trial. The second SAP described the analysis that was conducted on the secondary outcomes for the blinded phase of the trial and the third SAP described the analyses that were conducted for the open-label and follow-up phases of the trial. All three SAPs are available at www.journalslibrary.nihr.ac.uk/programmes/hta/095101 (accessed 4 February 2019).

General statistical considerations

The primary and secondary outcomes were all analysed using the (two-sided) 5% level of significance and 95% confidence intervals (CIs) are presented throughout. There were no adjustments for multiple testing; rather, all secondary analyses were treated as hypothesis generating.

The primary and secondary analyses used the principle of intention to treat (ITT) based on all the randomised participants, meaning that participants who consented and were randomised were analysed on the basis of the treatment they were randomised to, regardless of whether or not they received it. If consent for treatment was withdrawn but the participant was happy to remain in the study for follow-up, they were

followed up until completion. However, if they decided to withdraw consent completely, then the reasons for withdrawal of consent were collected (if possible) and reported for both groups.

All statistical analyses were conducted using SAS® V9.3 (SAS Institute, Cary, NC, USA), except for the joint modelling and competing risk analyses, which were conducted in R (R Foundation for Statistical Computing, Vienna, Austria).

Analysis of baseline data

Demographic and baseline characteristics were summarised for each treatment group and overall, using descriptive statistics. No formal statistical testing was performed on these data. Descriptive statistics, including the number of observations; mean; standard deviation (SD); median, minimum and maximum for continuous variables; and counts and percentages for discrete variables, are presented as appropriate.

Analysis of the primary outcome

The primary outcome of 'treatment failure' was a time-to-event outcome. For those patients who entered the trial and whose eyes (both) met the entry criteria, the time to the first eye to fail treatment was used. This was not observed in all participants; those participants who did not experience an event were classed as censored. The event time or censoring was calculated by subtracting the randomisation date from one of the following scenarios:

- Participants who failed treatment – date of the visit at which they failed treatment.
- Participants who completed the trial treatment phase without failing treatment – censored at date of 18-month treatment visit.
- Participants who discontinued treatment early and agreed to follow-up –
    - if they were assessed to be a treatment failure during a follow-up visit within 18 months following randomisation: date of follow-up visit
    - if they were not assessed to be a treatment failure during their follow-up visits: censored at date of last follow-up visit within 18 months following randomisation.
- Participants that were lost to follow-up – censored date of last treatment visit.

Survival estimates were calculated using the method of Kaplan and Meier, with curves for each treatment group presented graphically with numbers at risk.

The *p*-value obtained from the log-rank test and the hazard ratios (HRs) with 95% CIs were used to assess differences in failure estimates across treatment groups. The statistical test for the primary end point was performed at a two-sided significance level of 0.05.

Participants who withdrew from trial treatment (providing they did not withdraw from the entire study or withdraw consent) moved to the follow-up phase of the trial, were assessed for the primary outcome and could still contribute to the ITT analysis.

Any participants who withdrew from follow-up contributed primary outcome data until the point at which they withdrew from the trial.

Missing data were monitored and strategies developed to minimise this occurrence. Missing data were handled by considering the robustness of the complete-case analysis to sensitivity analyses using various imputation assumptions; this was informed by data collected on the reasons for missing data.

Nine sensitivity analyses were carried out to determine the robustness of the results from the primary analysis:

1. Best case – all participants who withdrew from treatment were treated as censored at time of treatment withdrawal.
2. Worst case – all participants who withdrew from treatment were treated as treatment failures (i.e. events at time of treatment withdrawal).
3. Methotrexate – any participants who withdrew from treatment because of MTX intolerance were classified as treatment failures at the time of treatment withdrawal.
4. Component 1 of primary outcome – all participants who failed for component 1 at a treatment failure assessment had their event date as the mid-point between this visit and the previous visit instead of the date of this visit.
5. Component 2 of primary outcome – all participants who failed for component 2 at a treatment failure assessment had their event date as the date that they commenced concomitant medications (a) used against predefined acceptable criteria (see SYCAMORE protocol[49]) or (b) any of the concomitant medications not allowed. The event date was determined by the co-chief investigators making a clinical decision following review of the participants' concomitant medications taken since their previous visit.
6. Component 3 – all participants who failed for component 3 at a treatment failure assessment had their event date as the exact date that they qualified as 'intermittent or continuous suspension of study treatment (adalimumab/placebo) for a cumulative period longer than 4 weeks'.[28] The event date was determined by the chief investigator making a clinical decision following review of a participant's trial treatment dose recordings in the treatment diaries.
7. Any missing primary outcome data – any cases of missing data for any of the primary outcome components (except for unscheduled visits) had data imputed on a worst-case basis, because the missing data could have meant that a participant failed earlier than recorded. All participants were treated the same, regardless of whether or not they had a treatment failure.
8. Loss to follow-up – in the primary analysis of the primary outcome, participants who were lost to follow-up were treated as withdrawals, assuming that they were non-informative. The reasons for loss to follow-up, when available, were blindly reviewed by Michael W Beresford (co-chief investigator) and Andrew Dick (ophthalmology expert on the TMG) to see whether or not any might be related to the prognosis. If any were deemed to be related, a sensitivity analysis would be undertaken, assuming these participants to be a treatment failure at the time of last recorded visit.
9. Incorrectly identified to be a treatment failure – once a participant was deemed to have failed treatment, treatment was stopped and they entered the follow-up phase of the study, providing that they still wished to be followed up. Any participants wrongly identified as treatment failures by the assessing physician would be classed as a withdrawal at their time of 'treatment failure'.

Analysis of secondary outcomes

The secondary continuous outcomes were analysed using the following methods:

- Chi-squared test, relative risk (RR) and 95% CI for the number of participants –
  - failing treatment
  - needing pulsed corticosteroids
  - having uveitis disease flares
  - having resolution of associated optic nerve or macular oedema
  - with uveitis disease control
  - entering disease remission for uveitis
  - undergoing JIA disease flare
  - with minimum disease activity of JIA
  - having remission of their JIA on and off medication
  - requiring a change in biologics due to failure to respond from arthritis.

- Change from baseline –
  - laboratory parameters (haematological and biochemical assessments).
- Poisson regression –
  - total oral corticosteroid dose
  - systemic corticosteroid dose.
- Competing risks –
  - reduction in systemic corticosteroid dose
  - topical corticosteroid use.
- Joint modelling of longitudinal and time-to-treatment failure data –
  - visual acuity
  - CHAQ and CHQ
  - ACR 30, 50, 70, 90 and 100
  - JADAS.
- Random intercept model –
  - duration of sustaining inactive disease.

No between-group statistical analyses were conducted for compliance data or urinalysis data; instead, summary data are presented for these outcomes.

Adverse events were tabulated by the Medical Dictionary for Regulatory Activities (MedDRA) version 18.0 system by organ class and preferred term. In addition, summaries by severity and relationship to study drug were completed. SAEs and events that led to premature withdrawal were listed in detail. No formal testing of AE or SAE data was planned.

Chapter 4 Interim analysis results

Initial meeting

The first meeting of the IDSMC took place on 2 August 2011. During this meeting, the IDSMC reviewed the study protocol, was updated on study progress and agreed the IDSMC charter and also the expedited safety reports that it wished to receive.

Future meetings

The IDSMC met at regular intervals following the initial meeting (11 April 2012, 18 December 2012, 3 July 2013 and 18 February 2014). During these meetings, the committee was updated on the progress of the trial and was also presented with a report that contained data on recruitment, data completeness and safety.

There were two sessions held during the meetings, an open and closed session. Present at the open session were the independent members of the IDSMC and also relevant members of the TMG (i.e. co-chief investigators, lead trial ophthalmologist, trial co-ordinator, statistical team). During the open session, data were presented overall and not split by treatment group. The open session was then followed by a closed session, which was attended only by the independent members of the IDSMC and the statistical team responsible for the production of the report.

On 18 February 2014, the IDSMC decided that the recruited sample was approaching a size at which an interim analysis was needed in order to allow them to protect participants from potential harm or to stop the trial early if there was a clear benefit. This allowed for avoidance of delay by bringing the benefits to patients once the question that had been posed in the trial had been answered with sufficient statistical certainty.

The IDSMC, therefore, requested that an interim analysis be conducted and the results be presented at the next IDSMC meeting, which was to be held on 29 September 2015.

Statistical methods

A full SAP was written prior to conducting the interim analysis.

The Peto–Haybittle stopping rule was applied to the interim analysis of the primary outcome. This required an extreme p-value of < 0.001 as evidence to stop for benefit. This approach was used to allow the IDSMC flexibility with the number and timings of further analyses, based on current safety and efficacy data, as it had the added benefit of preserving an overall two-sided type I error of 0.05 for the final analysis.

Survival estimates were calculated using the method of Kaplan and Meier, with curves for each treatment group presented graphically along with numbers at risk.

The log-rank test was used to assess differences in failure estimates across treatment groups.

Interim analysis 1

The first interim analysis report was based on follow-up data from 71 participants who had been randomised (adalimumab, $n = 48$; placebo, $n = 23$). Safety data (SAE/AE) were based on data from 64 participants (adalimumab, $n = 43$; placebo, $n = 21$).

There was a total of nine treatment failures recorded in 48 participants in the adalimumab group (19%) and 13 treatment failures recorded in 21 participants in the placebo group (62%), and five withdrawals from 48 participants recorded in the adalimumab group (10%) and four withdrawals from 23 participants recorded in the placebo group (17%).

The Kaplan–Meier plot is shown in *Figure 2*. The log-rank chi-squared statistic was 15.77 and the associated log-rank *p*-value was < 0.0001.

At the time of the first interim analysis, 353 AEs had been reported in 34 of the 43 participants in the adalimumab group who qualified for the safety analysis set (i.e. received at least one dose of treatment). There had been 89 AEs reported in 14 out of the 21 participants in the placebo group who qualified for the safety analysis set (i.e. received at least one dose of treatment).

There had been 10 SAEs reported in 9 participants from a total of 43 participants in the adalimumab group (21%). There had been one SAE reported from a total of 21 participants in the placebo group (5%).

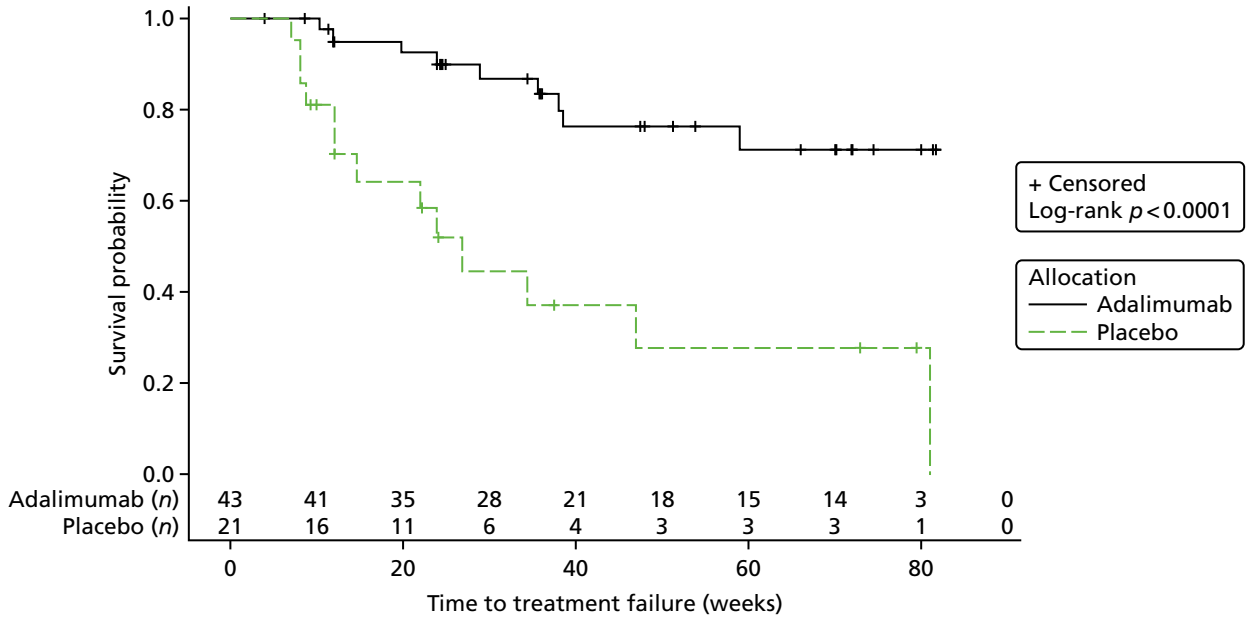


FIGURE 2 Interim analysis 1: Kaplan–Meier plot.

The IDSMC considered the report and made the recommendation that the trial should continue with recruitment. However, it did make three observations with regard to the trial based on the report that it received:

1. We (the IDSMC) have been much reassured over recent months, and in the current report, that the recruitment rate is now running just ahead of the amended estimated rate. We would like to commend the TMG on overcoming significant difficulties to achieve this favourable situation.
2. We do, however, remain concerned that some centres are performing exceptionally badly; there is, for example, a marked contrast between the performance of Bristol, where ≈50% of those screened are recruited, and Birmingham, where < 1% of those screened are being recruited. While these two are at the extreme ends, there are several other poorly recruiting centres – this appears as a weakness with potential implications for the representativeness of the trial sample. An investigation into the problems in these centres, with a view to resolving their issues, would be time well spent.
3. We are also concerned about the levels of missing data, which seem high for certain variables. For example, in table 10.2 [referring to the meeting report], in 14% the relationship between the AE and the trial medication is missing and in 5% the severity of the AE is missing. Whilst we appreciate that you are taking steps to reduce these rates of missing data, we would like to register our concern in regard to this problem of missing data, which is evident in other parts of the report. Please take all steps to recover missing data and reduce the levels going forward.

The TMG provided further information with regards to missing data for both the primary outcome and the safety data. The response contained a more detailed breakdown of missing and unobtainable data for each component of the primary outcome and safety data, by site and overall.

This thorough investigation of the missing and unobtainable data reassured the IDSMC that the monitoring procedures being implemented by the TMG and the engagement of sites with the data manager were ensuring that these figures were kept to a minimum.

The IDSMC requested that a further interim analysis be conducted at their next meeting in March 2015.

Interim analysis 2

The IDSMC met on the 25 March 2015 to discuss the results of the second interim analysis of the SYCAMORE data.

At the time of the report, there were a total of 85 participants who had been randomised (adalimumab, $n = 57$; placebo, $n = 28$). From these 85 participants:

- 80 were included in the analysis (adalimumab, $n = 54$; placebo, $n = 26$).
- Five were excluded –
    - four had no randomisation CRF input on the trial database
    - one had their randomisation CRF input on the trial database but had not had any further follow-up visits input to the trial database.

There were a total of 10 withdrawals from the trial: five withdrawals from the adalimumab group ($n = 57$) (9%) and five withdrawals from the placebo group ($n = 28$) (18%). There were a total of 27 treatment failures in the trial: 12 treatment failures on adalimumab (21%) and 15 on placebo (54%).

The Kaplan–Meier plot is shown in *Figure 3*. The log-rank chi-square statistic was 14.63 and the associated log-rank *p*-value was 0.0001.

The safety data set was based on 80 participants (adalimumab, $n = 54$; placebo, $n = 26$).

There were a total of 10 withdrawals from the trial: five withdrawals from the adalimumab ($n = 57$) (9%) and five withdrawals from the placebo group ($n = 28$) (18%). There were a total of 27 treatment failures in the trial: 12 treatment failures on adalimumab (21%) and 15 on placebo (54%).

Following the review of the second interim analysis, the IDSMC carefully considered evidence from the first interim analysis, the subsequent satisfactory conclusion of the vast majority of missing data, and also the continued presence of such a strong treatment effect. The IDSMC subsequently agreed unanimously that:

- The levels of missing data were acceptable with all reasonable efforts being made to collect outstanding missing data items where feasible, or to confirm the fact that the data were unobtainable.
- The AEs and SAEs were in keeping with expectations for the medications in use, based on clinical experience and previous published reports.
- The statistical significance of the beneficial effect of the investigational medicinal product (IMP) in the interim analysis substantially exceeded the predetermined requirement for consideration of stopping the trial on the basis of a powerful positive treatment effect.
- The IDSMC should obtain guidance on procedure prior to making any stopping recommendation. Options for stopping included either to immediately stop and fully close the trial or to stop recruitment and continue collecting data until all current participants had completed their passage through the protocol.

It was decided by the IDSMC that no immediate recommendation should be made, but that the IDSMC chairperson should take advice in a timely manner, following which the IDSMC would communicate further among themselves before arriving at a final recommendation.

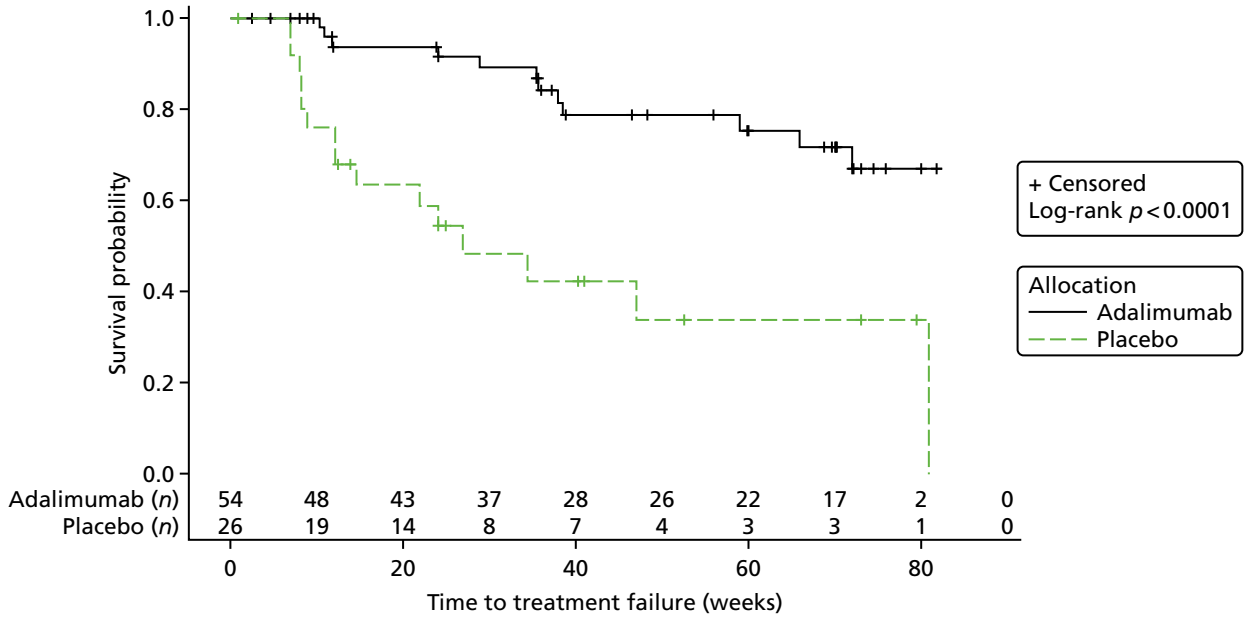


FIGURE 3 Interim analysis 2: Kaplan–Meier plot.

Summary of Independent Data and Safety Monitoring Committee and Trial Steering Committee meetings following interim analysis 2

The IDSMC and TSC met on 8 April 2015 in a combined meeting that involved all of the independent members of both committees, as well as both co-chief investigators and the lead statistician (non-independent members). The IDSMC advised the TSC that the trial should stop recruiting with immediate effect. They further recommended that all participants currently in the trial should continue in their randomly allocated treatment regimen, blinded, and follow treatment scheduling as per protocol. The IDSMC did not unblind the TSC (or co-chief investigators) to the results of the trial during the meeting. The TSC decided to consider the recommendations of the IDSMC overnight and meet again on 9 April 2015.

The independent members of the TSC met with the co-chief investigators and lead statistician (non-independent members of the TSC) again on 9 April 2015. The chairperson of the TSC contacted the chairperson of the IDSMC, requesting that the IDSMC make formal recommendations to the TSC in a formal document; they agreed to meet again on 10 April 2015.

The same independent members of the TSC, the co-chief investigators and lead statistician met on 10 April 2015 and discussed the formal recommendations that had been made by the IDSMC.

The voting members of the TSC (the three independent members and one non-independent member) then voted unanimously in favour of the following specific IDSMC recommendations:

- Recruitment to SYCAMORE should not be reinstated. This was based on a positive signal of efficacy of the IMP (adalimumab) versus placebo, which exceeded the prespecified level.
- All participants in the trial should be invited to attend a final blinded assessment visit. On completion of assessments, their treatment allocation should then be unblinded.
- All participants in the active arm of the trial (adalimumab) should continue follow-up in an open-label fashion, as this long-term follow-up would contribute important additional data on quality of life, utilities and long-term efficacy. Subsequent changes in therapy would be at the discretion of the treating clinical team.

Chapter 5 Clinical effectiveness results: blinded phase of study

The results presented in this chapter are from the blinded period of the trial only.

Participant recruitment

The first participant was randomised into SYCAMORE on 27 October 2011 and the last participant was randomised on 31 March 2015. The last blinded visit took place on 16 June 2015.

Fourteen of the 17 sites randomised at least one participant and five centres randomised five or more participants. The flow of participants through the trial is represented in the Consolidated Standards of Reporting Trials (CONSORT)[64] flow diagram in *Figure 4*.

A total of 332 patients were assessed for eligibility from 519 screenings (patients could be screened on multiple occasions).

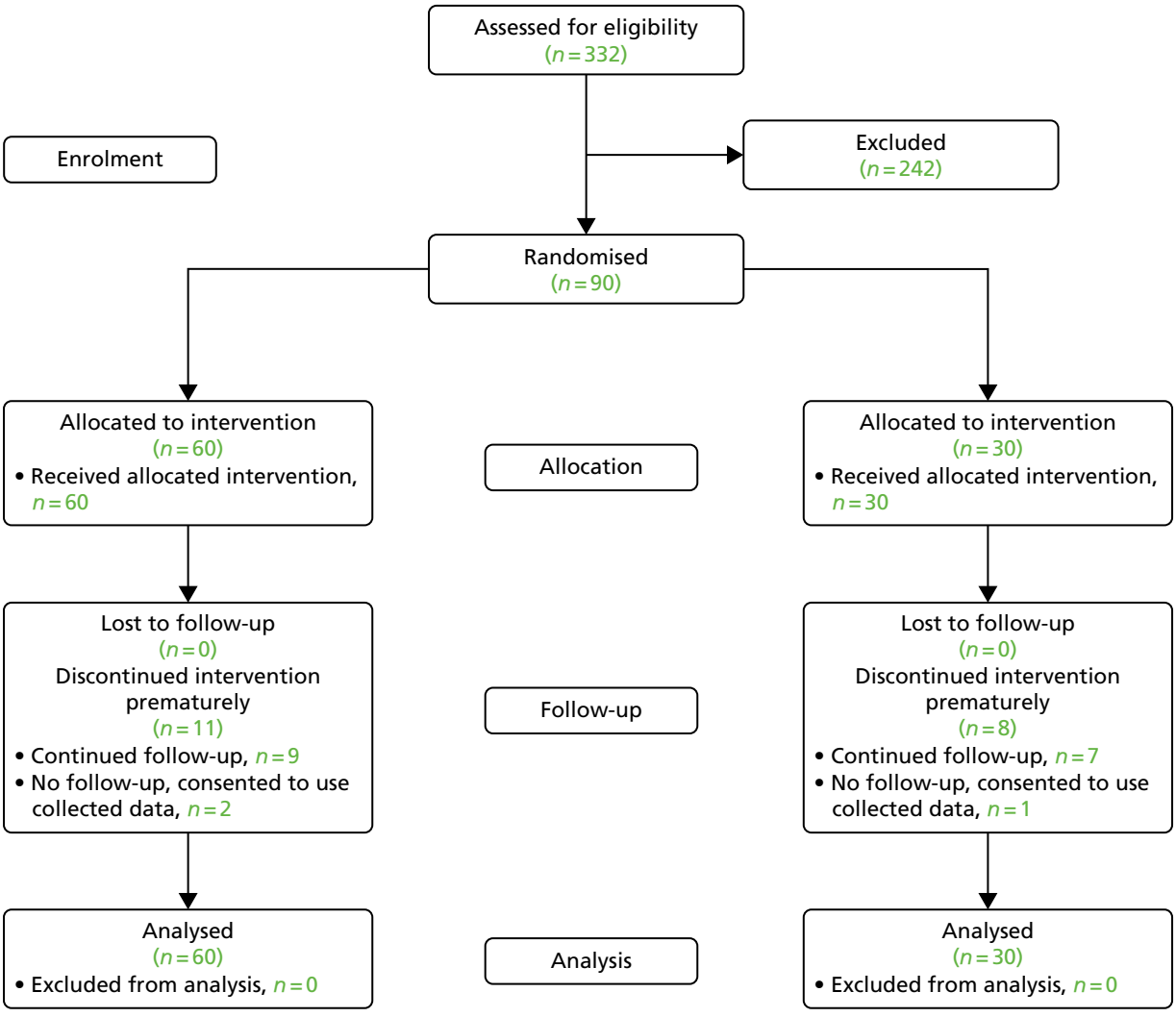


FIGURE 4 The CONSORT flow diagram for all trial participants.

The number of participants enrolled overall by month is provided in *Appendix 3* (see *Figure 13*); the screening overview by centre is also given in *Appendix 3* (see *Table 40*). The main reasons for ineligibility included the following: the patient did not have active uveitis (49%), the patient had not failed on MTX or been on MTX for at least 12 weeks with a stable dose (19%), the patient had been on another biological agent within the previous five half-lives of the agent (6%), the patient had more than six topical steroid eye drops per day at randomisation (6%) or other reasons (11%). For five patients, it was not clear whether or not they were eligible.

A total of 130 patients were eligible to participate in the trial from 139 screening visits; 90 patients were randomised. The reasons for the 45 patients (49 screening visits) not providing consent are given in *Appendix 3* (see *Table 41*).

Recruitment rates

The original target sample size of 154 participants was expected to be achieved within 30 months of recruitment. This original target was based on feasibility data provided by each of the centres that took part in the trial. The actual rates of recruitment during the trial were lower than anticipated (see *Appendix 3, Figure 13*) and, therefore, the recruitment period of the trial was extended by 36 months on 16 June 2014, to allow for additional time to recruit the necessary number of participants.

The sample size of the trial was also revised, which meant that the target sample size was reduced from 154 to 114 participants. Other strategies were used to improve recruitment, including the aligning of the rheumatology and ophthalmology clinics in any sites that did not already have this service and holding a series of regional investigator meetings and local investigator meetings each month via teleconference, which included members of the CTRC and the co-chief investigators and lead SYCAMORE ophthalmologists. Regular newsletters were sent to sites to keep sites aware of recruitment and to maintain interest in the trial. All sites were also encouraged to build referral links with district general hospitals to allow referrals of potential patients for screening.

Comparison of interventions

The ITT analysis population included all 90 participants who were randomised (see *Figure 4*). There were no exclusions from either the safety or the ITT population.

All participants who withdrew consent for trial continuation contributed outcome data up until the point of withdrawal.

The memberships of the analysis set for the primary outcome and safety data set were determined and documented prior to the blinding being broken and the treatment allocations being requested.

Trial completion and trial exit

There were 19 participants who withdrew prematurely during the blinded treatment phase of the trial (*Table 1*). There were a total of 11 (18%) withdrawals in the adalimumab group (nine continued into the follow-up phase of the trial and two withdrew complete consent) and eight (23%) in the placebo group (seven continued into the follow-up phase of the trial and one withdrew complete consent). The majority of premature withdrawals were for non-safety reasons (see *Table 1*). The most common reason for withdrawal in the adalimumab group was because of MTX intolerance and in the placebo group it was the worsening of uveitis (that did not meet the exit criteria).

TABLE 1 Participants withdrawn from trial treatment, by treatment group

Reasons	Treatment group, *n* (%)		Total, *n* (%)
	Adalimumab	Placebo	
Safety	2 (3.3)	1 (3.3)	3 (3.3)
AE	2 (3.3)	0 (0)	2 (2.2)
SAE	0 (0)	1 (3.3)	1 (1.1)
Non-safety	9 (15)	7 (23.3)	16 (17.8)
Consultant discretion owing to disease activity	0 (0)	1 (3.3)	1 (1.1)
Family circumstances	0 (0)	1 (3.3)	1 (1.1)
Flare of JIA	0 (0)	1 (3.3)	1 (1.1)
MTX intolerance	4 (6.7)	0 (0)	4 (4.4)
Needle phobia	1 (1.7)	0 (0)	1 (1.1)
Participant felt no benefit	0 (0)	1 (3.3)	1 (1.1)
Recurrent infections	1 (1.7)	0 (0)	1 (1.1)
Refused injections	1 (1.7)	0 (0)	1 (1.1)
Unable to tolerate adalimumab/placebo	0 (0)	1 (3.3)	1 (1.1)
Use of medication that was not permitted	1 (1.7)	0 (0)	1 (1.1)
Withdrawal of consent – no reason	1 (1.7)	0 (0)	1 (1.1)
Worsening of uveitis (not meeting exit criteria)	0 (0)	2 (6.7)	2 (2.2)
Overall	11 (18.3)	8 (26.7)	19 (21.1)

Baseline characteristics

The demographic baseline data of the 90 participants randomised across all centres were comparable between the two groups (*Table 2*). The mean age in the placebo group was slightly lower than that in the adalimumab group and the proportion of females and males was approximately the same in the two treatment groups, with more females than males.

The distribution in weight was similar in both groups, as was physical global assessment of disease activity, antinuclear antibody and double-stranded deoxyribonucleic acid.

A total of 65 (72%) participants entered the trial with one eye that was eligible for evaluation (i.e. they met the inclusion criteria for active uveitis in one eye only) and 25 (28%) participants entered the study with two eyes that were eligible (i.e. they met the inclusion criteria for active uveitis in both eyes). Therefore, a total of 115 eligible eyes entered into the study.

Table 3 shows ocular data collected at baseline, presented at the eye level rather than the individual level for ease of reading. The overall mean for logMAR score was 0.05; this was slightly higher in the placebo group than in the treatment group. Of the eligible eyes, 76 (66%) had a score of 1+ for the AC score; the numbers in each of these categories were similar in both groups, as were the flare score and vitreous haze grading. The mean IOP in each group was similar, with an overall mean of 14.54 mmHg.

When the best and worst scores were entered for those with two eligible eyes, the baseline results were very similar to those when the eyes were looked at independently.

TABLE 2 Demographic baseline data: individual patient level

Variable	Treatment group		
	Adalimumab (*N* = 60)	Placebo (*N* = 30)	Total (*N* = 90)
Number of study eyes, *n* (%)			
Unilateral	43 (72)	22 (73)	65 (72)
Bilateral	17 (28)	8 (27)	25 (28)
Age at randomisation (years)			
Mean (SD)	9.07 (3.94)	8.56 (3.79)	8.90 (3.88)
Sex, *n* (%)			
Female	47 (78)	23 (77)	70 (78)
Male	13 (22)	7 (23)	20 (22)
Weight[a] (kg), *n* (%)			
< 30kg	33 (60)	17 (57)	50 (56)
≥ 30kg	26 (44)	13 (43)	39 (44)

a One unobtainable value from the adalimumab group.

TABLE 3 Ocular baseline data: eye level

Variable	Treatment group		
	Adalimumab (*N* = 77)	Placebo (*N* = 38)	Total (*N* = 115)
Topical steroid drops score[a]			
Mean (SD)	2.04 (1.38)	2.20 (1.57)	2.09 (1.44)
LogMAR score[b]			
Mean (SD)	0.04 (0.15)	0.07 (0.12)	0.05 (0.14)
AC cells (SUN) (%)			
1+	52 (68)	24 (63)	76 (66)
2+	18 (23)	11 (29)	29 (25)
3+	6 (8)	3 (8)	9 (8)
4+	1 (1)	0 (0)	1 (1)
Flare score (SUN), *n* (%)			
0	18 (23)	12 (32)	30 (26)
1+	49 (64)	23 (61)	72 (63)
2+	10 (13)	3 (8)	13 (11)
LOCS III grading: pseudophakic, *n* (%)			
No	77 (100)	38 (100)	115 (100)
LOCS III grading: nuclear,[c] *n* (%)			
N0	69 (96)	36 (97)	105 (96)
NI	3 (4)	1 (3)	4 (4)

TABLE 3 Ocular baseline data: eye level (*continued*)

Variable	Treatment group		
	Adalimumab (*N* = 77)	Placebo (*N* = 38)	Total (*N* = 115)
LOCS III grading: cortical,[d] *n* (%)			
No cortical cataract	56 (88)	29 (94)	85 (90)
Control	3 (5)	0 (0)	3 (3)
CI	4 (6)	2 (7)	6 (6)
CII	1 (1)	0 (0)	1 (1)
LOCS III grading: posterior,[e] *n* (%)			
0	68 (92)	29 (81)	97 (88)
PI	5 (7)	4 (11)	9 (8)
PII	1 (1)	3 (8)	4 (4)
Other structural changes: central band keratopathy covering visual axis, *n* (%)			
No	75 (97)	38 (100)	113 (98)
Yes	2 (3)	0 (0)	2 (2)
Other structural changes: synchiae, *n* (%)			
No	59 (77)	32 (84)	91 (79)
Yes	18 (23)	6 (16)	24 (21)
Other structural changes: iris bombe, *n* (%)			
No	77 (100)	38 (100)	115 (100)
Other structural changes: membrane formation, *n* (%)			
No	75 (97)	38 (100)	113 (98)
Yes	2 (3)	0 (0)	2 (2)
Other structural changes: neovascularisation, *n* (%)			
No	77 (100)	38 (100)	115 (100)
IOP (mmHg)			
Mean (SD)	14.76 (3.85)	14.11 (4.27)	14.54 (3.99)
Vitreous haze grading, *n* (%)			
0	65 (84)	32 (84)	97 (84)
0.5+	8 (10)	4 (11)	12 (10)
1+	3 (4)	2 (5)	5 (4)
2+	1 (1)	0 (0)	1 (1)

LOCS, Lens Opacities Classification System.
a Two adalimumab and 3 placebo unobtainable.
b One adalimumab unobtainable.
c Five adalimumab and 1 placebo unobtainable.
d Thirteen adalimumab and 7 placebo unobtainable.
e Three adalimumab and 2 placebo unobtainable.

Table 4 shows the baseline data describing the classification by disease subtype of the participants' JIA status. A total of 53 (59%) participants had persistent oligoarticular JIA and 21 (23%) had extended oligoarticular JIA. The proportions for each of the subcategories were similar for both groups. The mean overall JIA disease duration was 5.33 years, with the duration being slightly longer in the treatment group. A total of 66 (73%) participants had a negative rheumatoid factor (RF); this was slightly higher in the adalimumab group.

Unblinding of randomised treatment

There were 57 (63%) participants who were unblinded during the course of the trial: 38 (67%) in the adalimumab group and 19 (33%) in the placebo group. A breakdown of the stage of the trial that the participants were in at the time of unblinding is given in *Table 5*.

TABLE 4 Rheumatology baseline data: individual patient level

	Treatment group		
Variable	Adalimumab ($N = 60$)	Placebo ($N = 30$)	Total ($N = 90$)
Type of JIA (ILAR classification), *n* (%)			
Extended oligoarthritis	14 (23)	7 (23)	21 (23)
Persistent oligoarthritis	36 (60)	17 (57)	53 (59)
Polyarthritis RF negative	8 (13)	4 (13)	12 (13)
Polyarthritis RF positive	1 (2)	1 (3)	2 (2)
Psoriatic arthritis	1 (2)	1 (3)	2 (2)
Disease duration[a] (years)			
Mean (SD)	5.58 (3.69)	4.81 (3.19)	5.33 (3.53)
Physician global assessment of disease activity[b]			
Mean (SD)	0.76 (1.48)	0.83 (1.09)	0.78 (1.36)
Active joint count (all joints)			
Mean (SD)	0.57 (2.03)	1.1 (2.23)	0.74 (2.10)
Swollen joint count (all joints)			
Mean (SD)	0.55 (1.66)	1.0 (1.55)	0.70 (1.63)
Antinuclear antibody,[c] *n* (%)			
Negative	24 (42)	10 (40)	34 (42)
Positive	33 (58)	15 (60)	48 (58)
Double-stranded deoxyribonucleic acid,[d] *n* (%)			
Negative	47 (94)	22 (92)	69 (93)
Positive	3 (6)	2 (8)	5 (7)
RF,[e] *n* (%)			
Negative	46 (98)	20 (87)	66 (94)
Positive	1 (2)	3 (13)	4 (6)

ILAR, International League of Associations for Rheumatology; RA, rheumatoid factor.
a Six adalimumab and 4 placebo unobtainable.
b Two adalimumab and 1 placebo unobtainable.
c Three adalimumab and 5 placebo not carried out.
d Ten adalimumab and 6 placebo not carried out.
e Thirteen adalimumab and 7 placebo not carried out.

TABLE 5 Trial status of unblinded participants

Reason	Treatment group, *n* (%)	
	Adalimumab	Placebo
Completed 18 months of treatment	12 (32)	1 (5)
Based on recommendation of IDSMC	10 (26)	4 (21)
Treatment failure	11 (29)	8 (42)
Withdrawal	5 (13)	6 (32)
Total	38	19

Protocol deviations

Protocol deviations were monitored centrally via evaluation of inclusion/exclusion criteria at trial entry and throughout the course of the trial. During the course of the blinded phase of the trial, a total of 74 (82%) participants had at least one major protocol deviation (*Table 6*). All protocol deviations were agreed with the co-chief investigators before the final treatment allocations were requested on 11 September 2015.

TABLE 6 Important major protocol deviations

Institution	Total, *n*	Any protocol deviation, *n* (%)	At least one protocol deviation related to, *n* (%)			
			Inclusion criteria	Exclusion criteria	Treatment regimen	Study assessment
The Leeds Teaching Hospitals NHS Trust	2	2 (100)	0 (0)	0 (0)	1 (50)	2 (100)
University Hospitals of Leicester NHS Trust	3	3 (100)	2 (67)	0 (0)	2 (67)	2 (67)
Norfolk and Norwich University Hospitals NHS Foundation Trust	5	5 (100)	0 (0)	0 (0)	3 (60)	4 (80)
The Newcastle upon Tyne Hospitals NHS Foundation Trust	5	4 (80)	1 (20)	0 (0)	3 (60)	4 (80)
Hull and East Yorkshire Hospitals NHS Trust	1	1 (100)	0 (0)	0 (0)	1 (100)	1 (100)
University Hospital Southampton NHS Foundation Trust	4	4 (100)	2 (50)	1 (25)	2 (50)	4 (100)
University Hospitals Bristol NHS Foundation Trust	28	23 (82)	2 (7)	1 (4)	15 (54)	20 (71)
Birmingham Children's Hospital NHS Foundation Trust	1	1 (100)	0 (0)	0 (0)	0 (0)	1 (100)
Alder Hey Children's NHS Foundation Trust Hospital	7	6 (85)	1 (14)	0 (0)	4 (57)	6 (856)
Central Manchester University Hospitals NHS Foundation Trust	4	4 (100)	1 (25)	0 (0)	3 (75)	4 (100)
Sheffield Children's NHS Foundation Trust	4	4 (100)	0 (0)	0 (0)	2 (50)	4 (100)
Great Ormond Street Hospital for Children NHS Trust	22	13 (59)	2 (9)	0 (0)	9 (41)	12 (55)
Royal Hospital for Sick Children Edinburgh – NHS Lothian	1	1 (100)	0 (0)	0 (0)	1 (100)	1 (100)
Royal Belfast Hospital for Sick Children	3	3 (100)	0 (0)	0 (0)	2 (67)	3 (100)
Total	90	74 (82)	11 (12)	2 (2)	48 (53)	68 (76)

Primary outcome

Adalimumab plus MTX significantly delayed the time to treatment failure compared with placebo and MTX. There were a total of 14 (23%) treatment failures for the 60 participants in the adalimumab group and 17 (57%) failures for the 30 participants in the placebo group. The median time to treatment failure was 24.10 weeks (95% CI 14.70 weeks to 81.00 weeks) in the placebo group and was not reached in the adalimumab group within the 18-month treatment period because fewer than half of the subjects experienced treatment failure at the conclusion of the trial (*Figure 5*).

Reasons for the treatment failure of each participant can be found in *Appendix 3* (see *Table 42*).

In the adalimumab group, five participants (trial numbers 0114011, 0116006, 0116026, 0249024 and 0030073) were classified as treatment failures because they had taken permitted concomitant medications against the acceptable criteria, three participants (trial numbers 0243023, 0249043 and 0133058) were given non-permitted concomitant medications, three participants (trial numbers 0069039, 0116062 and 0116066) had missed doses that met the failure criteria, two participants (trial numbers 0246055 and 0069076) had sustained SUN scores (as recorded at entry grade) that were still present after 6 months of therapy and one participant (trial number 0030035) had both taken permitted concomitant medications against the acceptable criteria and missed doses that met the failure criteria.

In the placebo group, two participants (trial numbers 0114033 and 0116067) received permitted concomitant medications against the acceptable criteria, seven participants (trial numbers 0249019, 0249025, 0246030, 0243032, 0540037, 0393075 and 0249086) were given non-permitted concomitant medications, one participant (trial number 0116003) missed doses that met the failure criteria and seven participants (trial numbers 0116008, 0036018, 0116005, 0249029, 0249047, 0116051 and 0249059) had sustained SUN scores (as recorded at entry grade) that were still present after 6 months of therapy.

Four participants who were classified as treatment failures did not subsequently enter the follow-up phase of the trial and withdrew completely from the trial with no further follow-up. One of these was in the adalimumab group (2%) and three were in the placebo group (10%).

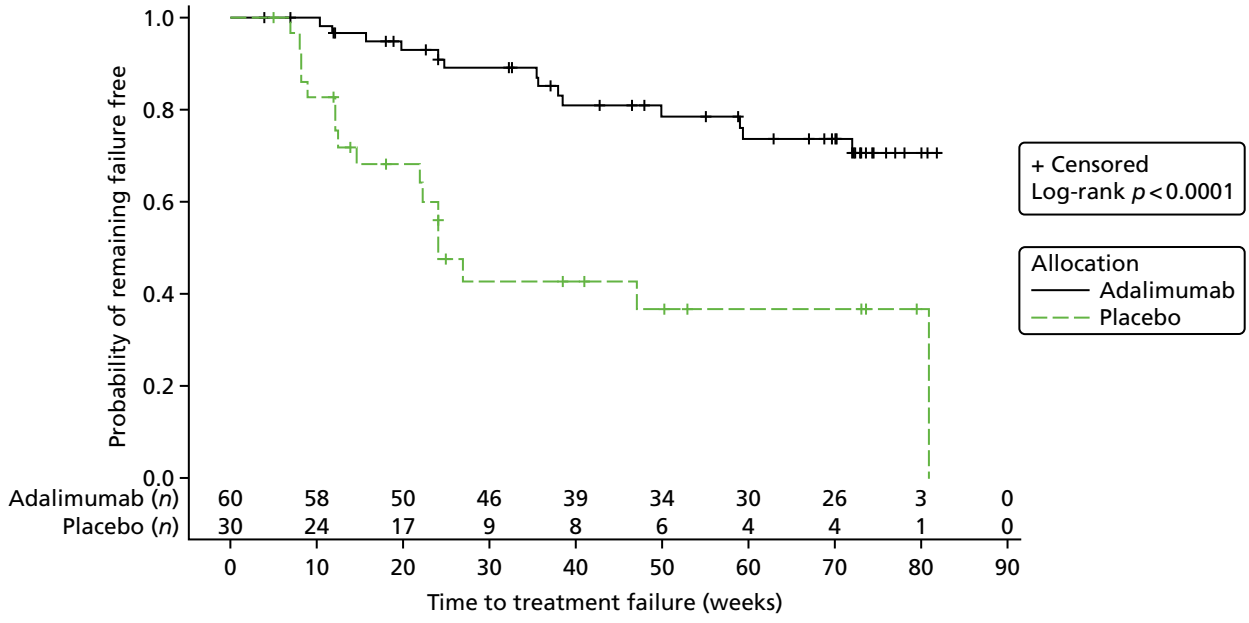


FIGURE 5 Primary outcome ITT Kaplan–Meier plot.

The HR indicated that treatment with adalimumab significantly decreased the hazard of treatment failure by 75% (HR 0.25, 95% CI 0.12 to 0.51). The results of the log-rank test offered strong statistical evidence that the placebo group and adalimumab group differed with respect to time to treatment failure ($p < 0.0001$), relative to placebo. The HR was derived using Statistical Analysis Systems Procedure (SAS PROC) proportional hazards regression methods with no stratification factors.

Test of proportional hazards assumption

The assumption of proportional hazards was tested by including an interaction between time and treatment group in the Cox proportional hazards model. There was no evidence ($p = 0.15$) that the interaction was not zero and, therefore, no evidence that the HR was not constant over time.

Sensitivity analyses

The results of the nine sensitivity analyses can be seen in *Table 7*, which contains information on the number of participants analysed in each group, the number of treatment failures, the number of participants censored, the log-rank chi-squared statistic, the log-rank *p*-value, the HR and the 95% CIs.

There were no losses to follow-up and no incorrect treatment failures; therefore, sensitivity analyses eight and nine were not conducted. The results of the other sensitivity analyses indicate that the original conclusion from the primary analysis was robust with regard to the assumptions that were made. The overall statistical significance in the sensitivity analyses did not change.

Additional analyses

Development of uveitis in non-study eye

There were 43 (72%) participants who had unilateral vision in the adalimumab group and 22 (73%) participants who had unilateral vision in the placebo group. Those participants who had bilateral vision [17 (28%) in the adalimumab group and 8 (27%) in the placebo group] were not eligible for this analysis as they had uveitis in both eyes at baseline.

There were five (17%) participants in the placebo group who developed uveitis (defined as sustained AC cell scores of ≥ 1+ over two consecutive visits) in the non-study eye and one (2%) participant in the adalimumab group who developed uveitis in the non-study eye [the participant in the adalimumab group had a baseline AC cell score of 1+ in their non-eligible eye, but they were taking too many drops in this eye (left) for it to be eligible].

There were two participants (one in the adalimumab group and one in the placebo group) who had a single AC cell score of ≥ 1+ and had a treatment failure in their study eye at the same visit.

Time-to-treatment failure in both eyes

This analysis was not possible because only one participant (in the placebo group) failed in both eyes at different times.

Development of comorbidity on treatment failure

One participant developed cataract in the adalimumab group; none in the placebo group developed cataract. Three participants developed IOP in the adalimumab group, whereas none in the placebo group developed IOP.

There were so few participants in either of the two treatment groups who developed a comorbidity that any modelling, including the development of a comorbidity, was not possible.

TABLE 7 Primary outcome ITT analysis and sensitivity analyses results

		Treatment group									
		Adalimumab			Placebo						
Analysis	Participants, *N*	Participants, *n*	Treatment failures, *n*	Censored, *n*	Participants, *n*	Treatment failures, *n*	Censored, *n*	Log-rank chi-squared statistic	Log-rank *p*-value	HR	95% CI
ITT	90	60	14	46	30	17	13	16.72	< 0.0001	0.25	0.12 to 0.51
1: best case	90	60	13	47	30	15	15	19.98	< 0.0001	0.21	0.10 to 0.44
2: worst case	90	60	24	36	30	23	7	24.17	< 0.0001	0.25	0.14 to 0.46
3: MTX	90	60	19	41	30	17	13	10.45	0.001	0.34	0.18 to 0.68
4: component 1	90	60	14	46	30	17	13	17.67	< 0.0001	0.24	0.12 to 0.49
5: component 2	90	60	14	46	30	17	13	16.93	< 0.0001	0.24	0.12 to 0.50
6: component 3	90	60	14	46	30	17	13	16.77	< 0.0001	0.25	0.12 to 0.51
7: missing PO	90	60	14	46	30	17	13	16.72	< 0.0001	0.25	0.12 to 0.51
8: loss to follow-up[a]	–	–	–	–	–	–	–	–	–	–	–
9: incorrect TF[b]	–	–	–	–	–	–	–	–	–	–	–

PO, primary outcome; TF, treatment failure.
a No losses to follow-up observed; therefore, this sensitivity analysis is not applicable.
b No incorrect treatment failures observed; therefore, this sensitivity analysis is not applicable.

Post hoc analyses

Time to treatment response

There were 44 participants in the adalimumab group and eight participants in the placebo group who were classified as having a treatment response; the difference between the two groups was statistically significant (log-rank *p*-value = 0.002). The HR indicated that those participants on adalimumab were over three times more likely to achieve a treatment response than those on placebo (HR 3.01, 95% CI 1.41 to 6.41).

Proportion of responders/failures/no change

Proportion of responders/failures/no change at 3 months

There were 20 (35%) participants in the adalimumab group and three (10%) participants in the placebo group who were classified as having a treatment response before 3 months. The Cochran–Armitage trend test showed a significant difference between the treatment groups at 3 months ($p = 0.004$).

There were three patients excluded from the analyses because they had not reached the 3-month time point.

Proportion of responders/failures/no change at 6 months

There was a total of 20 (37%) patients in the adalimumab group and three (11%) patients in the placebo group who were classified as having a treatment response prior to 6 months. The Cochran–Armitage trend test showed a significant difference between the treatment groups at 6 months ($p = 0.004$).

Nine participants were excluded from the analyses because they had not reached the 6-month time point.

Area under the curve of anterior chamber cells in eligible eye

There was a significant difference in the median number of AC cells between the two groups (median number of AC cells –0.79, 95% CI –0.96 to –0.63; $p < 0.0001$) in favour of the adalimumab group. Similar results were obtained when the best or worst score was used for participants with two eligible eyes.

Secondary outcomes

Number of participants failing treatment

Fourteen (23%) participants in the adalimumab group and 17 (57%) participants in the placebo group were classified as having treatment failures. The risk of having a treatment failure was statistically significantly reduced by 60% (RR 0.40, 95% CI 0.23 to 0.72; $p = 0.002$) in the adalimumab group compared with placebo.

Safety, tolerability and compliance

Adverse events and serious adverse events

Throughout the course of the trial, 733 (non-serious, $n = 713$; serious, $n = 20$) AEs were recorded. A total of 85 participants (out of 90) experienced at least one AE. There were 619 AEs reported in 59 (98%) participants in the adalimumab group and 114 AEs reported in 26 (87%) participants in the placebo group. The rate of AEs in the adalimumab group (10.60 per patient-year, 95% CI 9.77 per patient-year to 11.44 per patient-year) was greater than that in the placebo group (7.21 per patient-year, 95% CI 5.89 per patient-year to 8.53 per patient-year).

The commonest AEs in the adalimumab group were classified as infections and infestations (83%), respiratory, thoracic and mediastinal disorders (55%), general disorders and administration-site conditions (52%), gastrointestinal disorders (47%), investigations (32%), musculoskeletal and connective tissue disorders (27%), nervous system disorders (27%) and eye disorders (25%). Aside from eye disorders (27%), common AEs reported in the placebo group were consistently lower [infections and infestations

(47%), respiratory (20%), thoracic and mediastinal disorders (27%), general disorders and administration-site conditions (30%), gastrointestinal disorders (13%), investigations (23%), musculoskeletal and connective tissue disorders (13%) and nervous system disorders (27%) (*Table 8*)].

The majority of AEs in both treatment groups were deemed to be mild or moderate in intensity. Overall, 8% (five events in five participants) of the adalimumab group had at least one severe AE and 7% (three events in two participants) of the placebo group had one severe AE. The five severe AEs in the adalimumab group were cataract, injection-site reaction, glaucoma, arthralgia and arthritis; the three severe AEs in the placebo group were AC flare (two events in the same participant) and uveitis.

TABLE 8 Adverse events, by treatment group

	Treatment group								
	Adalimumab			Placebo			Total		
System Organ Class	Events (*n*)	Patients (*n*)	% of patients	Events (*n*)	Patients (*n*)	% of patients	Events (*n*)	Patients (*n*)	% of patients
Blood and lymphatic system disorders	5	5	8	0	0	0	5	5	6
Eye disorders	19	15	25	9	8	27	28	23	26
Gastrointestinal disorders	79	28	47	14	9	30	93	37	41
General disorders and administration-site conditions	130	31	52	15	8	27	145	39	43
Immune system disorders	3	3	5	1	1	3	4	4	4
Infections and infestations	149	50	83	30	14	47	179	64	71
Injury, poisoning and procedural complications	15	12	20	5	3	10	20	15	17
Investigations	39	19	32	6	4	13	45	23	26
Metabolism and nutrition disorders	3	3	5	0	0	0	3	3	3
Musculoskeletal and connective tissue disorders	31	16	27	8	7	23	39	23	26
Neoplasms benign, malignant and unspecified (including cysts and polyps)	5	5	8	0	0	0	5	5	6
Nervous system disorders	31	16	27	10	4	13	41	20	22
Psychiatric disorders	5	2	3	2	1	3	7	3	3
Reproductive system and breast disorders	6	2	3	0	0	0	6	2	2
Respiratory, thoracic and mediastinal disorders	84	33	55	9	6	20	93	39	43
Skin and subcutaneous tissue disorders	13	8	13	5	4	13	18	12	13
Surgical and medical procedures	2	2	3	0	0	0	2	2	2

A total of 17 SAEs were reported in 13 (22%) participants in the adalimumab group and three SAEs in two (7%) participants in the placebo group during the course of the blinded phase of the trial. The rate of SAEs was greater in the adalimumab group (0.29 per patient-year) than in the placebo group (0.19 per patient-year).

A participant listing of SAEs for adalimumab and placebo can be found in *Appendix 3* (see *Table 43*). All but one of the SAEs were classified as mild to moderate. This SAE was reported in a participant on placebo whose vision had deteriorated while on medication; the participant's treatment allocation was revealed and, consequently, they commenced on dexamethasone drops and anti-TNF-α.

Laboratory parameters

Haematological

The data relating to haematological parameters are summarised below.

Table 9 gives the mean difference [standard error (SE)] of change in haematological laboratory parameters from baseline to each treatment visit of adalimumab compared with placebo. Differences marked by an asterisk were significant at the 5% level. None of the mean changes in haematological assessments was considered to be clinically significant.

There was evidence of a greater change in lymphocytes from baseline to months 1 and 2 and in eosinophils from baseline to 3 months in the adalimumab group than in the placebo group. The placebo group experienced a greater change in mean red blood cell count from baseline to 6 months than the adalimumab group.

Biochemical

The data relating to biochemical parameters are summarised below.

Table 10 gives the mean difference (SE) of change in biochemical laboratory parameters from baseline to each treatment visit of adalimumab compared with placebo. Differences marked by an asterisk were significant at the 5% level.

There was evidence of a greater change in urea from baseline to months 1, 2, 3 and 18; in potassium from baseline to 6 months; and in creatinine from baseline to 18 months in the placebo group than in the adalimumab group. None of the mean changes in biochemical assessments was considered to be clinically significant.

Urinalysis

Table 11 shows the number of abnormal urinalysis assessments in each treatment group over time. Details on the microscopic analysis are presented in *Table 12*. Overall, the results from the urinalysis were not clinically significant.

Participant diaries and dosing records

Participant diaries and dosing records determined tolerability and compliance throughout the trial treatment period. Treatment compliance was estimated using participant treatment diaries and accountability logs.

Treatment diaries were used to estimate participant compliance by dividing the number of doses recorded as taken in the treatment diary by the expected number of doses the participant should have taken (on the basis of the time the participant was on treatment). According to the treatment diaries, compliance of adalimumab was 84% and compliance of placebo was 74%. MTX compliance was estimated to be 62% for the adalimumab group and 50% for the placebo group (see *Appendix 3*, *Tables 44* and *45*, respectively).

TABLE 9 Mean difference in haematological variables from baseline to each treatment visit of adalimumab compared with placebo

	Month, mean difference (SE)							
Variable	1	2	3	6	9	12	15	18
Haematocrit (%)	0.44 (0.60)	0.27 (0.56)	–0.73 (0.67)	–1.23 (0.76)	–0.81 (1.24)	–1.93 (1.54)	0.12 (1.69)	1.62 (1.88)
Haemoglobin (g/dl)	0.08 (0.17)	0.02 (0.17)	–0.12 (0.18)	–0.41 (0.25)	–0.38 (0.37)	–0.52 (0.41)	–0.37 (0.44)	–0.09 (0.68)
Red blood cell count (× 10^{12}/l)	0.00 (0.06)	–0.00 (0.06)	–0.06 (0.06)	–0.20 (0.08)[a]*	–0.18 (0.11)	–0.18 (0.14)	–0.25 (0.14)	–0.17 (0.17)
White blood cell count (× 10^{12}/l)	0.33 (0.53)	0.09 (0.66)	–0.22 (1.17)	1.17 (0.69)	0.06 (0.99)	0.90 (1.36)	1.36 (1.32)	0.75 (1.63)
Neutrophils (× 10^{9}/l)	–0.07 (0.45)	–0.66 (0.52)	–0.83 (1.10)	0.64 (0.58)	–0.45 (0.70)	0.04 (0.95)	0.40 (1.08)	0.03 (1.29)
Lymphocytes (× 10^{9}/l)	0.39 (0.15)*	0.52 (0.20)*	0.42 (0.23)	0.32 (0.19)	0.53 (0.38)	0.72 (0.42)	0.61 (0.63)	0.34 (0.32)
Monocytes (× 10^{9}/l)	0.04 (0.04)	0.07 (0.05)	0.07 (0.06)	0.12 (0.06)	0.09 (0.09)	0.10 (0.10)	0.20 (0.11)	0.10 (0.13)
Basophils (× 10^{9}/l)	0.01 (0.01)	0.00 (0.01)	–0.00 (0.01)	–0.00 (0.01)	–0.01 (0.01)	–0.01 (0.01)	0.01 (0.01)	–0.01 (0.01)
Eosinophils (× 10^{9}/l)	0.04 (0.06)	0.06 (0.05)	0.14 (0.05)*	0.11 (0.08)	–0.02 (0.06)	–0.02 (0.26)	0.06 (0.10)	0.17 (0.13)
Platelet count (× 10^{9}/l)	–3.34 (12.80)	–6.79 (11.60)	–21.86 (13.48)	–17.27 (13.30)	–14.41 (20.23)	–6.78 (30.89)	–15.56 (37.23)	–15.05 (29.94)
ESR (mm/hour)	0.09 (3.49)	–0.85 (2.71)	–0.03 (2.43)	–1.84 (4.25)	–2.49 (3.40)	3.40 (5.34)	–1.50 (6.25)	5.39 (8.31)
Plasma viscosity[a]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

*$p < 0.05$.

ESR, erythrocyte sedimentation rate; N/A, not applicable.

a In the placebo arm, only one assessment was carried out at baseline and at months 1, 2, 3 and 6; none was carried out at months 9, 12, 15 and 18; therefore, no mean difference could be calculated between the two groups.

TABLE 10 Mean difference (SE) in biochemical variables from baseline to each treatment visit of adalimumab compared with placebo

	Month, mean difference (SE)							
Variable	1	2	3	6	9	12	15	18
CRP (mg/l)	1.15 (2.43)	0.19 (1.43)	0.06 (3.09)	–0.99 (1.78)	–1.82 (2.16)	–0.25 (2.22)	1.26 (3.69)	6.06 (12.90)
Urea (mmol/l)	–0.43 (0.21)*	–0.55 (0.25)*	–0.57 (0.27)*	–0.38 (0.36)	–0.69 (0.49)	–1.02 (0.54)	–1.45 (0.86)	–1.57 (0.72)*
Creatinine (mmol/l)	–1.19 (1.86)	–2.22 (2.27)	0.51 (2.29)	0.45 (1.86)	–0.94 (5.36)	0.88 (3.09)	0.15 (3.89)	–23.64 (8.68)*
Sodium (mmol/lL)	1.07 (0.61)	1.14 (0.64)	–0.05 (0.55)	0.19 (0.96)	0.05 (1.11)	0.39 (1.29)	–0.59 (1.88)	0.57 (2.04)
Potassium (mmol/l)	–0.05 (0.10)	0.01 (0.11)	0.00 (0.13)	–0.29 (0.14)*	0.15 (0.33)	0.18 (0.32)	0.07 (0.21)	–0.09 (0.19)
Calcium (mmol/l)	0.02 (0.02)	0.01 (0.03)	0.04 (0.03)	0.01 (0.03)	–0.03 (0.05)	0.03 (0.05)	0.02 (0.06)	–0.06 (0.08)
Inorganic phosphate (mmol/l)	0.05 (0.06)	0.05 (0.06)	–0.03 (0.06)	0.02 (0.07)	0.08 (0.12)	–0.11 (0.10)	–0.06 (0.14)	–0.09 (0.14)
Glucose (mmol/l)	–0.06 (0.30)	–0.33 (0.30)	0.15 (0.30)	0.43 (0.40)	0.11 (0.77)	0.10 (0.77)	0.69 (0.74)	0.17 (0.84)
Chloride (mmol/l)	0.86 (0.63)	0.31 (0.68)	1.19 (0.76)	1.24 (0.98)	0.41 (1.23)	0.45 (1.33)	–1.25 (1.78)	–0.38 (1.96)
Bicarbonate (mmol/l)	0.28 (1.08)	–0.41 (1.00)	–1.34 (1.01)	0.02 (1.53)	–3.70 (2.42)	1.52 (2.00)	0.39 (3.36)	0.20 (2.90)
Total bilirubin (mmol/l)	1.08 (0.89)	1.25 (0.93)	–0.35 (0.96)	0.84 (1.50)	2.11 (1.69)	2.74 (1.75)	0.06 (3.43)	–3.40 (2.13)
ALT (IU/l)	2.67 (8.05)	6.80 (7.31)	–0.86 (6.11)	1.51 (9.53)	25.83 (41.90)	0.66 (10.92)	9.19 (14.94)	4.29 (13.68)
AST (IU/l)	–3.32 (2.47)	–3.63 (2.72)	–1.02 (4.31)	–4.41 (4.89)	6.03 (26.32)	–11.75 (6.85)	–12.00 (13.41)	8.76 (13.63)

*$p < 0.05$.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein.

TABLE 11 Number of abnormal urinalysis assessments at each visit

Visit	Allocation	Number of abnormal assessments (number of participants)
Baseline	Adalimumab	19 (17)
	Placebo	15 (13)
Month 1	Adalimumab	20 (15)
	Placebo	12 (8)
Month 2	Adalimumab	23 (18)
	Placebo	9 (7)
Month 3	Adalimumab	15 (13)
	Placebo	9 (7)
Month 6	Adalimumab	17 (11)
	Placebo	4 (4)
Month 9	Adalimumab	15 (12)
	Placebo	5 (4)
Month 12	Adalimumab	12 (11)
	Placebo	4 (3)
Month 15	Adalimumab	8 (8)
	Placebo	1 (1)
Month 18	Adalimumab	6 (6)
	Placebo	1 (1)

The accountability logs were used to provide another estimate of adalimumab and placebo compliance by dividing the sum of the number of used vials returned (and the number of missing vials) by the number of vials issued. Estimated compliance for the adalimumab group was 94% and for the placebo group was 90%.

Four participants in the adalimumab group (0069039, 0030035, 0116062 and 0116066) had their medication stopped. Participant 0030035 failed treatment because of missed doses that met failure criteria and taking permitted concomitant medications against acceptable criteria, and one participant (0116003) in the placebo group failed treatment because they missed more than the required number of doses while on treatment.

Four participants had their study medication stopped because of missed doses of MTX: 0116052, 0248064, 0540060 and 0246055. These participants were all receiving adalimumab at the time that they met the threshold for missed doses of MTX.

Use of corticosteroids over duration of study period

Total oral corticosteroid dose

One participant in the placebo group and five participants in the adalimumab group received oral corticosteroids during the course of the blinded treatment phase. The five participants in the adalimumab group were on study treatment for a total of 5.28 years and the placebo participant was on study treatment for 0.17 years.

TABLE 12 Microscopic urinalysis results

Time point	Allocation	Assessments, *n*	Normal assessments, *n* (%)	Abnormal assessments, *n* (%)	If abnormal, clinically significant, *n* (%)	Assessment recorded as not applicable, *n* (%)	Missing, *n* (%)
Baseline	Adalimumab	17	9 (53)	7 (41)	1 (14)	1 (6)	0 (0)
	Placebo	13	7 (54)	4 (31)	0 (0)	2 (15)	0 (0)
1 month	Adalimumab	15	8 (53)	3 (20)	0 (0)	4 (27)	0 (0)
	Placebo	8	4 (50)	3 (38)	0 (0)	1 (13)	0 (0)
2 months	Adalimumab	18	11 (61)	3 (17)	1 (33)	3 (17)	1 (6)
	Placebo	7	3 (43)	3 (43)	0 (0)	0 (0)	1 (14)
3 months	Adalimumab	13	9 (69)	3 (23)	0 (0)	1 (8)	0 (0)
	Placebo	7	4 (57)	2 (29)	0 (0)	0 (0)	1 (14)
6 months	Adalimumab	11	6 (55)	3 (28)	2 (67)	2 (18)	0 (0)
	Placebo	4	4 (100)	0 (0)	N/A	0 (0)	0 (0)
9 months	Adalimumab	12	6 (50)	6 (50)	2 (33)	0 (0)	0 (0)
	Placebo	4	3 (75)	0 (0)	N/A	0 (0)	1 (25)
12 months	Adalimumab	11	7 (64)	3 (27)	2 (67)	1 (9)	0 (0)
	Placebo	3	1 (33)	2 (67)	0 (0)	0 (0)	0 (0)
15 months	Adalimumab	8	5 (63)	2 (25)	0 (0)	1 (13)	0 (0)
	Placebo	1	0 (0)	0 (0)	N/A	1 (100)	0 (0)
18 months	Adalimumab	6	2 (40)	1 (20)	1 (100)	2 (40)	0 (0)
	Placebo	1	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)

The total oral dose for the placebo group was 640 mg (standardised per patient-year, was 3767.74 mg) and 4248.5 mg for the adalimumab group (standardised per patient-year 804.31 mg). A rate ratio of 0.21 (95% CI 0.20 to 0.23; $p < 0.0001$) indicated that participants on placebo required more oral corticosteroids per patient-year than those randomised to adalimumab and there was evidence at the 5% level of a statistically significant difference between the two groups.

Reduction in and rate of systemic corticosteroid dose from entry dose

Reduction in systemic corticosteroid dose from entry dose

Reduction in systemic corticosteroid dose from entry dose to 0 mg

At the beginning of the study, there were six participants (adalimumab group, $n = 5$; placebo group, $n = 1$) who were prescribed systemic corticosteroids (permitted dose < 0.2 mg/kg/day; median dose 0.14 mg/kg/day). Three adalimumab-treated participants stopped systemic corticosteroids (median duration 18.14 weeks). The placebo group participant stopped systemic corticosteroids after 5.57 weeks.

No comparative analysis could be performed because the statistical algorithm did not converge.

Reduction in systemic corticosteroid dose from entry dose to < 5 mg

At the beginning of the study, there were three participants (adalimumab group, $n = 2$; placebo group, $n = 1$) who were on ≥ 5 mg of systemic corticosteroids.

No comparative analysis could be performed because the statistical algorithm did not converge.

One participant on adalimumab had a reduction to < 5 mg of systemic corticosteroids and one participant ended treatment before having a reduction to < 5 mg. The participant on placebo had a reduction to < 5 mg.

Rate of systemic corticosteroid dose from entry dose

The result of this analysis was the same as that of the total oral corticosteroid analysis.

Topical corticosteroid use (frequency) compared with entry use

Time to reduction to fewer than two drops in topical corticosteroid

The outcome was time to reduction to fewer than two drops per day for those participants already at more than two drops per day at baseline. There were 63 participants who were on more than two drops per day at baseline [18 (60%) in the placebo group and 45 (75%) in the adalimumab group] and who were, therefore, included in the analysis.

Twenty-four (53.3%) of the 45 participants on adalimumab and three (16.70%) of the 18 participants on placebo reached fewer than two drops per day before treatment failure (or the 18-month treatment visit). Five participants (11.10%) on adalimumab and one (5.60%) participants on placebo reached the 18-month visit before reaching fewer than two drops per day and 16 (35.6%) of the adalimumab group and 14 (77.8%) of the placebo group had a treatment failure/withdrawal before reaching fewer than two drops per day.

The time to reduction to fewer than two drops per day was statistically significant in favour of adalimumab (HR 3.99, 95% CI 1.18 to 13.48; $p = 0.03$); the incidence plot is shown in *Figure 6*.

Time to reduction to zero drops in topical steroid (post hoc analysis)

The outcome was time to reduction to zero drops for those participants already at more than zero drops at randomisation. There were 74 participants [25 (34%) on placebo and 49 (66%) on adalimumab] who were on more than zero drops at randomisation and who were, therefore, included in the analysis.

Twenty-five (51%) of the 49 participants on adalimumab and four (16%) of the 25 participants on placebo reached zero drops before treatment failure (or the 18-month treatment visit). Six participants (12%) on adalimumab and two participants (8%) on placebo reached the 18-month visit before reaching zero drops and 18 (37%) of the adalimumab group and 19 (76%) of the placebo group had a treatment failure/withdrawal before reaching zero drops.

The time to reduction to zero drops was statistically significant in favour of adalimumab (HR 4.01, 95% CI 1.40 to 11.51; $p = 0.01$); the incidence plot is shown in *Figure 7*.

Need for pulsed corticosteroid

One participant in the placebo group (3%) and two participants in the adalimumab group (3%) required pulsed corticosteroids during the course of the blinded phase. There was no evidence of a difference in the risk of requiring pulsed corticosteroids between the two treatment groups (RR 1.00, 95% CI 0.09 to 10.59; $p > 0.99$).

Optic and ocular

Number of participants having disease flares (as defined by worsening on standardised uveitis nomenclature criteria) following 3 months of disease control

One of the 30 participants in the placebo group (3%) and 5 of the 60 participants in the adalimumab group (8%) experienced 3 months of disease control with a subsequent disease flare; there was no statistically significant difference between the two groups (RR 2.50, 95% CI 0.31 to 20.45; $p = 0.66$).

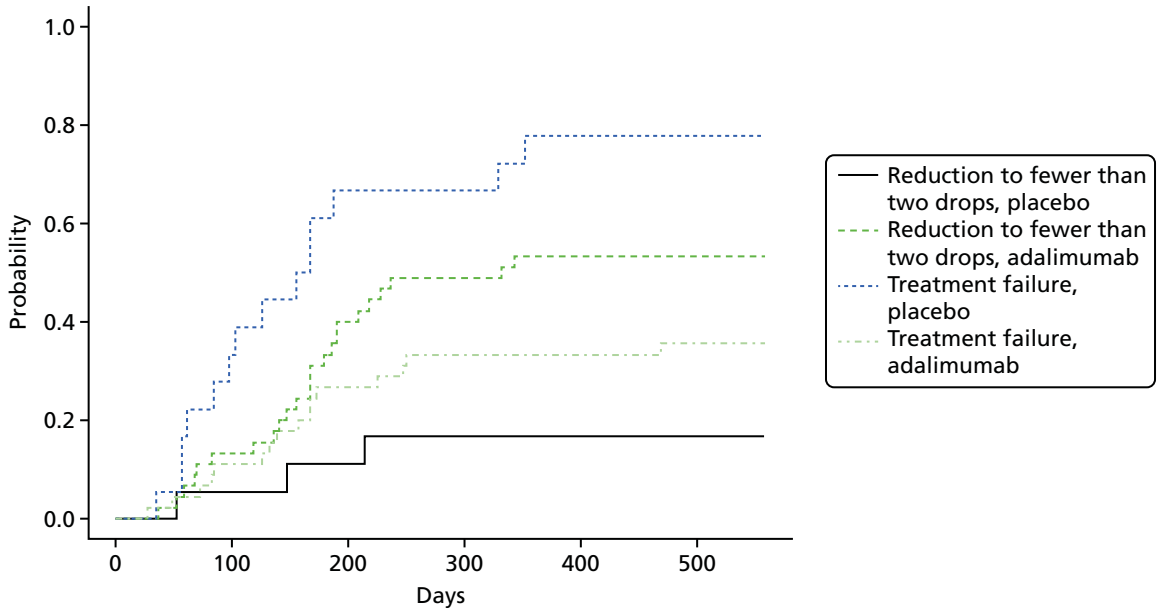


FIGURE 6 Incidence plot of time to reduction to fewer than two drops per day.

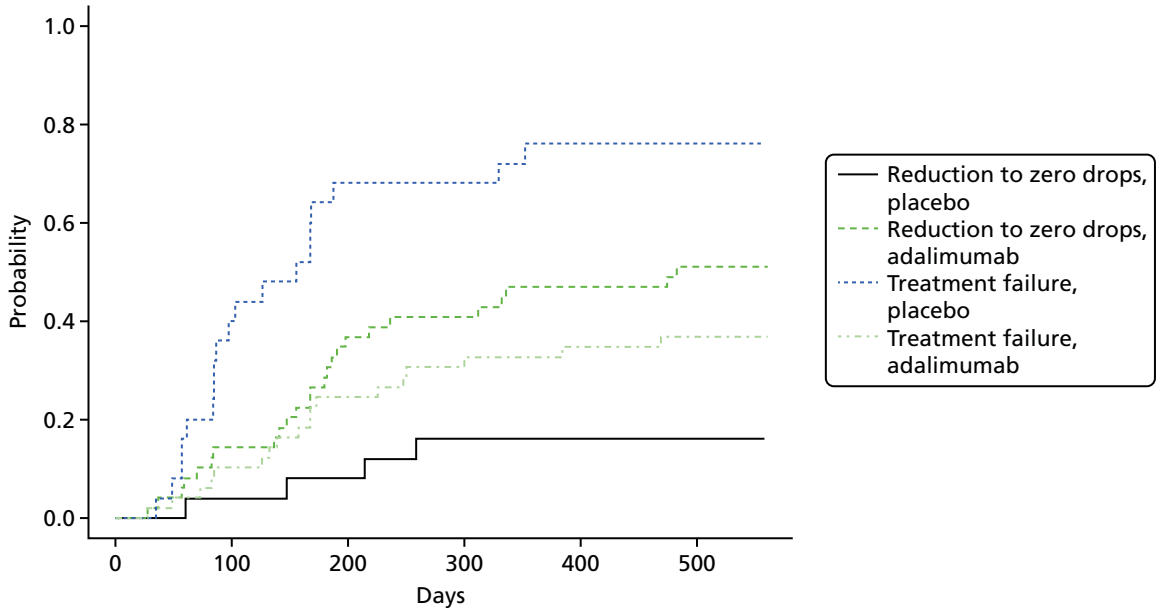


FIGURE 7 Incidence plot for time to reduction to zero drops.

The inference from the analysis of participants who had disease control in both eligible eyes followed by a flare in at least one eye was the same as the analysis of disease control in one eye.

Number of participants having disease flare within the first 3 months

Three participants in the placebo group (10%) and no participants in the adalimumab group had a disease flare in the first 3 months of treatment. There was statistically significant evidence at the 5% level ($p = 0.03$) of a difference (RR 0.07, 95% CI 0.004 to 1.36) between the two groups.

No participants in the placebo group who had a flare within the first 3 months entered the study with two eligible eyes; therefore, the analysis on both eyes was not possible.

Visual acuity measured by age-appropriate logarithm of the minimum angle of resolution assessment

Two analyses were conducted using joint modelling. In each analysis, when only one eye was involved, the single logMAR value was used. When there were two eyes involved, the two analyses were:

- analysis 1 – taking the best logMAR measurement (the minimum of the two values)
- analysis 2 – taking the worst logMAR measurement (the maximum of the two values).

The parameter estimates for analyses 1 and 2 are presented in *Table 13*. For analyses 1 and 2, the results of the joint modelling showed that the treatment effects (adalimumab) on the longitudinal logMAR are –0.01 (95% CI –0.07 to 0.02) and –0.02 (95% CI –0.07 to 0.02), respectively, implying that there is no significant difference between the treatments on logMAR. These estimates are adjusted for failure because of treatment dropout from the trial.

Appendix 3 presents data on the logMAR score for participants in the trial, split by treatment group and time point (see *Table 46*, and *Figures 14* and *15*).

Sensitivity analysis

The residuals from the separate fitted linear missed models (LMMs) for the logMAR indicated slight departures from the normality assumption. In general, fixed-effects estimates are robust to non-normal errors in LMMs.[65] The histograms of baseline logMAR scores (for analyses 1 and 2) appeared approximately normal (not shown) and, therefore, no further analysis from log-transformed data was considered.

In the primary analysis, a random-intercepts model for the longitudinal submodel was fitted. The second sensitivity analysis investigated fitting a random-intercepts and random-slopes model. This showed that inferences remained similar. For analyses 1 and 2, the treatment effect on the longitudinal outcome was –0.01 (95% CI –0.05 to 0.03) and for the random-intercepts and random-slopes model the treatment effect was –0.01 (95% CI –0.05 to 0.03); these were not statistically significant.

TABLE 13 Model parameters for joint modelling of logMAR analyses 1 and 2

Analysis	Component	Parameter	Estimate	95% CI	*p*-value
1	Longitudinal	Intercept	0.01	–0.02 to 0.04	0.76
		Baseline	0.71	0.51 to 0.93	< 0.0001
		Time	–0.001	–0.01 to 0.001	0.22
		Adalimumab	–0.01	–0.07 to 0.02	0.51
	Survival	Adalimumab	–1.37	–2.26 to –0.70	0.001
		HR	0.25	0.10 to 0.50	0.001
	Association	γ_0	3.29	–2.42 to 12.15	0.39
2	Longitudinal	Intercept	0.02	–0.02 to 0.05	0.36
		Baseline	0.82	0.61 to 1.07	< 0.0001
		Time	–0.002	–0.01 to 0.0004	0.21
		Adalimumab	–0.02	–0.07 to 0.02	0.36
	Survival	Adalimumab	–1.36	–2.35 to –0.69	0.001
		HR	0.26	0.10 to 0.50	0.001
	Association	γ_0	3.52	–3.09 to 9.44	0.29

Number of participants with resolution of associated optic nerve or macular oedema (as assessed by slit lamp biomicroscopy or optical coherence tomography, where available)

Four participants in the adalimumab group (6.67%) had associated optic nerve at baseline or developed it at some point during the study, two (50%) of these cases were resolved during the study. There were no participants who had associated optic nerve at baseline or developed this during the course of the study in the placebo group. It was, therefore, not possible to carry out the planned statistical test of these data.

Two participants in the placebo group (7%) had macular oedema at baseline or developed it during the course of the study, compared with four participants in the adalimumab group (7%).

Three participants in the adalimumab group (75%) and no participants in the placebo group had resolution of the macular oedema (RR 5.00, 95% CI 0.34 to 74.52). This was based on the assumption that, if the macular oedema occurred in both eligible study eyes, then resolution only had to occur in at least one of these eyes.

Two of the three participants who had resolution of macular oedema were eligible in both eyes. Because both of these participants experienced resolution in both eyes, there was no difference in results when considering the assumption that the resolution must occur in both eligible eyes.

Number of participants with disease control (defined as zero cells, with topical treatment for 3 and 6 months)

Three months

Two participants in the placebo group (7%) and 23 in the adalimumab group (38%) had disease control for at least 3 months (RR 5.75, 95% CI 1.45 to 22.78; $p = 0.001$).

One (50%) of the two participants with disease control in the placebo group had both eyes eligible at baseline and did not have disease control in both eyes. Of the 23 participants in the adalimumab group, five participants (22%) had both eyes eligible at baseline and all five participants had disease control in both study eyes for at least 3 months. The inference of the analysis when both eligible eyes had to have disease control was the same as that for at least one eligible eye.

Six months

At 6 months, one participant (3%) in the placebo group and 17 participants in the adalimumab group (28%) had disease control in at least one of their eligible eyes (RR 8.50, 95% CI 1.19 to 60.87; $p = 0.005$). Four of the 17 participants (24%) had two eyes eligible at the beginning of the study.

All four participants in the adalimumab group, who were eligible in both eyes at the beginning of the study, had disease control in both eyes for at least 6 months. The inference of the analysis when both eligible eyes had to have disease control was the same as that for at least one eligible eye.

Number of participants entering disease remission (defined as zero cells, without topical treatment for 3 and 6 months)

Three months

At 3 months, one participant in the placebo group (3.33%) and 15 in the adalimumab group (25%) had entered disease remission in any of their eligible eyes (RR 7.50, 95% CI 1.04 to 54.12; $p = 0.02$).

One participant in the placebo group was eligible in both eyes at the beginning of the study, but had disease remission in only one eye; four participants in the adalimumab group were eligible in both eyes at the beginning of the study and all four had disease remission in both eyes. The inference of the analysis when both eligible eyes had to be in remission was the same as that for at least one eligible eye.

Six months

At 6 months, no participants in the placebo group and 13 in the adalimumab group (23%) had entered disease remission in both of their eligible eyes (RR 13.72, 95% CI 0.84 to 223.26, $p = 0.004$).

Four participants in the adalimumab group (29%) were eligible in both eyes at the beginning of the study. After 6 months, three of these four participants had entered remission in both of their eligible eyes and one had not. The inference of the analysis when both eligible eyes had to be in remission was the same as that for at least one eligible eye.

Duration of sustaining inactive disease (zero cells in the anterior chamber, with or without topical treatment)

The difference in the total amount of time that participants sustained inactive disease was statistically significant between the two treatment groups. The estimated mean days of sustained inactive disease was 16.36 days (SE 23.79 days) for the placebo group and 180.91 days (SE 16.81 days) for the adalimumab group, with participants in the adalimumab group spending 164.55 more days (95% CI 104.41 days to 224.69 days; $p < 0.0001$) with inactive disease than those in the placebo group.

Quality-of-life assessment

Childhood Health Questionnaire

Overall, the mean scores for the CHQ psychosocial subscale (PsS) were very similar in both treatment groups, with the adalimumab group having slightly higher scores (see *Appendix 3, Table 47*, and *Figure 16*). The treatment effect on the longitudinal CHQ PsS score was 2.31 (95% CI –0.44 to 5.40), implying that there is no difference between the treatments on the score; however, the *p*-value (0.06) is close to the margin of statistical significance (*Table 14*).

TABLE 14 Joint modelling results (random intercepts only) for PsS and PhS summary scores

Outcome	Component	Parameter	Estimate	95% CI	*p*-value
PsS	Longitudinal	Intercept	15.84	7.49 to 23.13	0.0002
		Baseline	0.68	0.54 to 0.83	< 0.0001
		Time	0.05	–0.17 to 0.23	0.66
		Adalimumab	2.31	–0.44 to 5.40	0.15
	Survival	Adalimumab	–1.66	–2.55 to –0.89	0.0002
		HR	0.19	0.08 to 0.41	0.0002
	Association	γ_0	–0.14	–0.28 to –0.01	0.04
PhS	Longitudinal	Intercept	20.85	12.32 to 30.54	< 0.0001
		Baseline	0.57	0.39 to 0.75	< 0.0001
		Time	–0.02	–0.21 to 0.12	0.83
		Adalimumab	1.16	–2.41 to 5.05	0.55
	Survival	Adalimumab	–1.40	–2.35 to –0.67	0.001
		HR	0.25	0.10 to 0.51	0.001
	Association	γ_0	–0.06	–0.17 to 0.03	0.18

PhS, physical subscale.

The summary statistics for each time point for CHQ physical subscale (PhS) and the mean profile plots are presented in *Appendix 3* (see *Table 48* and *Figure 17*). The treatment effect on the longitudinal CHQ-PhS score was 1.16 (95% CI –2.41 to 5.05), which implies that there is no difference between the treatments on this score (see *Table 14*). This estimate is adjusted for failure because of dropout from the trial.

Sensitivity analysis

The normality assumption was considered for each CHQ score. The log-transform of baseline CHQ scores resulted in distributions that were more normal (not shown), although they still remained somewhat skewed. The residuals from the separate fitted LMMs for the CHQ scores indicated departures from the normality assumption. The log-transformations did not lead to an improvement in model fit according to the Q–Q plot of the residuals (not shown). In general, fixed-effects estimates are robust to non-normal errors in LMMs; therefore, the inferences from the untransformed (raw) CHQ scores are used.

The log-likelihood values for the primary analysis (random-intercepts only) and the sensitivity analysis model (random-intercepts and random-slopes) were calculated. Although the likelihood is increased for the random-intercepts and random-slopes model, it estimates two additional parameters: a variance component for the random slope and a correlation term. Trading off the improvement in goodness of fit against model complexity, only marginal model improvement for PhS was found. However, for PsS, there was greater evidence in favour of the random-intercepts and random-slopes models. The inference on the PhS score remained the same: 1.49 (95% CI –1.87 to 5.45). The treatment effect on the longitudinal PsS score was 2.09 (95% CI –0.74 to 5.21), implying that there was no difference between the treatments on this score too.

As a sensitivity analysis, the missing baseline values ($n = 15$) were imputed with the mean observed values for the other participants and the 57 intermediate missing measurements; the approach was used as per the predefined methodology in the SAP. After imputing the data, the joint model was refitted. The treatment effect on PhS is halved for the imputation analysis; however, both the primary and the imputation analysis treatment effects remain statistically non-significant. The treatment effect on the CHQ-PsS also remained non-significant.

Childhood Health Assessment Questionnaire

The treatment effect on the longitudinal CHAQ is –0.14 (95% CI –0.31 to 0.02) and implies that there is no difference between the treatments on CHAQ (*Table 15*). This estimate is adjusted for failure because of dropout from the trial. However, the *p*-value (0.08) is close to the margin of statistical significance.

TABLE 15 Random-intercepts model: CHAQ

Component	Parameter	Estimate	95% CI	*p*-value
Longitudinal	Intercept	0.20	0.05 to 0.35	0.01
	Baseline	0.65	0.49 to 0.75	< 0.0001
	Time	–0.01	–0.01 to 0.001	0.06
	Adalimumab	–0.14	–0.31 to 0.02	0.09
Survival	Adalimumab	–1.46	–2.23 to –0.80	0.0001
	HR	0.23	0.11 to 0.45	0.0001
Association	γ0	0.64	–0.89 to 2.04	0.35

The summary statistics for the CHAQ are shown for each treatment group for each scheduled study visit. The mean profile plots for each treatment group are given in *Appendix 3* (see *Table 49* and *Figure 18*).

Sensitivity analysis

The distribution of baseline CHAQ scores is non-normal. This is predominantly because of the large proportion of zero baseline scores ($n = 12$ out of 87 remaining participants). However, the effect of the log-transformation had little effect on the normality assumption of the residuals; therefore, no further analysis was carried out.

In the first sensitivity analysis that considered the model specification, the model included a treatment-to-time interaction term, as the treatment effect in the longitudinal submodel in the primary analysis, it was significant at a 10% level. The interaction term in the fitted model was statistically significant. Furthermore, the fixed effects for time and treatment were both significant at the 5% level under this model. The joint log-likelihood values for the model with and without the interaction term indicated an improvement in model fit.

The treatment effects on the longitudinal outcome CHAQ were –0.20 (95% CI –0.37 to –0.06) and implied that CHAQ was significantly lower in the adalimumab group.

The second sensitivity analysis considered a random-intercepts and random-slopes model. There was no apparent increase in likelihood for the random-intercepts and random-slopes model. In addition, the random-intercepts and random-slopes model estimates two additional parameters: a variance component for the random slope and a correlation term. Trading off the improvement in goodness of fit against model complexity, there was no model improvement. The sensitivity analysis that examined missing data used imputation; the joint model was refitted and the inferences remained statistically significant.

American College of Rheumatology Pedi core set criteria at ACR 30, 50, 70, 90 and 100

The results for the joint model of the ACR Pedi and time-to-treatment failure can be seen in *Table 16*. None of the improvements on ACRs is significantly different between treatments. The treatment effect on ACR30 is 0.04 (95% CI –1.37 to 1.59), ACR50 is –0.70 (95% CI –2.15 to 0.77), ACR70 is –1.08 (95% CI –2.70 to 0.46), ACR90 is –0.33 (95% CI –2.22 to 1.39) and ACR100 is –0.32 (95% CI –1.85 to 1.17). These estimates are adjusted for an informatively missing outcome because of treatment failure.

Sensitivity analysis

The time effect was significant at the 10% level for all ACRs except for ACR 30 and 100. Models (estimates not shown in this report) were assessed with time-by-treatment interaction term, but resulted in non-significant effects for time, treatment and time–treatment.

For each model, the deviance information criterion (DIC) statistic was extracted, which can be thought of as the Bayesian analogue of the Akaike information criterion (AIC).

For ACR 90 and 100, the separate longitudinal submodels did not fit or appear to converge. Model fit and convergence problems were not unexpected, because the event (ACR = 1) rates were relatively low for ACR 90 and 100. The event rates were:

- ACR30 – 35.5% ($n = 125$)
- ACR50 – 28.7% ($n = 101$)
- ACR70 – 18.5% ($n = 65$)
- ACR90 – 13.4% ($n = 47$)
- ACR100 – 5.4% ($n = 19$).

TABLE 16 Parameter estimates for ACR 30, 50, 70, 90 and 100

Outcome	Component	Parameter	Estimate	95% CI	*p*-value
ACR30	Longitudinal	Intercept	–1.35	–2.65 to –0.23	0.02
		Time	0.03	–0.03 to 0.09	0.36
		Adalimumab	0.04	–1.37 to 1.59	0.98
	Survival	Adalimumab	–2.13	–3.10 to –1.22	< 0.001
		HR	0.12	0.05 to 0.29	< 0.001
	Association	γ0	–0.23	–0.51 to 0.01	0.07
ACR50	Longitudinal	Intercept	–1.68	–2.98 to –0.53	0.003
		Time	0.06	–0.003 to 0.13	0.06
		Adalimumab	–0.70	–2.15 to 0.77	0.37
	Survival	Adalimumab	–2.22	–3.30 to –1.23	< 0.001
		HR	0.11	0.037 to 0.29	< 0.001
	Association	γ0	–0.27	–0.58 to –0.02	0.04
ACR70	Longitudinal	Intercept	–2.67	–3.93 to –1.46	< 0.001
		Time	0.07	–0.001 to 0.14	0.06
		Adalimumab	–1.08	–2.70 to 0.46	0.16
	Survival	Adalimumab	–2.29	–3.58 to –1.28	< 0.001
		HR	0.10	0.03 to 0.28	< 0.001
	Association	γ0	–0.32	–0.79 to 0.003	0.05
ACR90	Longitudinal	Intercept	–4.48	–6.03 to –3.06	< 0.001
		Time	0.09	0.01 to 0.17	0.04
		Adalimumab	–0.33	–2.22 to 1.39	0.72
	Survival	Adalimumab	–2.59	–4.40 to –1.37	< 0.001
		HR	0.07	0.01 to 0.26	< 0.001
	Association	γ0	–0.41	–0.93 to –0.04	0.03
ACR100	Longitudinal	Intercept	–4.98	–6.25 to –3.88	< 0.001
		Time	0.05	–0.05 to 0.15	0.30
		Adalimumab	–0.32	–1.85 to 1.17	0.65
	Survival	Adalimumab	–2.17	–3.55 to –1.22	< 0.001
		HR	0.11	0.03 to 0.29	< 0.001
	Association	γ0	–0.28	–1.08 to 0.22	0.34

For ACR 70, 90 and 100, the event rates had decreased immensely, from 35.5% for ACR30 to 18.5% for ACR70, 13.4% for ACR90 and 5.4% for ACR100. The primary models for ACR 30, 50 and 70 (compared with the model in sensitivity analysis 1) had overwhelmingly smaller DIC values; therefore, no further models were considered. Note that owing to the problems outlined above, it was not possible to assess whether or not there was an improvement between the primary model and all additional models fitted for ACR 70, 90 and 100.

Number of participants undergoing disease flare, in remission on and/or off medication for their juvenile idiopathic arthritis, and with minimum disease activity

Number of participants undergoing disease flare

Three participants (10%) in the placebo group and no participants in the adalimumab group had at least one case of disease flare of their JIA. In total, there were three episodes of disease flare in the three participants in the placebo group.

The RR for disease flare was 0.07 (95% CI 0.004 to 1.36; $p = 0.03$). The inferences drawn from the 95% CI and *p*-value are different with respect to showing statistical significance; this may be because there were low numbers of participants who had a disease flare in each group.

Number of participants in remission on and/or off medication for their juvenile idiopathic arthritis

These outcomes will be reported in *Chapter 6* because this outcome can be reported only during the follow-up period.

Number of participants with minimum disease activity

There were 74 participants (82.2%) who had oligoarticular JIA, of whom 21 (23.3%) had extended oligoarthritis and 53 (58.9%) had persistent oligoarthritis. Fourteen participants (15.6%) had polyarticular JIA, of whom 12 (13.3%) had RF-positive polyarthritis and two (2.2%) had RF-negative polyarthritis. Two participants (2.2%) had psoriatic arthritis.

Of the 74 participants who had oligoarticular JIA, 50 (68%) received adalimumab [14 (28%) out of 50 participants had extended oligoarthritis and 36 (72%) had persistent oligoarthritis] and 24 (32%) received placebo [seven (29%) out of 24 participants had extended oligoarthritis and 17 (71%) had persistent oligoarthritis].

Of the 14 participants who had polyarticular JIA, nine (64%) received adalimumab [eight (89%) had RF-negative polyarthritis and one (11%) had RF-positive polyarthritis] and five (36%) received placebo [four (80%) out of five had RF-negative polyarthritis and one (20%) had RF-positive polyarthritis).

At baseline, one (3%) participant in the placebo group and four (7%) participants in the adalimumab group had minimum disease activity. The number of participants with minimum disease activity at each time point is reported in *Table 17*. A total of 19 (32%) participants in the adalimumab group and four participants in the placebo group had at least one case of minimum disease activity during the course of the trial. The RR was 2.33 (95% CI 0.87 to 6.24) and the associated *p*-value from the chi-squared test was 0.08, indicating that there was no statistically significant difference between the two groups.

Number of participants requiring change in biological or disease-modifying antirheumatic drugs therapy because of a failure to respond from arthritis

One (3%) participant in the placebo group and two (3%) participants in the adalimumab group required a change in their biological drug therapy or DMARD therapy because of failure to respond from their arthritis. This result was not statistically significant (RR 1.00, 95% CI 0.20 to 5.09; $p = 0.99$).

Juvenile Arthritis Disease Activity Score

The parameter estimates for each of the joint models of JADAS 10, 27 and 71 can be seen in *Table 18*.

The distribution of baseline JADAS scores showed that a log-transformation led to a reduction in skewness. Therefore, the primary analysis joint models are fitted under this transformation.

TABLE 17 Minimum disease activity by treatment group at each time point

Treatment visit	Treatment group: Adalimumab		Placebo		Total	
	Number with oligoarticular JIA or polyarticular JIA	Number (%) with minimum disease activity	Number with oligoarticular JIA or polyarticular JIA	Number (%) with minimum disease activity	Number with oligoarticular JIA or polyarticular JIA	Number (%) with minimum disease activity
Baseline	59	4 (7)	29	1 (3)	88	5 (6)
1 month	59	5 (8)	29	0 (0)	88	5 (6)
2 months	57	1 (2)	24	1 (4)	81	2 (3)
3 months	55	8 (15)	18	3 (17)	73	11 (15)
6 months	47	5 (10)	12	0 (0)	59	5 (8)
9 months	42	4 (10)	7	0 (0)	49	4 (8)
12 months	34	3 (9)	5	1 (20)	39	4 (10)
15 months	27	3 (11)	3	0 (0)	30	3 (10)
18 months	23	2 (9)	3	0 (0)	26	2 (8)

TABLE 18 Parameter estimates from joint modelling (random intercepts only) for JADAS 10, 27 and 71

Outcome	Component	Parameter	Estimate	95% CI	*p*-value
JADAS10	Longitudinal	Intercept	0.62	0.24 to 1.07	0.003
		Baseline	0.42	0.25 to 0.56	< 0.0001
		Time	–0.01	–0.03 to 0.01	0.27
		Adalimumab	–0.35	–0.78 to 0.01	0.07
	Survival	Adalimumab	–2.38	–3.92 to –1.48	0.25
		HR	0.09	0.02 to 0.23	0.25
	Association	$\gamma 0$	1.11	0.11 to 2.85	0.10
JADAS27	Longitudinal	Intercept	0.62	0.25 to 1.06	0.003
		Baseline	0.42	0.24 to 0.57	< 0.0001
		Time	–0.01	–0.03 to 0.01	0.27
		Adalimumab	–0.34	–0.76 to 0.03	0.08
	Survival	Adalimumab	–2.37	–3.97 to –1.47	0.25
		HR	0.09	0.02 to 0.23	0.25
	Association	$\gamma 0$	1.10	0.08 to 2.88	0.11
JADAS71	Longitudinal	Intercept	0.63	0.24 to 1.08	0.003
		Baseline	0.42	0.25 to 0.56	< 0.0001
		Time	–0.01	–0.03 to 0.01	0.26
		Adalimumab	–0.36	–0.78 to 0.004	0.07
	Survival	Adalimumab	–2.38	–3.88 to –1.48	0.25
		HR	0.09	0.02 to 0.23	0.25
	Association	$\gamma 0$	1.11	0.11 to 2.81	0.0981

The treatment effects on the longitudinal JADAS 10, 27 and 71 were all non-significant at the 5% level, implying that there is no difference in scores between the treatments. However, all three *p*-values are close to the margin of statistical significance.

Sensitivity analysis

For each outcome, a treatment–time interaction term was fitted because the treatment effect in the longitudinal submodel was significant at the 10% level. In all cases, there was some negligible increase in likelihood, and the corresponding AICs were slightly higher for the models with interaction, which did not support selection of the models with interaction terms. The estimated treatment effect on the longitudinal JADAS 10 and 71 also had *p*-values slightly below the 5% level.

The second model-specification sensitivity analysis considered a random-intercepts and random-slopes model. The log-likelihood values for the primary analysis (random-intercepts only) and the sensitivity analysis model (random intercepts and random slopes) showed that the likelihood is increased for the random-intercepts and random-slopes model. Trading off the improvement in goodness of fit against model complexity, the AIC confers evidence of model fit improvement. The treatment effects on all three longitudinal JADAS scores are marginally significant, with *p*-values just above 5%.

When the sensitivity analysis was conducted examining the effects of missing data, the treatment effects for each outcome in the longitudinal submodel were statistically significant ($p < 0.05$). Moreover, the association parameters are also significant ($p < 0.05$), implying that high JADAS values lead to a significantly high risk of treatment failure. This would suggest that the additional data have led to an increased power to detect the treatment effects and latent association parameters.

Chapter 6 Clinical effectiveness results: open-label phase

The results reported in this chapter are based on the integrated analysis of the blinded and open-label phase for participants in the adalimumab group compared with the results from the blinded phase for participants in the placebo group. The last participant visit in the open-label phase took place on 29 June 2016.

Primary outcome

During the course of the open-label phase of the trial, there were three additional treatment failures that occurred in the adalimumab arm. One participant was classified as having a treatment failure because they had taken permitted concomitant medications against the acceptable criteria and two participants had sustained scores (as recorded at entry grade) that were still present after 6 months of therapy (see *Appendix 3, Table 50*).

There were a total of 17 (28.3%) treatment failures for the 60 participants in the adalimumab group and 17 (56.7%) failures for the 30 participants in the placebo group. Median time to treatment failure was 24.1 weeks (95% CI 14.7 weeks to 81 weeks) in the placebo group and not reached in the adalimumab group within the 18-month treatment period because fewer than half of the subjects experienced treatment failure at the conclusion of the study (*Figure 8*).

The results of the log-rank test from SAS PROC LIFETEST (SAS Institute In, Cary, NC, USA) offered strong statistical evidence that the placebo and adalimumab groups differed with respect to time to treatment failure.

The HR indicated that treatment with adalimumab significantly decreased the hazard of treatment failure by 74% (HR 0.26, 95% CI 0.13 to 0.51; $p < 0.0001$), relative to placebo.

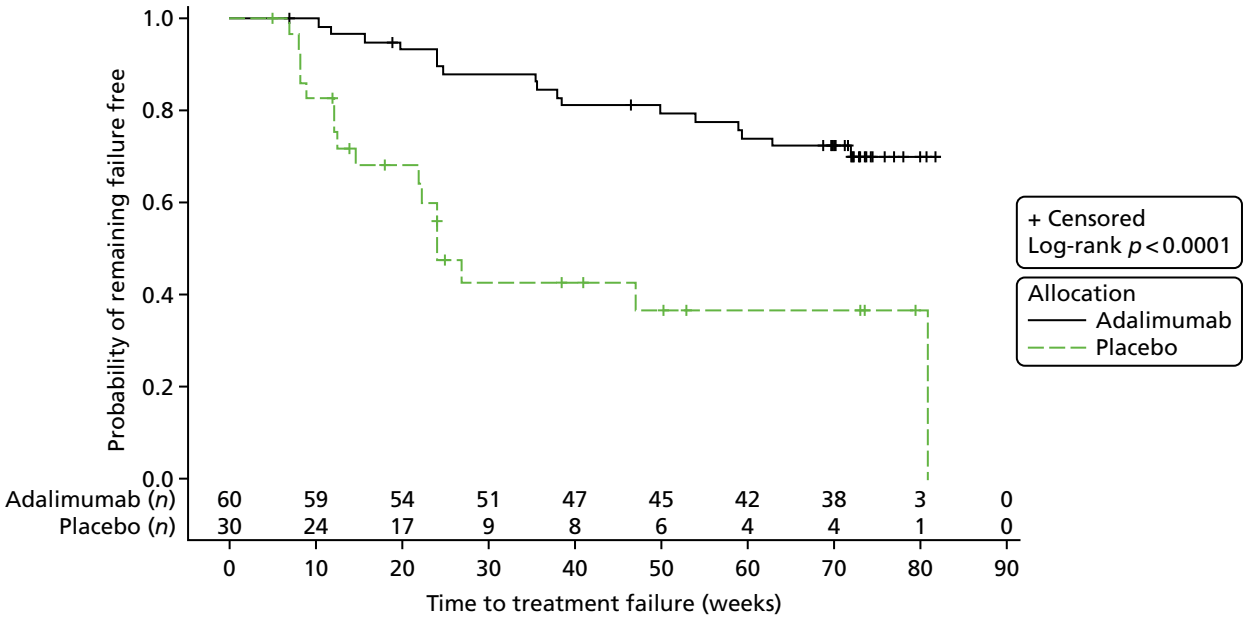


FIGURE 8 Primary outcome Kaplan–Meier plot for blinded and open-label phase.

Test of proportional hazards assumption

The assumption of proportional hazards was tested by including an interaction between time and treatment group in the Cox proportional hazards model. There was no evidence ($p = 0.1371$) that the interaction was not zero and, therefore, no evidence that the HR was not constant over time.

Sensitivity analyses

There were no losses to follow-up during the course of the trial and, therefore, sensitivity analysis 8 was not conducted. The results of the other sensitivity analyses indicate that the original conclusion from the primary analysis was robust with regard to the changes that were made. The overall statistical significance of the sensitivity analyses did not change.

Additional analyses

Development of uveitis in non-study eye

There were no additional occurrences of this outcome during the open-label phase of the trial.

Time to treatment failure in both eyes

This analysis was not possible because only one participant (in the placebo group) failed in both eyes at different times.

Development of comorbidity from treatment failure

There were no additional occurrences of this outcome during the open-label phase of the trial. There were so few numbers in the two treatment groups of those who developed a comorbidity that any modelling, including the development of a comorbidity, was not possible.

Post hoc analyses

Time-to-treatment response

During the open-label phase of the trial, there were three participants in the adalimumab group who achieved treatment response, meaning that, overall, during the blinded and open-label phases, a total of 47 participants in the adalimumab group were classified as having a treatment response. The difference between the two groups was statistically significant (log-rank p-value = 0.003). The HR indicated that participants on adalimumab were just under three times more likely to achieve a treatment response than those on placebo (HR 2.96, 95% CI 1.40 to 6.27).

Proportion of responders/failures/no change

Proportion of responders/failures/no change at 3 months

During the open-label phase of the trial, there were no further occurrences of response at 3 months and the overall conclusion showed a significant difference between the treatment groups at 6 months.

Proportion of responders/failures/no change at 6 months

During the open-label phase of the trial, there were no further occurrences of response at 6 months and the overall conclusion showed a significant difference between the treatment groups at 6 months.

Area under the curve of anterior chamber cells in eligible eye

There was a significant difference in the median number of AC cells between the two groups from the overall data of –0.81 (95% CI –0.99 to –0.64; $p < 0.0001$) (results from eye level favouring the adalimumab group), with similar results obtained when the best or worst score was used for participants with two eligible eyes.

Secondary outcomes

Number of participants failing treatment

Seventeen participants in the adalimumab group (28.33%) and 17 participants in the placebo group (56.67%) were classified as having treatment failures. The risk of having a treatment failure was statistically significantly reduced by 54% (RR 0.46, 95% CI 0.26 to 0.83; $p = 0.01$) in the adalimumab group compared with placebo.

Safety, tolerability and compliance

Adverse events and serious adverse events

During the open-label phase of the trial, 63 AEs occurred in 12 participants and two SAEs occurred in two participants (one SAE was reported outside the 30-day window of treatment cessation). For completeness, the SAE that was reported outside the reporting time window has been reported in *Appendix 3* (see *Table 43*) only and is not included in any of the total numbers. The SAE that was reported during follow-up was in relation to joint swelling of the right knee and the severity was classified as mild and judged 'unlikely' to be related to the study drug.

A total of 86 participants (out of 90) experienced at least one AE. A total of 682 AEs were reported in 60 participants (100%) in the adalimumab group and 114 AEs reported in 26 participants (86.7%) in the placebo group. The rate of AEs in the adalimumab group (9.86 per patient-year) was greater than that in the placebo group (7.21 per patient-year).

The most common AEs in the adalimumab group were classified as infections and infestations (85.0%); general disorders and administration-site conditions (55%); respiratory, thoracic and mediastinal disorders (55.0%); gastrointestinal disorders (48.3%); investigations (35.0%); nervous system disorders (31.7%); eye disorders (28.3%); musculoskeletal and connective tissue disorders (26.7%); and injury, poisoning and procedural complications (23.3%) (*Table 19*).

Laboratory parameters (haematological, biochemical analysis and urinalysis)

When the data from the open-label period were combined with the data from the blinded phase of the trial, there were no changes to the clinical conclusions of the analyses of the haematological, biochemical and urinalysis data.

Participant diaries and dosing records

On average, treatment compliance for the adalimumab group during the open-label phase of the study, was 84%, according to the participant diaries, and 87%, according to the accountability logs. Overall, treatment compliance for the adalimumab group during the blinded phase of the trial and the open-label phase of the study combined was 83%, according to the participant diaries, and 94%, according to the accountability logs.

The average compliance with MTX for the adalimumab group during the open-label phase of the trial (according to participant diaries) was 74%; the average compliance with MTX for the adalimumab group overall for both phases of the trial was 61%.

Use of corticosteroids over duration of study period

Total oral corticosteroid dose

One participant in the placebo group and five participants in the adalimumab group received oral corticosteroids during the course of the study. The five participants in the adalimumab group were on study treatment for a total of 6.03 years and the placebo participant was on study treatment for 0.17 years.

TABLE 19 Adverse events by treatment group (an integrated analysis of the blinded and open-label phases)

System Organ Class	Treatment group								
	Adalimumab			Placebo			Total		
	Events (*n*)	Patients (*n*)	% of patients	Events (*n*)	Patients (*n*)	% of patients	Events (*n*)	Patients (*n*)	% of patients
Blood and lymphatic system disorders	5	5	8.3	0	0	0.0	5	5	5.6
Ear and labyrinth disorders	1	1	1.7	0	0	0.0	1	1	1.1
Eye disorders	21	17	28.3	9	8	26.7	30	25	27.8
Gastrointestinal disorders	87	29	48.3	14	9	30.0	101	38	42.2
General disorders and administration-site conditions	135	33	55.0	15	8	26.7	150	41	45.6
Immune system disorders	4	4	6.7	1	1	3.3	5	5	5.6
Infections and infestations	164	51	85.0	30	14	46.7	194	65	72.2
Injury, poisoning and procedural complications	18	14	23.3	5	3	10.0	23	17	18.9
Investigations	43	21	35.0	6	4	13.3	49	25	27.8
Metabolism and nutrition disorders	3	3	5.0	0	0	0.0	3	3	3.3
Musculoskeletal and connective tissue disorders	32	16	26.7	8	7	23.3	40	23	25.6
Neoplasms benign, malignant and unspecified (including cysts and polyps)	5	5	8.3	0	0	0.0	5	5	5.6
Nervous system disorders	36	19	31.7	10	4	13.3	46	23	25.6
Psychiatric disorders	5	2	3.3	2	1	3.3	7	3	3.3
Reproductive system and breast disorders	11	3	5.0	0	0	0.0	11	3	3.3
Respiratory, thoracic and mediastinal disorders	95	33	55.0	9	6	20.0	104	39	43.3
Skin and subcutaneous tissue disorders	14	9	15.0	5	4	13.3	19	13	14.4
Surgical and medical procedures	3	3	5.0	0	0	0.0	3	3	3.3

The total oral dose for the placebo group was 640 mg (which was 3767.74 mg standardised per patient-year) and 4267.5 mg for the adalimumab group (which was 707.70 mg standardised per patient-year). A rate ratio of 0.19 (95% CI 0.17 to 0.20) indicated that participants on placebo required more oral corticosteroids per patient-year than those on adalimumab and there was evidence at the 5% level of a statistically significant difference between the two groups ($p < 0.0001$).

Reduction in and rate of systemic corticosteroid dose from entry dose

Reduction in systemic corticosteroid dose from entry dose

Reduction in systemic corticosteroid dose from entry dose to 0 mg This analysis was not able to be performed because the statistical algorithm did not converge.

Reduction in systemic corticosteroid dose from entry dose to < 5 mg This analysis was not able to be performed because the statistical algorithm did not converge.

Rate of systemic corticosteroid dose from entry dose
The result of this analysis was the same as that of the total oral corticosteroid analysis.

Topical corticosteroid use (frequency) compared with entry use

Time to reduction to fewer than two drops in topical corticosteroid
The time to reduction to fewer than two drops per day was statistically significant in favour of adalimumab (HR 4.25, 95% CI 1.26 to 14.31; $p = 0.02$).

Time to reduction to zero drops in topical steroid (post hoc analysis)
The time to reduction to zero drops per day was statistically significant in favour of adalimumab (HR 4.26, 95% CI 1.49 to 12.2; $p = 0.01$).

Need for pulsed corticosteroid
During the open-label phase of the trial, there were no additional participants who required pulsed steroids. In total, one participant in the placebo group (3.33%) and two participants in the adalimumab group (3.33%) required pulsed corticosteroids during the course of the study. The RR showed that there was no evidence of a difference in the risk of requiring pulsed corticosteroids between the two treatment groups (RR 1.00, 95% CI 0.09 to 10.59; $p > 0.99$).

Optic and ocular

Number of participants having disease flares (as defined by worsening on Standardisation of the Uveitis Nomenclature criteria) following 3 months' disease control
All events of disease flare following disease control took place in the blinded phase of the trial (i.e. there were no further events within the open-label phase).

Number of participants having disease flares within the first 3 months
One participant in the adalimumab arm failed treatment within the open-label phase of the study.

Overall, three participants in the placebo group (10%) and one participant in the adalimumab group (3%) had a disease flare in the first 3 months of treatment. There was no statistically significant evidence at the 5% level ($p = 0.11$) of a difference (RR 0.17, 95% CI 0.02 to 1.54) between the two groups.

Visual acuity measured by age-appropriate logarithm of the minimum angle of resolution assessment
The integrated analysis for the data on the logMAR score for participants in the trial split by treatment group and time point can be found in *Table 20*.

The parameter estimates from the joint modelling for analyses 1 and 2 (for the blinded and open-label phase of the trial combined) are shown in *Table 21*.

The results for integrated analyses 1 and 2 for the treatment effects (adalimumab) on the longitudinal logMAR are 0.01 (95% CI –0.06 to 0.02) and –0.02 (95% CI –0.07 to 0.02), respectively, implying that there is no significant difference between the treatments on logMAR.

These estimates are adjusted for the failure caused by treatment dropout from the trial.

TABLE 20 The logMAR results for best/worst score by treatment group for each time point

	Treatment group																	
	Adalimumab						Placebo						Total					
	Best score			Worst score			Best score			Worst score			Best score			Worst score		
Visit	*n*	Mean (SD)	Median (Range)	*n*	Mean (SD)	Median (Range)	*n*	Mean (SD)	Median (Range)	*n*	Mean (SD)	Median (Range)	*n*	Mean (SD)	Median (Range)	*n*	Mean (SD)	Median (Range)
Baseline	60	0.04 (0.15)	0.00 (–0.23 to 0.56)	60	0.05 (0.16)	0.00 (–0.23 to 0.56)	30	0.06 (0.12)	0.05 (–0.13 to 0.40)	30	0.08 (0.12)	0.06 (–0.10 to 0.40)	90	0.04 (0.14)	0.00 (–0.23 to 0.56)	90	0.06 (0.14)	0.03 (–0.23 to 0.56)
1 month	60	0.03 (0.17)	0.00 (–0.30 to 0.80)	60	0.04 (0.18)	0.00 (–0.30 to 0.80)	30	0.02 (0.16)	0.00 (–0.28 to 0.38)	30	0.06 (0.17)	0.04 (–0.28 to 0.38)	90	0.02 (0.17)	0.00 (–0.30 to 0.80)	90	0.05 (0.18)	0.00 (–0.30 to 0.80)
2 months	58	0.02 (0.17)	0.00 (–0.20 to 0.56)	58	0.04 (0.19)	0.00 (–0.20 to 0.75)	25	0.05 (0.18)	0.00 (–0.15 to 0.76)	25	0.06 (0.18)	0.02 (–0.15 to 0.76)	83	0.03 (0.17)	0.00 (–0.20 to 0.76)	83	0.04 (0.19)	0.00 (–0.20 to 0.76)
3 months	57	0.00 (0.16)	0.00 (–0.20 to 0.80)	57	0.02 (0.19)	0.00 (–0.20 to 0.88)	19	0.01 (0.11)	0.00 (–0.13 to 0.24)	19	0.03 (0.12)	0.00 (–0.13 to 0.28)	76	0.00 (0.14)	0.00 (–0.20 to 0.80)	76	0.02 (0.18)	0.00 (–0.20 to 0.88)
6 months	51	0.02 (0.19)	–0.02 (–0.20 to 0.88)	51	0.02 (0.19)	0.00 (–0.20 to 0.88)	12	0.05 (0.16)	0.02 (–0.18 to 0.30)	12	0.07 (0.19)	0.02 (–0.18 to 0.38)	63	0.02 (0.18)	0.00 (–0.20 to 0.88)	63	0.03 (0.19)	0.00 (–0.20 to 0.88)
9 months	48	–0.01 (0.14)	0.00 (–0.25 to 0.40)	48	–0.01 (0.14)	0.00 (–0.25 to 0.40)	7	0.00 (0.17)	–0.08 (–0.10 to 0.36)	7	0.04 (0.20)	–0.08 (–0.10 to 0.36)	55	–0.01 (0.14)	0.00 (–0.25 to 0.40)	55	0.00 (0.14)	0.00 (–0.25 to 0.40)
12 months	43	–0.02 (0.14)	–0.02 (–0.23 to 0.34)	43	–0.01 (0.14)	0.00 (–0.23 to 0.34)	5	0.03 (0.14)	0.02 (–0.10 to 0.26)	5	0.08 (0.17)	0.03 (–0.10 to 0.26)	48	–0.02 (0.14)	–0.01 (–0.23 to 0.34)	48	0.00 (0.14)	0.00 (–0.23 to 0.34)
15 months	38	–0.01 (0.12)	0.00 (–0.25 to 0.40)	38	0.00 (0.12)	0.00 (–0.25 to 0.40)	3	0.00 (0.26)	–0.10 (–0.20 to 0.30)	3	0.00 (0.26)	–0.10 (–0.20 to 0.30)	41	–0.01 (0.13)	0.00 (–0.25 to 0.40)	41	0.00 (0.13)	0.00 (–0.25 to 0.40)
18 months	34	0.00 (0.13)	0.00 (–0.22 to 0.28)	34	0.01 (0.12)	0.00 (–0.22 to 0.28)	3	0.02 (0.21)	–0.10 (–0.10 to 0.26)	3	0.02 (0.21)	–0.10 (–0.10 to 0.26)	37	0.00 (0.13)	0.00 (–0.22 to 0.28)	37	0.01 (0.12)	0.00 (–0.22 to 0.28)

TABLE 21 Model parameters for joint modelling of logMAR analyses 1 and 2

Analysis	Component	Parameter	Estimate	95% CI	*p*-value
1	Longitudinal	Intercept	0.01	–0.03 to 0.04	0.76
		Baseline	0.70	0.51 to 0.92	< 0.0001
		Time	–0.002	-0.004 to 4×10^{-4}	0.17
		Adalimumab	–0.01	–0.06 to 0.02	0.53
	Survival	Adalimumab	–1.33	–2.25 to –0.73	0.001
		HR	0.26	0.11 to 0.48	0.001
	Association	γ_0	2.86	–2.41 to 10.37	0.41
2	Longitudinal	Intercept	0.02	–0.02 to 0.05	0.37
		Baseline	0.81	0.60 to 1.06	< 0.0001
		Time	–0.002	-0.004 to 3×10^{-4}	0.17
		Adalimumab	–0.02	–0.07 to 0.02	0.37
	Survival	Adalimumab	–1.32	–2.23 to –0.70	0.001
		HR	0.27	0.11 to 0.50	0.001
	Association	γ_0	3.31	–2.14 to 8.43	0.27

Sensitivity analysis

The inferences of the sensitivity analyses for the data from the blinded phase of the trial combined with the open-label data were the same as those from the blinded phase alone.

Number of participants with resolution of associated optic nerve or macular oedema (as assessed by slit lamp biomicroscopy or optical coherence tomography, where available)

There were no further occurrences of optic nerve resolution or macular oedema in the open-label phase of the study.

Number of participants with disease control (defined as zero cells, with topical treatment for 3 and 6 months)

Three months

There were four participants in the adalimumab group who achieved disease control for 3 months during the open-label phase in at least one eligible eye. This meant that, overall, two participants in the placebo group (7%) and 27 in the adalimumab group (45%) had disease control for at least 3 months (RR 6.75, 95% CI 1.72 to 26.51; $p = 0.0002$).

The inferences for disease control in all eligible eyes were the same as those for disease control in one eligible eye.

Six months

There were five participants in the adalimumab group who achieved disease control for 3 months during the open-label phase in at least one eligible eye meaning that, overall, one participant (3%) in the placebo group and 22 participants in the adalimumab group (36.67%) had disease control in at least one of their eligible eyes (RR 11.00, 95% CI 1.56 to 77.74; $p = 0.0003$).

The inferences for disease control in all eligible eyes were the same as those for disease control in one eligible eye.

Number of participants entering disease remission (defined as zero cells, without topical treatment for 3 and 6 months)

Three months

There were no further cases of disease remission in the open-label phase.

Six months

There were no further cases of disease remission in the open-label phase.

Duration of sustaining inactive disease (zero cells in the anterior chamber, with or without topical treatment)

The difference in the total number of days that participants sustained inactive disease was statistically significant between the two treatment groups [16.31 days (SE 25.69 days) for the placebo group and 225.43 days (SE 18.15 days) for the adalimumab group], with participants in the adalimumab group spending approximately 209 (mean difference 208.80, 95% CI 143.91 to 273.69) more days with inactive disease than those in the placebo group ($p < 0.0001$).

Quality-of-life assessment

Childhood Health Questionnaire

The treatment effect on the longitudinal CHQ-PsS score (blinded and open-label phases) was 2.37 (95% CI –0.41 to 5.47), which implies that there is no difference between the treatments on the score (*Table 22*).

The treatment effect on the longitudinal CHQ-PhS score (blinded and open-label phases) was 1.23 (95% CI –2.31 to 5.28), which implies that there is no difference between the treatments on this score (see *Table 22*). This estimate is adjusted for the failure due to dropout from the trial.

Sensitivity analysis

The inferences of the sensitivity analyses for the data from the blinded phase of the trial combined with the open-label data were the same as those from the blinded phase alone.

Childhood Health Assessment Questionnaire

The overall treatment effect (blinded and open-label phases) on the longitudinal CHAQ was –0.14 (95% CI –0.32 to 0.003), which implies that there is no difference between the treatments on CHAQ (*Table 23*). This estimate is adjusted for the failure due to dropout from the trial. However, the *p*-value (0.08) is close to the margin of statistical significance.

Sensitivity analysis

The inferences of the sensitivity analyses for the data from the blinded phase of the trial combined with the open-label data were the same as those from the blinded phase alone.

TABLE 22 Joint modelling results (random intercepts only) for the PsS and PhS summary score

Outcome	Component	Parameter	Estimate	95% CI	*p*-value
PsS	Longitudinal	Intercept	15.37	6.54 to 22.59	0.0004
		Baseline	0.69	0.55 to 0.85	< 0.0001
		Time	0.08	–0.10 to 0.23	0.34
		Adalimumab	2.37	–0.41 to 5.47	0.14
	Survival	Adalimumab	–1.56	–2.45 to –0.85	0.0002
		HR	0.21	0.09 to 0.43	0.0002
	Association	γ_0	–0.11	–0.24 to –0.01	0.07
PhS	Longitudinal	Intercept	20.68	12.17 to 30.70	< 0.0001
		Baseline	0.58	0.38 to 0.75	< 0.0001
		Time	0.04	–0.11 to 0.16	0.56
		Adalimumab	1.23	–2.31 to 5.28	0.53
	Survival	Adalimumab	–1.34	–2.30 to –0.67	0.001
		HR	0.26	0.10 to 0.51	0.001
	Association	γ_0	–0.05	–0.15 to 0.03	0.24

TABLE 23 Random intercepts model (overall data): CHAQ

Component	Parameter	Estimate	95% CI	*p*-value
Longitudinal	Intercept	0.20	0.05 to 0.35	0.01
	Baseline	0.65	0.49 to 0.76	< 0.0001
	Time	–0.01	-0.01 to 4×10^{-4}	0.01
	Adalimumab	–0.14	–0.32 to 0.01	0.08
Survival	Adalimumab	–1.42	–2.19 to –0.73	0.0001
	HR	0.24	0.11 to 0.48	0.0001
Association	γ_0	0.43	–1.29 to 1.70	0.54

American College of Rheumatology Pedi core set criteria at ACR 30, 50, 70, 90 and 100

The results for the joint modelling of ACR Pedi and time to treatment failure can be seen in *Table 24*. None of the improvements on ACRs is significantly different between treatments. All estimates are adjusted for the failure caused by dropout from the trial.

Sensitivity analysis

The inferences of the sensitivity analyses for the data from the blinded phase of the trial combined with the open-label data were the same as those from the blinded phase alone.

TABLE 24 Parameter estimates for ACR 30, 50, 70, 90 and 100

Outcome	Component	Parameter	Estimate	95% CI	*p*-value
ACR30	Longitudinal	Intercept	–1.35	–2.54 to –0.25	0.02
		Time	0.04	–0.01 to 0.09	0.11
		Adalimumab	0.01	–1.37 to 1.49	0.99
	Survival	Adalimumab	–1.98	–2.97 to –1.07	< 0.001
		HR	0.14	0.05 to 0.34	< 0.001
	Association	γ_0	–0.21	–0.50 to 0.03	0.10
ACR50	Longitudinal	Intercept	–1.69	–2.97 to –0.50	0.01
		Time	0.07	0.01 to 0.13	0.02
		Adalimumab	–0.71	–2.20 to 0.78	0.34
	Survival	Adalimumab	–2.12	–3.15 to –1.24	< 0.001
		HR	0.12	0.04 to 0.29	< 0.001
	Association	γ_0	–0.26	–0.58 to –0.02	0.04
ACR70	Longitudinal	Intercept	–2.72	–4.10 to –1.54	< 0.001
		Time	0.08	0.01 to 0.14	0.02
		Adalimumab	–1.11	–2.68 to 0.42	0.16
	Survival	Adalimumab	–2.34	–4.06 to –1.18	< 0.001
		HR	0.10	0.02 to 0.31	< 0.001
	Association	γ_0	–0.38	–0.99 to –0.04	0.02
ACR90	Longitudinal	Intercept	–4.74	–6.48 to –3.21	< 0.001
		Time	0.11	0.04 to 0.18	0.004
		Adalimumab	–0.48	–2.47 to 1.44	0.62
	Survival	Adalimumab	–2.55	–4.21 to –1.30	< 0.001
		HR	0.08	0.015 to 0.27	< 0.001
	Association	γ_0	–0.38	–0.85 to –0.07	0.01
ACR100	Longitudinal	Intercept	–5.13	–6.38 to –3.92	< 0.001
		Time	0.10	0.01 to 0.18	0.03
		Adalimumab	–0.43	–1.91 to 1.04	0.57
	Survival	Adalimumab	–2.37	–4.52 to –1.15	< 0.001
		HR	0.09	0.01 to 0.32	< 0.001
	Association	γ_0	–0.44	–1.18 to 0.15	0.18

Number of participants undergoing disease flare, in remission on and/or off medication for their juvenile idiopathic arthritis, and with minimum disease activity

Number of participants undergoing disease flare

During the open-label phase of the trial, there were no additional occurrences of participants undergoing a disease flare; therefore, the results of the combined analyses are the same as those reported during the blinded phase.

Number of participants in remission on and/or off medication for their juvenile idiopathic arthritis

Number of participants in remission on medication for their juvenile idiopathic arthritis

Seven participants (12%) in the adalimumab group and 17 (57%) participants in the placebo group could not be included in the analysis because they had not been on medication for the required amount of time (6 months).

Ten (19%) of those in the adalimumab analysis population achieved remission; none of the placebo participants did. The risk of having remission while on medication in the adalimumab group was greater than for those on placebo but was not statistically significant (RR 5.40, 95% CI 0.30 to 87.40; $p = 0.19$).

Number of participants in remission off medication for their juvenile idiopathic arthritis

There were 45 (75%) participants in the adalimumab group and 21 (70%) in the placebo group who could not be included in the analysis because they had not been off medication for the required amount of time (12 months).

No participants in either the adalimumab group or the placebo group achieved remission off medication for their JIA.

Number of participants with minimum disease activity

During the open-label phase of the trial, 22 (37%) participants in the adalimumab group (this was three more than the result from the blinded phase alone) and four participants in the placebo group had at least one case of minimum disease activity during the course of the trial. The RR was 2.70 (95% CI 1.03 to 7.12) and the associated *p*-value from the chi-squared test was 0.03, indicating that there was a statistically significant difference between the two groups.

Number of participants requiring change in biological or disease-modifying antirheumatic drug therapy as a result of failure to respond from arthritis

There were no further cases of participants requiring a change in biological or DMARD therapy as a result of failure to respond from arthritis in the open-label phase.

Juvenile Arthritis Disease Activity Score

The parameter estimates for each of the joint models of JADAS 10, 27 and 71 can be seen in *Table 25*. The treatment effect on the longitudinal JADAS 10, 27 and 71 was non-significant at the 5% level, implying that there is no difference between the treatments on the scores. However, all three *p*-values are close to the margin of statistical significance.

Sensitivity analysis

The inferences of the sensitivity analyses for the data from the blinded phase of the trial combined with the open-label data were the same as those from the blinded phase alone.

TABLE 25 Parameter estimates from joint modelling (random intercepts only) for JADAS 10, 27 and 71

Outcome	Component	Parameter	Estimate	95% CI	*p*-value
JADAS10	Longitudinal	Intercept	0.61	0.22 to 1.07	0.004
		Baseline	0.43	0.24 to 0.57	< 0.0001
		Time	–0.01	–0.02 to 0.007	0.26
		Adalimumab	–0.35	–0.76 to 0.02	0.08
	Survival	Adalimumab	–2.25	–3.65 to –1.37	0.15
		HR	0.11	0.03 to 0.25	0.15
	Association	γ_0	1.07	–0.02 to 2.56	0.09
JADAS27	Longitudinal	Intercept	0.60	0.21 to 1.04	0.004
		Baseline	0.42	0.24 to 0.57	< 0.0001
		Time	–0.01	–0.02 to 0.01	0.28
		Adalimumab	–0.33	–0.75 to 0.04	0.09
	Survival	Adalimumab	–2.24	–3.67 to –1.35	0.15
		HR	0.11	0.03 to 0.26	0.15
	Association	γ_0	1.05	–0.01 to 2.54	0.09
JADAS71	Longitudinal	Intercept	0.62	0.22 to 1.08	0.004
		Baseline	0.43	0.24 to 0.57	< 0.0001
		Time	–0.01	–0.02 to 0.01	0.26
		Adalimumab	–0.35	–0.77 to 0.01	0.07
	Survival	Adalimumab	–2.25	–3.63 to –1.37	0.15
		HR	0.11	0.03 to 0.25	0.15
	Association	γ_0	1.07	–0.03 to 2.49	0.09

Chapter 7 Clinical effectiveness results: follow-up phase

The corticosteroid data results reported in this chapter are based on the integrated analysis of the blinded, open-label and follow-up phases for participants in the adalimumab group compared with the results from the blinded and follow-up phases for participants in the placebo group.

The laboratory data results reported in this chapter are from the follow-up period of the trial only.

The follow-up period for the trial was reduced from 18 months (six follow-up visits) to 6 months (two follow-up visits) in the revision to version 3.0 of the protocol, following the advice of the funders (HTA and Arthritis Research UK; 1 March 2013). The last participant visit took place on 14 December 2016.

Laboratory parameters (haematological, biochemical analysis and urinalysis)

The reduced follow-up period meant that only a small proportion of participants had data at six time points. Therefore, only data from the first two follow-up visits have been presented in this report.

Haematological

Overall, statistically significant changes from baseline to follow-up visits 1 and 2 were not observed in haematological assessments. None of the mean changes to either follow-up visit in haematological assessments was considered to be clinically significant.

Biochemical

Overall, statistically significant changes from baseline to follow-up visits 1 and 2 were not observed in biochemical assessments. None of the mean changes to either follow-up visit in biochemical assessments was considered to be clinically significant.

Urinalysis

- Follow-up visit 1:
  - There were nine abnormal assessments from five participants (the results were greater than a trace, and so they needed microscopic urinalysis) in the placebo group. The results of the microscopic urinalysis showed that one was normal and four were abnormal (one of these four was clinically significant).
  - There were 19 abnormal assessments from 12 participants (the results were greater than a trace, and so they needed microscopic urinalysis) in the adalimumab group. The results of the microscopic urinalysis showed that five were normal and five were abnormal (two of these five were clinically significant); two were classified as not applicable.
- Follow-up visit 2:
  - There were 10 abnormal assessments from seven participants (the results were greater than a trace, and so they needed microscopic urinalysis) in the placebo group. The results of the microscopic urinalysis showed that four were normal and three were abnormal (one of these three was clinically significant).
  - There were seven abnormal assessments from six participants (the results were greater than a trace, and so they needed microscopic urinalysis) in the adalimumab group. The results of the microscopic urinalysis showed that four were normal and two were abnormal (none of these two was clinically significant).

Use of corticosteroids over duration of study period (blinded, open-label and follow-up phases)

Total oral corticosteroid dose

One participant in the placebo group and five participants in the adalimumab group were receiving oral corticosteroids at the start of the study. The five participants in the adalimumab group were in the study for a total of 8.65 years and the placebo participant was in the study for 0.17 years.

The total oral dose for the placebo group was 640 mg (standardised per patient-year, 3767.74 mg) and 6837.5 mg in the adalimumab group (standardised per patient-year, 790.27 mg). A rate ratio of 0.21 (95% CI 0.19 to 0.23) indicated that participants on placebo required more oral corticosteroids per patient-year than those on adalimumab; there was evidence at the 5% level of a statistically significant difference between the two groups.

Reduction in and rate of systemic corticosteroid dose from entry dose

Reduction in systemic corticosteroid dose from entry dose

Reduction in systemic corticosteroid dose from entry dose to 0 mg

This analysis was not able to be performed because the statistical algorithm did not converge.

Reduction in systemic corticosteroid dose from entry dose to < 5 mg

This analysis was not able to be performed because the statistical algorithm did not converge.

Rate of systemic corticosteroid dose from entry dose

The result of this analysis was the same as that of the total oral corticosteroid analysis.

Topical corticosteroid use (frequency) compared with entry use

Time to reduction to fewer than two drops in topical corticosteroid

The time to reduction to fewer than two drops per day was statistically significant, in favour of adalimumab (HR 4.74, 95% CI 1.41 to 16; $p = 0.01$).

Time to reduction to zero drops in topical steroid (post hoc analysis)

The time to reduction to zero drops per day was statistically significant, in favour of adalimumab (HR 5.24, 95% CI 1.82 to 15.1; $p = 0.002$).

Need for pulsed corticosteroid

During the follow-up period of the trial, two participants required pulsed corticosteroids. One participant in the placebo group (3%) and four participants in the adalimumab group (7%) required pulsed corticosteroids during the course of the study. There was no evidence ($p = 0.66$) of a difference in the risk of requiring pulsed corticosteroids between the two treatment groups (RR 2.00, 95% CI 0.23 to 17.12).

Chapter 8 Economic evaluation

Methods

The economic analysis adopted the perspective of the NHS and Personal Social Services providers in England. A trial-based evaluation was extrapolated by 10 years using a Markov model in order to assess the costs and consequences of adalimumab treatment over an appropriate analytical time horizon. The primary outcome of the economic evaluation is the incremental cost per QALY with adalimumab in addition to MTX versus MTX alone.

Resource use and costs

Within-trial costs were estimated by measuring health-care resource use associated with both arms of the trial during the study period, including (1) adalimumab, MTX and other concomitant medication costs; (2) outpatient and accident and emergency (A&E) visits and contact with health-care professionals, including general practitioners (GPs) and school nurses; (3) hospitalisations; and (4) management of AEs.

The measurement of resource use required complementary approaches using data collected as part of the trial and as part of routine care. Trial participants' use of health-care services was obtained from:

- Medication forms. All medication use from 3 months before randomisation was recorded by trial physicians at each trial visit and was supplemented by participant diary records.
- Baseline forms. Research nurses completed the relevant sections of the baseline forms to identify participant contact with hospital and health-care professionals in the 3 months before randomisation.
- Three-monthly patient questionnaires. Research nurses completed the relevant sections of the patient questionnaires during face-to-face interviews with trial participants to identify overnight hospital stays, number of nights, reason for admission and type of ward. The patient questionnaires were also used to identify contacts with health-care professionals including GPs, consultants, nurses, psychologists and rheumatologists, as well as the places and/or means of contact (i.e. A&E, outpatient, GP practice, home visits, telephone, text and e-mail).
- Electronic PLICS data and/or patient administration systems (PAS) data. These were accessed via the participating hospitals' finance departments to identify inpatient stays, use of intensive care or high-dependency units, and outpatient visits.
- AE or SAE forms. Research nurses completed the AE and SAE forms when trial participants were admitted to hospital for events considered possibly related to the study drug, which included bronchopneumonia, herpes simplex infection, pharyngitis and pneumonia.
- Participant diaries recorded GP, social worker, district nurse and hospital visits.

In addition, for the estimation of long-term costs, longitudinal data for patients with JIA-associated and idiopathic uveitis were obtained from the Bristol Regional Tertiary Paediatric Uveitis clinic. This cohort provided data on the number and nature of surgeries performed from diagnosis with follow-up at 1, 3, 5 and 10 years.

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 costs of adalimumab, MTX and all other concomitant medications were based on the cost of items dispensed by Pharmacy and Appliance Contractors in England,[66] supplemented by the *British National Formulary*[67] and retail pharmacy prices when necessary (*Table 26*). The cost of adalimumab, which is not dose sensitive, was based on a once-per-fortnight subcutaneous injection. The formulation of MTX used, which is available in injectable, oral tablet or oral solution form, was recorded

TABLE 26 Unit costs of trial medications

Medication	Formulation	Cost per unit (£)	Source
Adalimumab	Humira® 40 mg or 80 mg pre-filled syringe[a]	352.14	BNF[67]
MTX	Metoject® PEN (medac GmbH, Stirling, UK) 7.5 mg/0.15 ml[b]	14.85	PCA[66]
MTX	Metoject PEN 10 mg/0.2 ml	15.29	PCA[66]
MTX	Metoject PEN 12.5 mg/0.25 ml	16.50	PCA[66]
MTX	Metoject PEN 15 mg/0.3 ml	16.57	PCA[66]
MTX	Metoject PEN 17.5 mg/0.35 ml	17.50	PCA[66]
MTX	Metoject PEN 20 mg/0.4 ml	17.84	PCA[66]
MTX	Metoject PEN 22.5 mg/0.45 ml	18.45	PCA[66]
MTX	Metoject PEN 25 mg/0.5 ml	18.48	PCA[66]
MTX	MTX tablet 2.5 mg	0.06	PCA[66]
MTX	MTX oral solution 2 mg/ml, S/F	2.65	PCA[66]

BNF, *British National Formulary*; PCA, Prescription Cost Analysis; S/F, sugar free.
a At the time of writing, there was no generic version of Humira® on the market. Both 20 mg and 40 mg of Humira (Adalimumab) were manufactured by AbbVie Inc., Ludwigshafen, Germany.
b MTX (Abbvie Inc., Ludwigshafen, Germany).

in the concomitant medication forms during follow-up. The cost of MTX was based on a once-weekly schedule; oral tablets were costed following best practice of all doses being made up as a multiple of a 2.5-mg dose tablet to avoid potential errors with combining different tablet strengths. All other medication costs were based on duration of use as recorded in the concomitant medication forms and participant diaries. All tablets and oral liquids were costed on a unit dose basis, whereas eye drops, creams, lotions and inhalers were costed on a per pack basis.

Healthcare Resource Groups (HRGs) were used as the main currency of the economic analysis for hospital episodes (*Tables 27* and *28*). These most closely reflect actual payments, with cost codes allocated based on the latest available National Tariff[68] (these are bundled care packages, reimbursed at a national level on the basis of the NHS Payment by Results Scheme)[69] and, for unbundled care packages, the latest National Schedule,[70] including A&E and outpatient contacts with time spent on consultations estimated through discussions with research nurses. Personal Social Services Research Unit[71] unit costs were applied to all other primary health-care resource use items (*Table 29*).

The costs of surgery were based on the *NHS National Schedule of Reference Costs*[70] paediatric ophthalmology and outpatient procedures (*Table 30*). Clinical opinion was used to assign the most relevant HRG code for each type of surgery.

Cost analysis

All medication, patient questionnaire and baseline form-reported hospital stays were costed irrespective of whether or not they were condition related or not.

Bundled National Tariff costs were based on the hospital spell and incorporated excess ward days and whether the case was elective or an emergency.[72] Tariff codes were obtained primarily from PLICS and PAS data, but if unavailable, were assigned an appropriate HRG code based on reason for admission, condition and any complications, by referring to AEs, SAEs, baseline forms and patient questionnaires. Locally negotiated unbundled costs were similarly identified and costs were assigned directly from the *National*

TABLE 27 Unit costs of outpatient attendances

Service code	HRG code	HRG name	Attendance	Cost per episode (£)	Source
130	BZ22Z	Intermediate Vitreous Retinal Procedures	OP procedure	142	National Tariff[68]
130	BZ23Z	Minor Vitreous Retinal Procedures	OP procedure	109	National Tariff[68]
130	WF01B	Ophthalmology	OP first attendance – single professional	113	National Tariff[68]
130	WF02B	Ophthalmology	OP first attendance – multi professional	125	National Tariff[68]
130	WF01A	Ophthalmology	OP follow-up attendance – single professional	64	National Tariff[68]
130	WF02A	Ophthalmology	OP follow-up attendance – multiprofessional	94	National Tariff[68]
216	WF01B	Paediatric Ophthalmology	OP first attendance – single professional	136	National Tariff[68]
216	WF01A	Paediatric Ophthalmology	OP follow-up attendance – single professional	82	National Tariff[68]
262	WF01A	Paediatric Rheumatology	OP attendance	203	*NHS Reference Costs 2015 to 2016*[70]
410	WF01A	Rheumatology	OP follow-up attendance – single professional	103	National Tariff[68]
410	WF01B	Rheumatology	OP first attendance – single professional	225	National Tariff[68]
410	WF02B	Rheumatology	OP first attendance – multi professional	246	National Tariff[68]
410	WF02A	Rheumatology	OP follow-up attendance – multiprofessional	165	National Tariff[68]
420	WF01B	Paediatrics	OP first attendance – single professional	222	National Tariff[68]
420	WF01A	Paediatrics	OP follow-up attendance – single professional	135	National Tariff[68]
420	WF02A	Paediatrics	OP follow-up attendance – multiprofessional	156	National Tariff[68]
650	WF01A/ WF01B	Physiotherapy	OP attendance	48	*NHS Reference Costs 2015 to 2016*[70]

OP, Outpatient.

Schedule of Reference Costs.[70] Reported health-care professional contacts in the patient questionnaires and baseline forms were multiplied by unit costs to estimate total costs.

Medication and hospitalisation use were costed for the trial-based analysis period of baseline to 18 months. If a medication administration spanned the period preceding randomisation, or beyond the 18-month time horizon, an adjustment was made to apportion costs to only those administered during the 0- to 18-month time horizon. Participants admitted to hospital were included if the hospital episode start date commenced within the 0- to 18-month time horizon.

TABLE 28 Unit costs of inpatient attendances, including day case

Service code	HRG code	HRG name	Attendance	Cost per episode (£)	Source
262/410	–	Rheumatology	Day case	246	National Tariff[68]
262/410	HB29Z	Minimal knee procedures for non-trauma, with length of stay 1 day or less	Day case	356	National Tariff[68]
262/410	PA64A	Non-surgical ophthalmology, with length of stay 0 days	Day case	552	National Tariff[68]
262/410	PH34D	Paediatric, musculoskeletal or connective tissue disorders, with CC score 0	Day case	590	*NHS Reference Costs 2015 to 2016*[70]
262/410	HB39Z	Minimal foot procedures for non-trauma, with length of stay 1 day or less	Day case	672	National Tariff[68]
262/410	PA34B	Musculoskeletal or connective tissue disorders, without CC	Day case	688	National Tariff[68]
262/410	PH34C	Paediatric, musculoskeletal or connective tissue disorders, with CC score 1–2	Day case	696	*NHS Reference Costs 2015 to 2016*[70]
262/410	PA34A	Musculoskeletal or connective tissue disorders, with CC	Day case	988	National Tariff[68]

CC, complication or comorbidity.

TABLE 29 Unit costs of health-care practitioner attendances

	Unit cost (£)							
Profession	Surgery	Home	Telephone	E-mail	Text message(s)	A&E	Outpatient visits	Additional visits
GP	44.00	65.00	26.98	19.00	7.60	44.00	44.00	44.00
Nurse	14.42	14.42	8.82	7.35	2.94	29.40	44.10	44.10
Consultant	36.34	69.00	16.33	11.50	4.60	46.00	69.00	69.00
Optometrist	79.19	79.19	16.33	11.50	4.60	79.19	79.19	79.19
Psychologist	26.10	26.10	6.18	4.35	1.74	26.10	26.10	26.10

Note
Item costs are based on pro rata Personal Social Services Research Unit costs,[71] according to the estimated time spent on consultations.

Outcomes

The health outcome for the economic evaluation was the QALY, calculated from utilities measured from responses to the Health Utilities Index (HUI) questionnaire administered at baseline and at 3, 6, 9, 12 and 18 months. This was selected in preference to the EuroQol-5 Dimensions (EQ-5D) for its validity in paediatric populations. The HUI is a 40-item questionnaire that assesses health-related quality of life on eight single attributes: vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain. Each HUI level code is estimated from responses to single questions or from a pattern of responses to a specific series of questions. Single attribute utility functions supply scores that express the morbidity for a person for each attribute. The health-related quality of life for a subject was determined by applying a multiattribute utility function to estimate HUI3 scores.[73]

TABLE 30 Unit costs applied to surgeries in longitudinal data

Recorded surgery	Code	Description in schedule	Unit cost (£)	Source
Cataract	BZ32B	Intermediate, cataract or lens procedures, with CC score 0–1	208	*NHS Reference Costs 2015 to 2016*[70]
Vitrectomy	BZ85Z	Very major or major, vitreous retinal procedures, 18 years and under	334	*NHS Reference Costs 2015 to 2016*[70]
Trabeculectomy	BZ94B	Intermediate, glaucoma or iris procedures, with CC score 0	401	*NHS Reference Costs 2015 to 2016*[70]
Iridectomy	BZ94B	Intermediate, glaucoma or iris procedures, with CC score 0	401	*NHS Reference Costs 2015 to 2016*[70]
Capsulotomy	BZ33Z	Minor, cataract or lens procedures	140	*NHS Reference Costs 2015 to 2016*[70]
Glaucoma tube	BZ93B	Major, glaucoma or iris procedures, with CC score 0–1	106	*NHS Reference Costs 2015 to 2016*[70]

CC, complication or comorbidity.

Modelled extrapolation

The Markov model was informed by a patient-level longitudinal data set of patients with idiopathic and JIA-associated uveitis. The only outcome recorded in both SYCAMORE and the Bristol data set[74] (see *Resource use and costs*), and which is expected to directly affect patients' health-related quality of life, was visual acuity, based on logMAR scores. To align with the model framework, the Bristol data[74] were stratified as no visual impairment (VI) (logMAR < 0.3) and VI (logMAR ≥ 0.3). Health states were defined by patients' vision in the worst eye as this was deemed the most clinically relevant. For trial participants, visual logMAR scores were recorded during all protocol-based visits and at unscheduled clinic visits. Data were ordered chronologically for each participant and time in each visual state (no VI, VI) was interpolated. The proportion of time in each state (no VI, VI) for each arm of the trial was used to determine the initial distribution of participants across the states of the Markov model (*Figure 9*). The cycle length was specified as 1 year, and a half-cycle correction applied.

The Bristol cohort provided logMAR scores at diagnosis and at 1, 3, 5 and 10 years. This provided four time periods over which transitions among states may occur. Transitions between visual states, or to the same visual state, were defined as being either with or without surgery, which, along with transitions to the death state, resulted in 11 possible transitions. Annual transition probabilities were estimated by converting pooled transition probabilities over the 10-year time horizon into rates and back into transition probabilities.

The cost of surgery was taken as being the mean cost of a transition with surgery according to the longitudinal data set, as some transitions were associated with multiple surgery costs.

Published all-cause mortality data[75] were adjusted for age but not sex because of the mixed cohort. A standardised mortality ratio of 3.9 (95% CI 0.8 to 11.3) for non-systematic JIA was applied.[76]

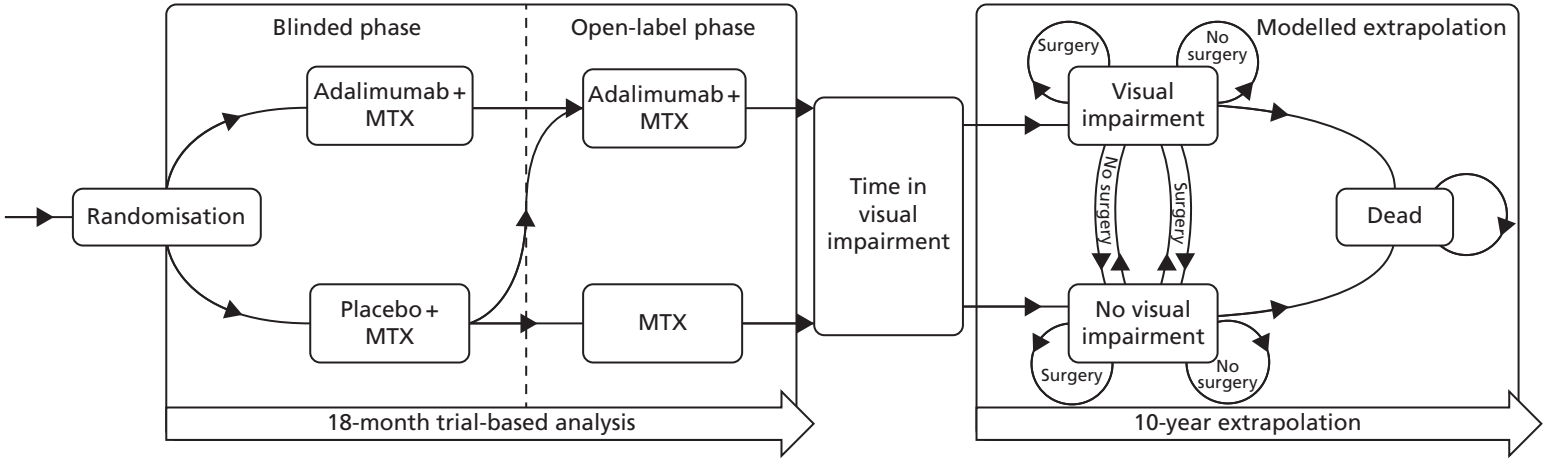


FIGURE 9 Markov model structure.

Incremental analysis

Base-case analysis

The cost-effectiveness of adalimumab plus MTX compared with MTX alone was evaluated by its ICER, calculated by the formula:

$$\text{ICER} = \Delta\text{Costs}/\Delta\text{QALY}, \quad (1)$$

where ΔCosts is the difference in mean total costs between intervention groups and ΔQALY is the difference in mean QALYs between intervention groups.

The base-case analysis was defined as pertaining to the 18-month trial period plus the 10-year extrapolation, based on an imputed data set to account for missing data and adjusting for the crossover of participants in the placebo arm who had access to adalimumab after the end of the blinded phase.

The base-case assumptions were that participants in the adalimumab arm of the trial had access to adalimumab for a further 3 years beyond the 18-month trial and then continued with MTX monotherapy [Michael Beresford (University of Liverpool), Andrew Dick (Bristol Eye Hospital), Athimalaipet Ramanan (Bristol Royal Hospital for Children), Eifiona Wood (Bangor University), Giovanna Culeddu (Bangor University) and Dyfrig Hughes (Bangor University), personal communication, 2017]. Trial drug costs are based on full adherence to adalimumab and MTX, in accordance with doses as defined in the protocol. Costs and QALYs beyond the first year were discounted at an annual rate of 3.5%.

Missing data and crossover

There were missing utility values at baseline and at 3, 6, 9, 12 and 18 months, and missing data for assessing the duration of time in visual impairment. Missing values were imputed using multiple imputation by chained equations.[77] Ten imputed data sets were created using predictive mean matching from a set of imputation models constructed from all potential prognostic factors (trial arm, age, sex, baseline visual impairment) and outcome variables (cost and exposure to adalimumab during the open-label phase).

The instrumental variable method was used to limit the bias that would result from participants randomised to placebo having access to adalimumab during post-trial closure follow-up.[78] Instrumental variable regressions for total costs and QALYs were calculated over the 18-month time horizon, considering received treatment (adalimumab), sex and age as covariates. For the 10-year modelled extrapolation, state-specific costs (excluding trial drug costs, which were added into the Markov model separately) and QALYs were derived using instrumental variable regressions, with treatment (adalimumab) and time in visual state as covariates.

Sensitivity analyses

Univariate sensitivity analysis

A number of sensitivity analyses were conducted to assess the robustness of the analysis. These included exploration of the impact of different time horizons of analysis and a series of sensitivity analyses relating to medication adherence, which tested assumptions based on the number of vials issued, accountability logs and recordings in participant diaries.

Separately, sensitivity analyses were conducted to assess the impact of participants having access to adalimumab for only the trial period (18 months) or for the duration of the model (18 months plus 10 years), based on the proportion of participants in the adalimumab arm who had access to adalimumab beyond the 18-month trial period in the open-label phase of the trial.

Owing to uncertainty in the proportion of participants who entered the Markov model with visual impairment, sensitivity analyses were conducted based on the CIs of these proportions. The Markov model was estimated with the proportions generated from upper to lower (H : L) and lower to upper (L : H) values of the CIs for both arms of the trial.

Finally, a sensitivity analysis was conducted without the discounting of future costs and QALYs.

Probabilistic sensitivity analysis

Mean costs and QALYs and differences between intervention groups in costs and QALYs were based on a bootstrapped analysis using 10,000 replicates. The 95% central range was based on the 2.5 and 97.5 percentiles of the bootstrap values.

A probabilistic sensitivity analysis of the base case was performed using a Monte Carlo simulation with 10,000 replicates, sampling each parameter simultaneously within its distribution. Probability distributions for regression-based analyses were generated using Cholesky decomposition.

Uncertainty in the ICER was represented as a cost-effectiveness plane and cost-effectiveness acceptability curves, which present the probability of adalimumab being cost-effective for given ceiling thresholds of costs per QALY.[79] Estimates of ICERs were compared with the £20,000- to £30,000-per-QALY threshold of cost-effectiveness set by NICE.[80]

Scenario analyses

Complete-case data

Scenario analyses were conducted for complete-case data over 18 months. This was also extended to the 10-year extrapolation by specifying an ordinary least squares regression, using complete-case resource use, non-trial drug costs and QALYs to determine state-specific costs and utilities for both the adalimumab and placebo arms, based on time in visual state.

Disregarding crossover

A further analysis was conducted without regard for post-trial closure crossover from placebo to adalimumab. This was based on the imputed data set over 18 months and the 10-year extrapolation phase. Seemingly unrelated regressions for total costs and QALYs predicted by trial arm were conducted for imputed data over the 18-month time horizon. For the corresponding extrapolation, resource use, non-trial drug costs and QALYs were generated by seemingly unrelated regressions with trial arm and time in visual state as covariates. Trial drug costs were added afterwards.

All summary data and regression-based analyses were conducted using Stata version 13. The Markov model was analysed in Microsoft Excel® 2013 (Microsoft Corporation, Redmond, WA, USA) and reported in accordance with the Consolidated Health Economic Evaluation Reporting Standards.[81]

Results

Resource use and cost analysis

Participants' use of health-care resources and the corresponding NHS costs were comparable at baseline in both intervention groups for the 3 months prior to randomisation (*Table 31*). Only resource use associated with concomitant medications (excluding MTX) was statistically different between groups. However, the costs of the concomitant medications were not major cost drivers and accounted for only 3% of the total costs for the adalimumab arm and 1% of total costs for the placebo arm. The main cost drivers for the 3 months prior to randomisation were inpatient admissions (52% of the total) and outpatient visits (35% of total costs).

Each trial participant had available a level of resource use data that was costed and treated as complete from baseline to 18 months' follow-up. *Tables 32* and *33* present the disaggregated health-care resource use and costs, respectively, over this period. Mean total costs were £15,980 (95% CI £14,213 to £17,943; $n = 60$) for adalimumab plus MTX and £6248 (95% CI £3922 to £8889; $n = 30$) for placebo plus MTX.

TABLE 31 Baseline costs in the 3 months prior to randomisation, by intervention group

Item of resource use	Treatment group, mean, (£) (95% CI)		Difference in mean, (£) (95% CI)
	Adalimumab ($n = 60$)	Placebo ($n = 30$)	
MTX	153 (127 to 179)	168 (131 to 200)	–14 (–56 to 31)
Other concomitant medications	51 (31 to 78)	19 (12 to 26)	32 (11 to 61)
Inpatient admissions	867 (542 to 1239)	768 (549 to 973)	100 (–299 to 525)
Outpatient visits	570 (450 to 705)	534 (345 to 759)	37 (–221 to 272)
GP visits	100 (66 to 143)	97 (56 to 147)	3 (–59 to 64)
Nurse visits	80 (54 to 109)	87 (49 to 126)	–7 (–53 to 40)
Other	166 (103 to 238)	184 (103 to 277)	–19 (–129 to 91)
Total costs	1614 (1312 to 1946)	1526 (1072 to 2047)	88 (–510 to 652)

TABLE 32 Disaggregated health-care resource use, including the most frequently observed HRGs over 18 months from randomisation, by intervention group

Item of resource use	Treatment group, mean count (range if > 0) [number of participants]		Difference in means
	Adalimumab	Placebo	
GP visits	3.5 (1–14) [35]	2.75 (1–6) [12]	0.75
Nurse visits	3.3 (1–12) [22]	3.5 (1–10) [4]	–0.20
Physiotherapist	2.9 (1–7) [10]	3.7 (3–4) [3]	–0.80
Optician	2.0 (1–3) [8]	0.0 (0) [0]	2.00
Psychologist	1.4 (1–3) [5]	1.75 (1–4) [4]	–0.35
OP – HRG BZ22B	2.0 (1–3) [4]	1.0 (1) [1]	1.00
OP – HRG BZ23Z	1.25 (1–2) [4]	1.0 (1) [1]	0.25
OP – HRG WF01A	6.07 (1–18) [26]	5.7 (1–15) [10]	0.37
OP – HRG WF01B	1.4 (1–2) [10]	1.16 (1–2) [6]	0.24
OP – HRG WF02A	3.6 (1–10) [5]	3.0 (1–5) [3]	0.60
IP – HRG PA34A	8.5 (1–31) [11]	5.25 (1–19) [8]	3.25
IP – HRG PA34B	10 (4–18) [3]	1.5 (1–3) [4]	8.50
IP – HRG PA64A	2.0 (1–3) [2]	2.0 (2–2) [1]	0.00
IP – HRG PH34C	1.2 (1–2) [5]	4.0 (3–5) [3]	–2.80
IP – HRG PH34D	3.4 (1–7) [5]	1.4 (1–3) [5]	2.00

IP, inpatient; OP, outpatient.

TABLE 33 Disaggregated and total 18-month costs from randomisation, by intervention group

Item of resource use	Treatment group, mean, (£) (95% CI)		Difference in means, (£) (95% CI)
	Adalimumab ($n = 60$)	Placebo ($n = 30$)	
Adalimumab	10340 (9392 to 11,245)	1761 (722 to 2951)	8579 (7065 to 9978)
MTX	778 (638 to 910)	637 (462 to 816)	141 (–80 to 364)
Concomitant medications	540 (379 to 743)	249 (92 to 471)	291 (11 to 549)
Inpatient HRGs	2522 (1195 to 4135)	2549 (1166 to 4267)	–27 (–2198 to 2158)
Outpatient HRGs	700 (434 to 1011)	692 (294 to 1191)	8 (–559 to 510)
GP visits	91 (64 to 122)	48 (23 to 79)	43 (2 to 84)
Optician	21 (8 to 37)	0	21 (8 to 37)
Nurse visits	18 (9 to 27)	7 (0 to 18)	11 (–3 to 23)
Physiotherapist	12 (4 to 21)	9 (0 to 20)	3 (–10 to 15)
Psychologist	3 (0 to 6)	6 (1 to 14)	–3 (–12 to 4)
Total cost	15,980 (14,213 to 17,943)	6248 (3922 to 8889)	9732 (6562 to 12,793)

Adalimumab use was the main driver of the differences in costs between groups, contributing to 88% of the difference in total costs. The cost of concomitant medications and optician visits differed between arms, but these were not major cost drivers, accounting for 3% and 0.2% of the difference in total costs, respectively. There was no statistical difference in resource use between the other items. The annualised cost of the trial medications (adalimumab and MTX) differed by £8720 between groups (£11,118 adalimumab plus MTX vs. £2398 MTX alone).

The Bristol cohort provided data from 91 patients with JIA-associated uveitis and 66 with idiopathic uveitis (*Table 34*). The mean age of the patients was 8 years (SD 3.8 years) and 60% were female, which is comparable with the SYCAMORE cohort. Thirty-seven surgeries in 25 patients were recorded in the Bristol data set,[74] corresponding to 7.87 per 100 patient-years of follow-up. The frequency of surgeries per patient in a single time period are summarised in *Table 35*. Drug data were not dated and were, therefore,

TABLE 34 Characteristics of patients included in the Bristol cohort

Characteristics	Patients
Age at diagnosis (years)	
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)

TABLE 34 Characteristics of patients included in the Bristol cohort (*continued*)

Characteristics	Patients
Aetiology, *n* (%)	
JIA	91 (58.3)
Idiopathic	66 (42.3)
Type of uveitis, *n*	
Anterior	120
Intermediate	28
Panuveitis	8
Posterior	1
Year of diagnosis, *n* (%)	
1997–2000	10 (6.4)
2001–5	37 (23.6)
2005–10	61 (38.9)
2011–15	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* (%)[a]	
Best eye	12 (9.5)
Worst eye	47 (37.3)
Surgical procedures, *n*[b]	
Capsulotomy	3
Cataract	15
Glaucoma tube	1
Iridectomy	2
Trabeculotomy	10
Vitrectomy	6

a LogMAR data at diagnosis were available for 126 patients.
b A total of 37 procedures out of 268 observations.

TABLE 35 Surgeries recorded in the Bristol data set

Surgeries in a single time period (*n*)	Number recorded	Cost per person (£)
None	243	0
Cataract	8	208
Glaucoma tube	1	106
Trabeculotomy	5	401
Vitrectomy	3	334
Capsulotomy; cataract	1	348
Capsulotomy (2), trabeculectomy (2)	1	1082
Cataract, iridectomy	1	610
Cataract (2), iridectomy	1	817
Cataract, trabeculectomy	1	610
Cataract, trabeculectomy (2)	1	1011
Cataract, vitrectomy	1	542
Vitrectomy (2)	1	667

not used to stratify the data, as it was assumed that, following a standard care pathway, only patients whose disease had progressed furthest would be prescribed biologics, which would bias the model against adalimumab. For the Bristol cohort, the mean cost of surgeries between any two points of follow-up was £419.

Outcomes

Utility and quality-adjusted life-years

Health Utility Index questionnaires were not completed for all participants, meaning that baseline utilities were missing for 12 participants in the adalimumab group and nine participants in the placebo group. For participants with complete baseline responses to the HUI questionnaire, mean utility values were 0.83 (95% CI 0.76 to 0.89; $n = 48$) for the adalimumab group and 0.87 (95% CI 0.78 to 0.96; $n = 21$) for the placebo group (*Table 36*). No significant differences in utility scores were noted at baseline; however, differences were reported for the 18-month utility scores, with a mean difference of 0.06 (95% CI 0.01 to 0.11) in favour of placebo.

Visual acuity

Quality-adjusted life-year scores were calculated for both the complete-case and imputed analyses. Owing to missing data, QALY values were calculated only for three participants randomised to placebo and 25 participants randomised to adalimumab. In the complete-case analysis, QALY scores were lower in the adalimumab group [1.40 (95% CI 1.35 to 1.45)] than in the placebo group [1.45 (95% CI 1.41 to 1.5)], although the difference was not significant. After imputation, the QALY scores were higher for adalimumab than placebo [1.35 (95% CI 1.30 to 1.41) and 1.28 (95% CI 1.15 to 1.41), respectively] but, again, not significantly different.

Figure 10 illustrates the distribution of HUI3 level scores by treatment arm, attributes and time. Fewer participants in the placebo arm than in the adalimumab arm completed the HUI3; completion rates further reduced in both arms over the trial period. At baseline, 82% of participants in the adalimumab group and 72% of participants in the placebo group reported level 1 vision (no visual impairment); by 18 months, 76% of participants in the adalimumab group and 75% of participants in the placebo group were in the

TABLE 36 Health outcomes 18 months from randomisation, by intervention group

Analysis	Health outcomes	Treatment group, mean (95% CI)		Difference in means (95% CI)
		Adalimumab	Placebo	
Complete case[a]	Baseline utility	0.83 (0.76 to 0.89)	0.87 (0.78 to 0.96)	–0.042 (–0.15 to 0.07)
	18-month analysis, time in VI (proportion)	0.03 (0.01 to 0.07)	0.02 (0.00 to 0.07)	0.01 (–0.04 to 0.06)
	Utility at 18 months	0.94 (0.88 to 0.98)	0.99 (0.97 to 1.00)	–0.06 (–0.11 to –0.01)
	QALYs over 18 months	1.40 (1.35 to 1.45)	1.45 (1.41 to 1.50)	–0.05 (–0.12 to 0.02)
Imputed data[b]	Baseline utility	0.84 (0.77 to 0.90)	0.86 (0.78 to 0.95)	–0.03 (–0.13 to 0.08)
	18-month analysis, time in VI (proportion)	0.05 (0.02 to 0.08)	0.11 (0.06 to 0.17)	–0.06 (–0.12 to –0.01)
	Utility at 18 months	0.93 (0.87 to 0.99)	0.92 (0.50 to 1.33)	0.01 (–0.18 to 0.20)
	QALYs over 18 months	1.35 (1.30 to 1.41)	1.28 (1.15 to 1.41)	0.07 (–0.04 to 0.18)

a The CIs are percentile based.
b The CIs are normal based.

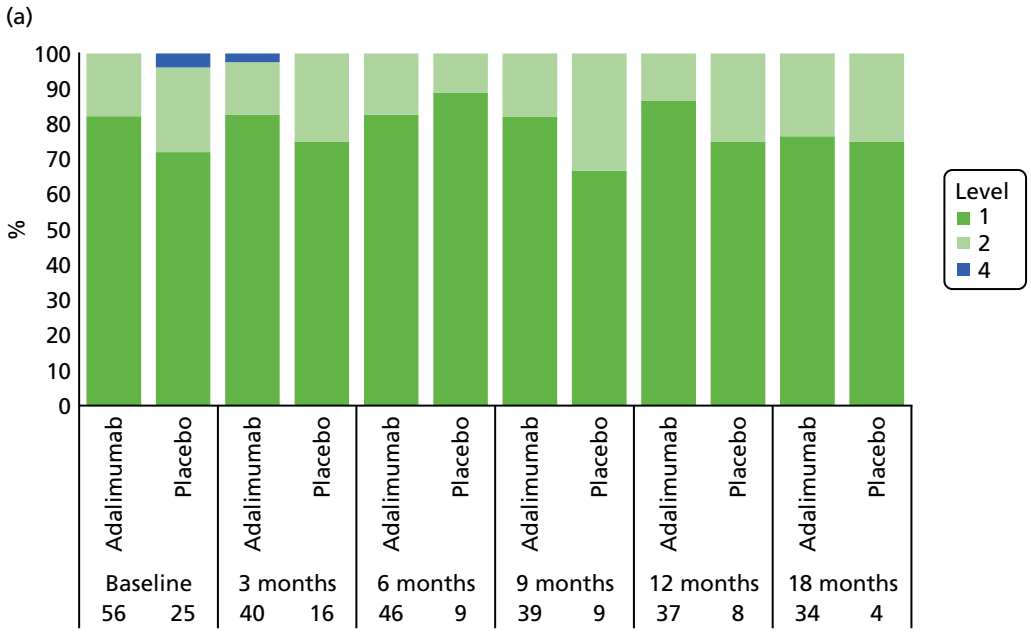


FIGURE 10 Distribution of participants' responses to each HUI3 attribute, by treatment allocated and time. Levels range from 1 to 6, with 6 representing the most severe problem. The numbers of completed responses are reported by treatment arm. (a) Vision; (b) hearing; (c) speech; (d) ambulation; (e) dexterity; (f) emotions; (g) cognition; and (h) pain. (*continued*)

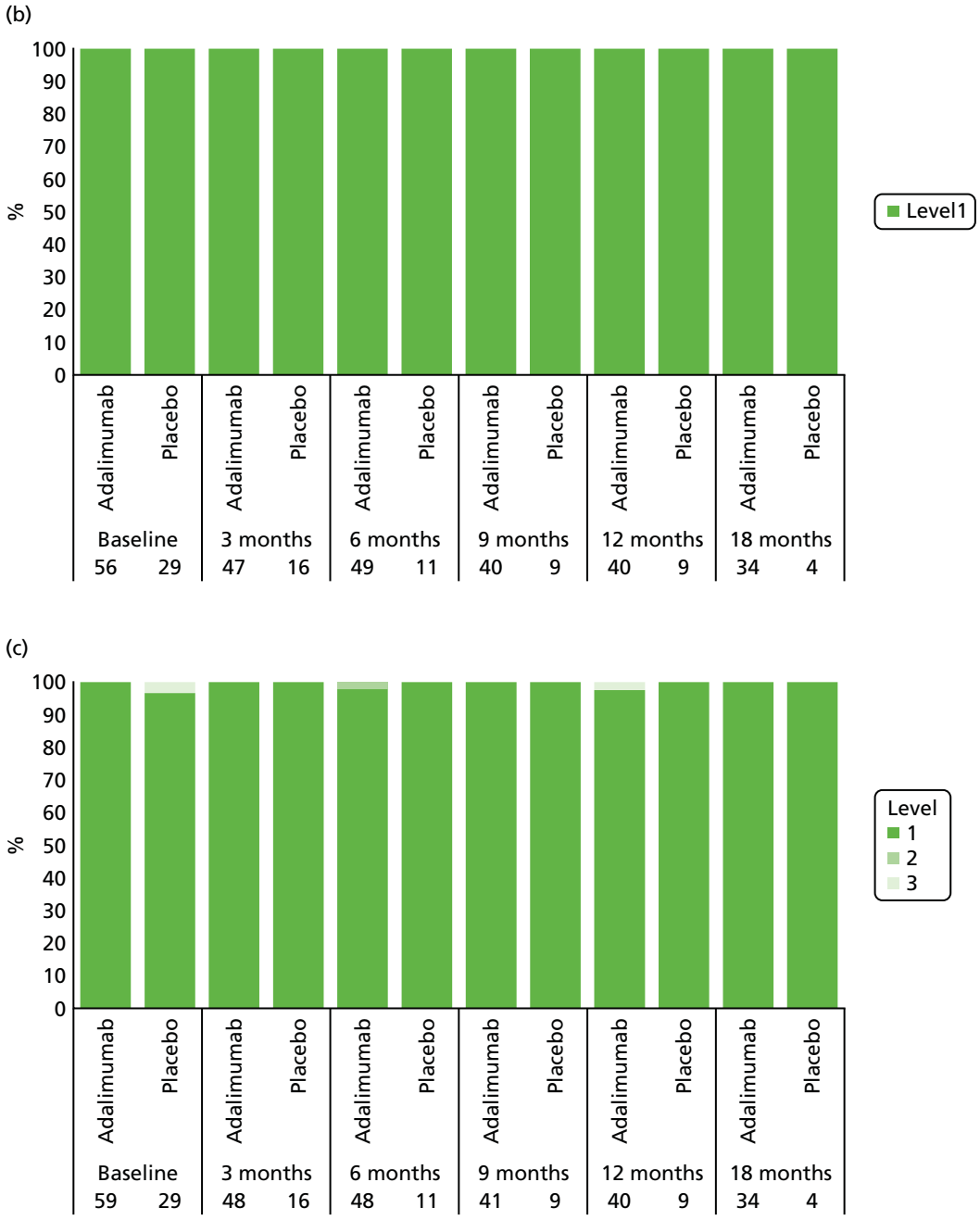
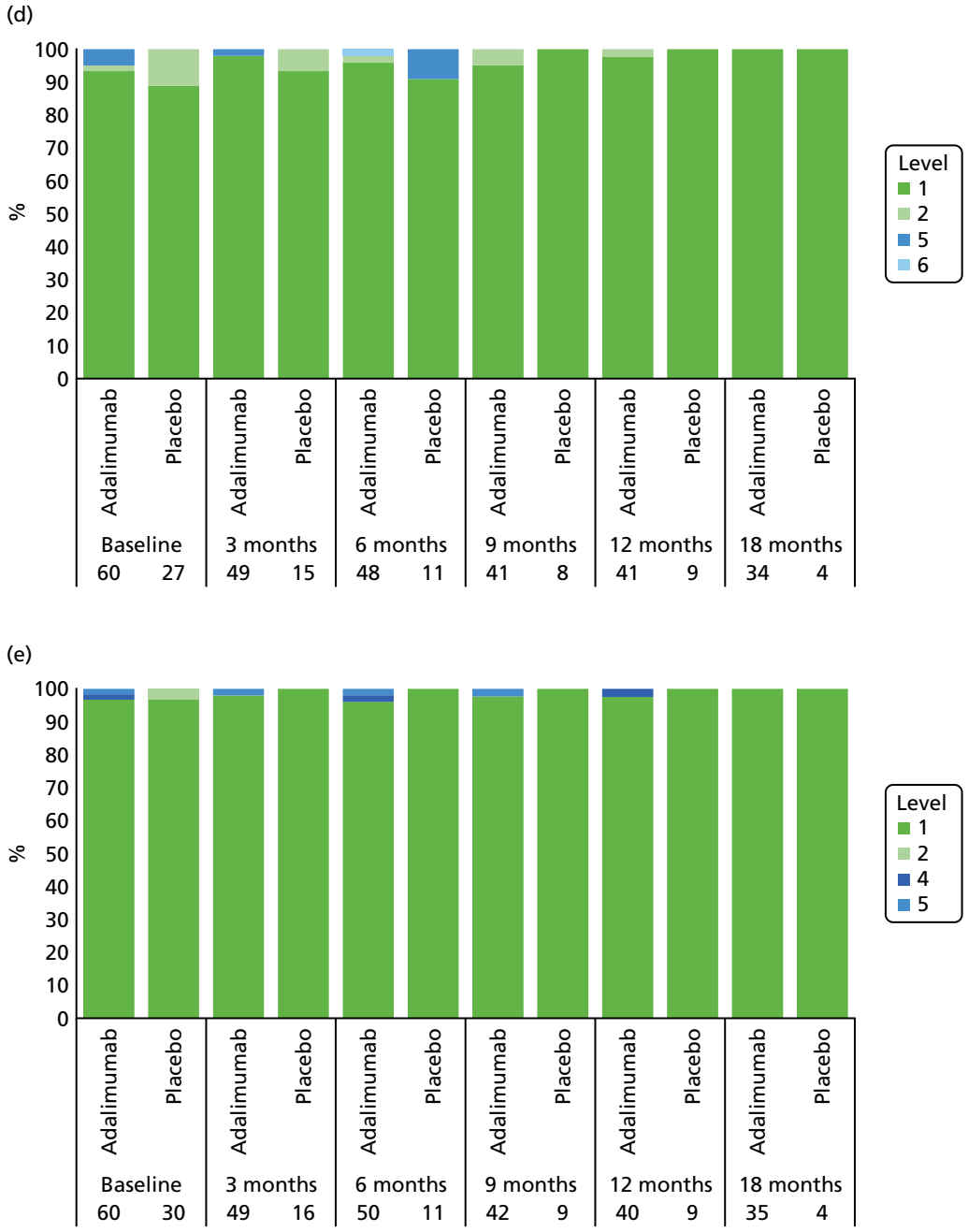


FIGURE 10 Distribution of participants' responses to each HUI3 attribute, by treatment allocated and time. Levels range from 1 to 6, with 6 representing the most severe problem. The numbers of completed responses are reported by treatment arm. (a) Vision; (b) hearing; (c) speech; (d) ambulation; (e) dexterity; (f) emotions; (g) cognition; and (h) pain. (*continued*)



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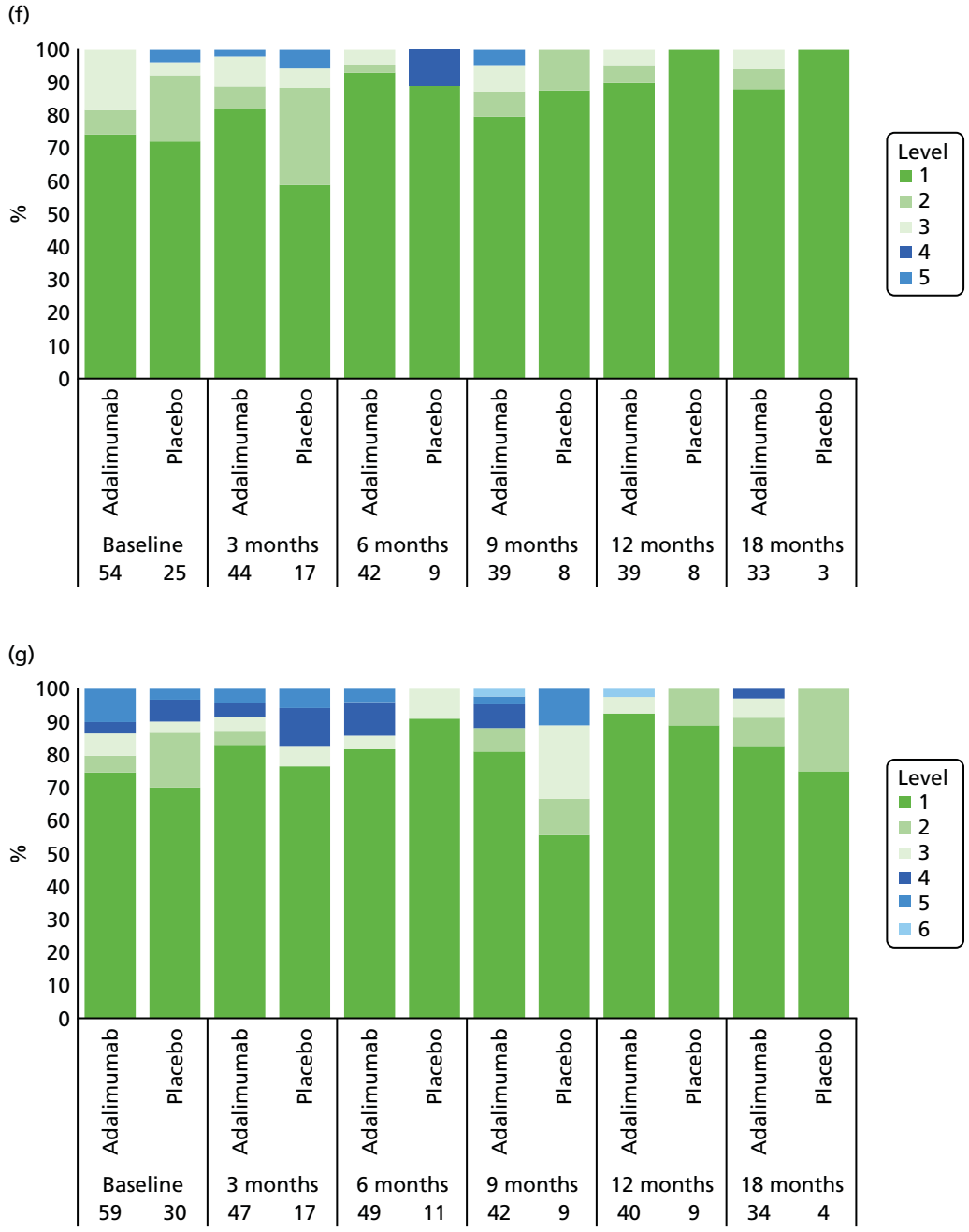

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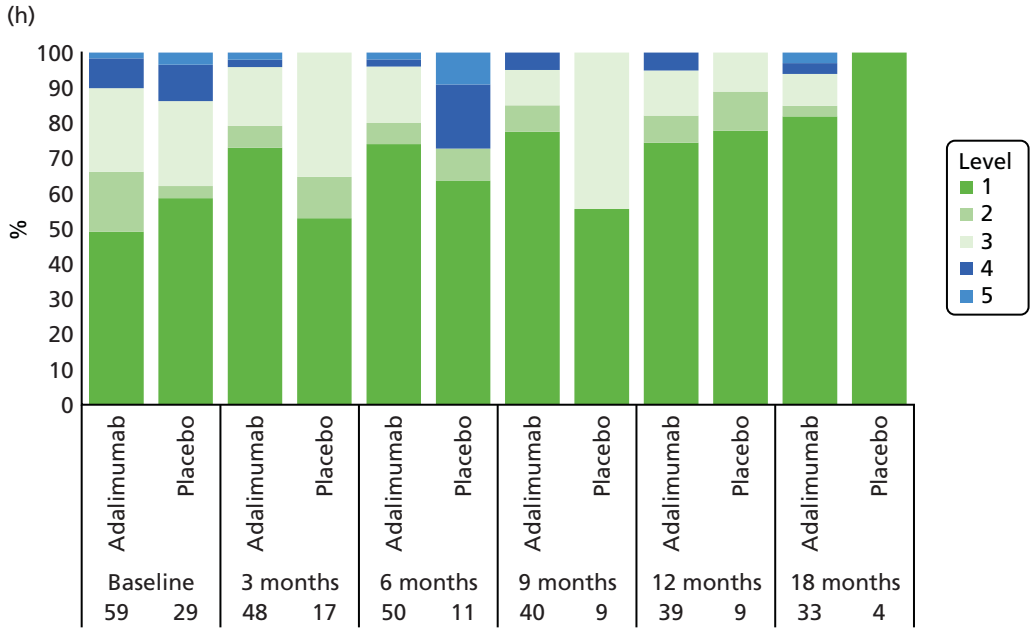

FIGURE 10 Distribution of participants' responses to each HUI3 attribute, by treatment allocated and time. Levels range from 1 to 6, with 6 representing the most severe problem. The numbers of completed responses are reported by treatment arm. (a) Vision; (b) hearing; (c) speech; (d) ambulation; (e) dexterity; (f) emotions; (g) cognition; and (h) pain.

level 1 vision category. However, at 18 months, responses to this attribute were reported for only four participants in the placebo group, compared with 34 participants in the adalimumab group. For pain, at baseline, 49% (29/59) of participants in the adalimumab group and 58% (17/29) of participants in the placebo group reported level 1 pain score (no pain). At 18 months, 82% (27/33) of participants in the adalimumab group and 100% (4/4) of participants in the placebo group reported level 1 pain score, but, again, interpretation is hampered by low reporting rates at 18 months, especially in the placebo arm. No participants reported hearing-related problems for the duration of the trial.

Visual acuity (logMAR) scores were available for 52 participants with complete-case data: 43 participants in the adalimumab group and nine participants in the placebo group. Baseline logMAR scores were complete and indicated the proportions of participants in the VI health state at baseline as 11.67% for adalimumab and 6.67% for placebo, which was anticipated to introduce bias in the 'time in visual impairment' outcome. At 18 months, 36 participants in the adalimumab arm of the trial and eight participants in the placebo arm had no time in the VI state. Mean proportion of time in the VI health state was 0.03 for participants in the adalimumab group and 0.02 for participants in the placebo group (difference 0.01, 95% CI –0.04 to 0.06) (see *Table 36*).

Following imputation, participants randomised to adalimumab spent 5.3% of time in VI during the 18-month analysis, whereas participants randomised to placebo spent 11.1% of time in VI. By including VI at baseline and time in VI, alongside demographics, costs and utility outcomes, the imputation model corrected for the imbalance in VI at baseline. In the imputed analyses, the rate of VI is higher in the placebo arm than in the adalimumab arm.

Data on logMAR from the Bristol cohort were available for 126, 117, 93, 75 and 22 patients at baseline and at 1, 3, 5 and 10 years, respectively. Based on the stratification of logMAR, 69 patients were recorded as having VI at one or more time point, whereas 88 patients were never recorded as having VI. There were 268 observed transitions over the four periods when transition was possible.

Analysis

Base-case analysis

All Markov model inputs and their distributions are presented in *Table 37*.

Over the time horizon of the 18-month trial plus 10-year extrapolation, the total costs of the adalimumab arm were £70,719. The total costs of the placebo arm were £31,403. Total QALYs were 8.60 for the adalimumab arm and 8.29 for the placebo arm.

The incremental costs and QALYs for adalimumab were £39,316 and 0.30, respectively, resulting in an ICER of £129,025 per QALY gained.

TABLE 37 Inputs from the Markov model

Parameter	Point estimate	Distribution (distribution parameters)	Source
18-month data (trial based)			
Cost coefficient			
Adalimumab	14,374.01	Cholesky decomposition	Trial data (SYCAMORE)
Age	–257.72		
Sex	–445.89		
Constant	3765.78		
QALY coefficient			
Adalimumab	0.11	Cholesky decomposition	Trial data (SYCAMORE)
Age	–0.00		
Sex	–0.02		
Constant	1.26		
Month 19–138 (Markov model): base-case model assumptions			
Cost coefficients			
Adalimumab arm (excluding trial drug costs)	1437.13	Cholesky decomposition	Trial data (SYCAMORE)
Time in visual impairment	2662.57		
Constant	1603.05		
Drug cost			
Adalimumab	7411.73	Gamma~(8.11, 1370.33)	Trial data (SYCAMORE)
MTX	1598.17	Gamma~(0.56, 4315.70)	Trial data (SYCAMORE)
Surgery cost (per surgery transition)	418.71	None (fixed)	Bristol data[74] (see *Resource use and costs*)
Discount rate: cost (per annum)	0.035	None (fixed)	NICE[80]
QALY coefficients			
Adalimumab arm (excluding trial drug costs)	0.07	Cholesky decomposition	Trial data (SYCAMORE)
Time in visual impairment	–0.00		
Constant	0.83		
Discount rate: QALY (per annum)	0.035	None (fixed)	NICE[80]

TABLE 37 Inputs from the Markov model (*continued*)

Parameter	Point estimate	Distribution (distribution parameters)	Source
Probabilities			
Proportion of VI			
Adalimumab arm	0.05	Beta~(4.75, 85.25)	Trial data (SYCAMORE)
Placebo arm	0.11	Beta~(10.04, 79.96)	Trial data (SYCAMORE)
Transition probability from			
No VI to no VI (no surgery)	0.95	Dirichlet~(162, 4, 14, 2) approximated by standardised series of gamma distributions	Bristol data[74] (see *Resource use and costs*)
No VI to no VI (surgery)	0.01		
No VI to VI (no surgery)	0.04		
No VI to VI (surgery)	0.01		
VI to no VI (no surgery)	0.33	Dirichlet~(29, 6, 38, 13) approximated by standardised series of gamma distributions	Bristol data[74] (see *Resource use and costs*)
VI to no VI (surgery)	0.06		
VI to VI (no surgery)	0.47		
VI to VI (surgery)	0.14		
Mortality rate[a]	0.000071	None (fixed)	Human Mortality Database[75]
Standardised mortality ratio	3.9	Log-normal~(3.9, 2.6785)	Davies *et al.*[76]

a Mortality rate in the model is dependent on age. The figure presented in the table corresponds to the mortality rate of an 8-year-old child.

Sensitivity analyses

Univariate sensitivity analysis

The results of the sensitivity analyses are presented in *Table 38*. These demonstrate that the model is most sensitive to adalimumab usage. The most cost-effective scenario is based on the assumption of adherence to MTX and adalimumab as recorded in the participant diaries over the 18-month time horizon (incremental cost of £117,514 per QALY gained) and the 18-month plus 10-year time horizon (incremental cost of £115,708 per QALY gained). However, participant diary recording of doses can be subject to unreliability and does not reflect the costs to the NHS of prescriptions issued. The least cost-effective analysis relates to adalimumab use being based on the number of vials issued, which was greater than the base-case assumption based on time in the study (110.55%), resulting in ICERs of £149,040 and £140,576 per QALY gained over 18 months and 18-month plus 10-year time horizons, respectively.

The analysis in which the duration of adalimumab treatment was increased resulted in a lower ICER (£127,646 per QALY gained). Conversely, a shorter duration of treatment of 18 months, compared with 3 years in the base case, reduces the incremental QALY gain and raises the ICER to £133,656 per QALY gained.

Probabilistic sensitivity analysis

Based on the results of the probabilistic sensitivity analysis applied to the base case, the mean total costs of the adalimumab arm were £70,951 [95% credible range (CR) £45,204 to £123,764]. The mean total costs of the placebo arm were £31,587 (95% CR £5308 to £83,320). Mean QALYs were 8.60 (95% CR 8.00 to 9.19) for the adalimumab arm and 8.29 (95% CR 7.42 to 9.17) for the placebo arm.

The mean incremental costs and QALYs for adalimumab were £39,364 (95% CR £24,728 to £58,235) and 0.31 (95% CR –0.04 to 0.66), respectively.

TABLE 38 Results of the sensitivity analyses

Sensitivity analysis	Costs (£)			QALY			
	Treatment group			Treatment group			
	Adalimumab	Placebo	Incremental	Adalimumab	Placebo	Incremental	ICER (£)
Base case[a]	70,719	31,403	39,316	8.60	8.29	0.30	129,025
Time horizon of analysis							
18 months							
Adalimumab adherence based on vials issued	17,399	1734	15,666	1.36	1.25	0.11	149,040
Adalimumab adherence based on accountability logs	15,716	2095	13,621	1.36	1.25	0.11	129,587
Adalimumab and MTX adherence based on participant diaries	14,345	1993	12,352	1.36	1.25	0.11	117,514
18 months + 10 years							
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
Adalimumab adherence based on vials issued	74,011	31,175	42,835	8.60	8.29	0.30	140,576
Adalimumab adherence based on accountability logs	68,800	31,536	37,264	8.60	8.29	0.30	122,291
Adalimumab and MTX adherence based on participant diaries	59,896	24,638	36,258	8.60	8.29	0.30	115,708
No discounting	77,634	36,743	40,621	9.88	9.57	0.32	128,886
23% of participants who were administered adalimumab beyond 18 months[b]	51,304	31,403	19,900	8.44	8.29	0.15	131,511
Adalimumab : placebo VI proportions H : L	70,864	31,147	39,716	8.60	8.29	0.30	130,586
Adalimumab : placebo VI proportions L : H	70,574	31,659	38,915	8.60	8.29	0.31	127,471

H : L, high to low; L : H, low to high.
a Based on a 7-year-old female (median demographic of SYCAMORE).
b This is the observed percentage of participants randomised to the adalimumab arm who were administered adalimumab beyond 18 months.

The cost-effectiveness plane (*Figure 11*) and the cost-effectiveness acceptability curve (*Figure 12*) indicate that adalimumab is highly unlikely to be cost-effective in the £20,000- to £30,000-per-QALY threshold range. The probability of being cost-effective at the £30,000-per-QALY threshold is < 1%. In 96% of simulations, adalimumab was both more costly and more effective; however, in 4% of simulations, adalimumab was seen to be less effective than placebo and remained more costly.

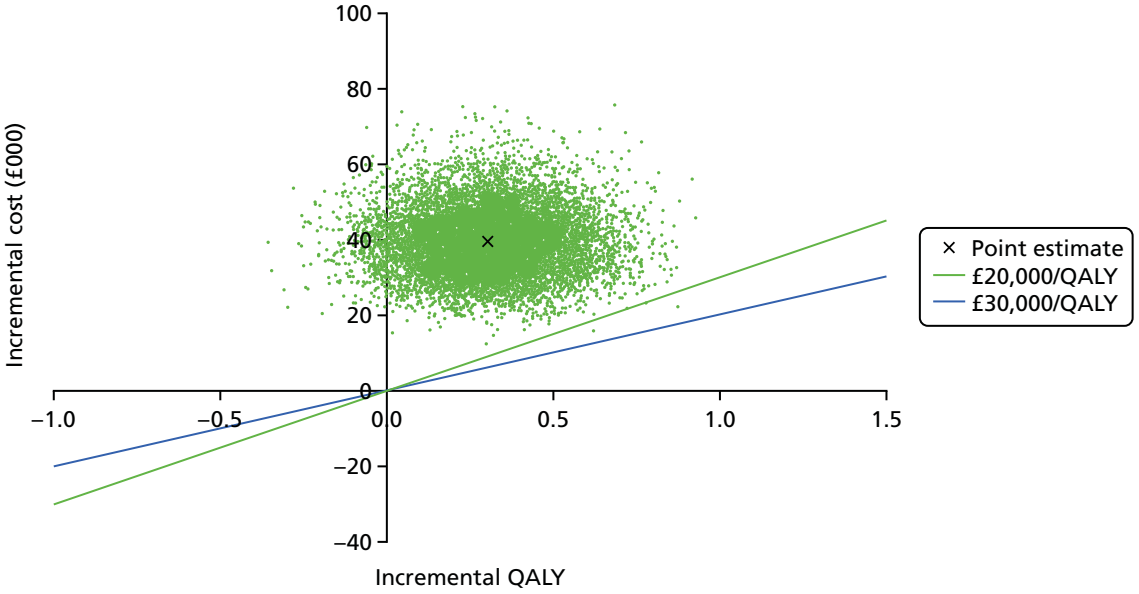

FIGURE 11 Cost-effectiveness plane.

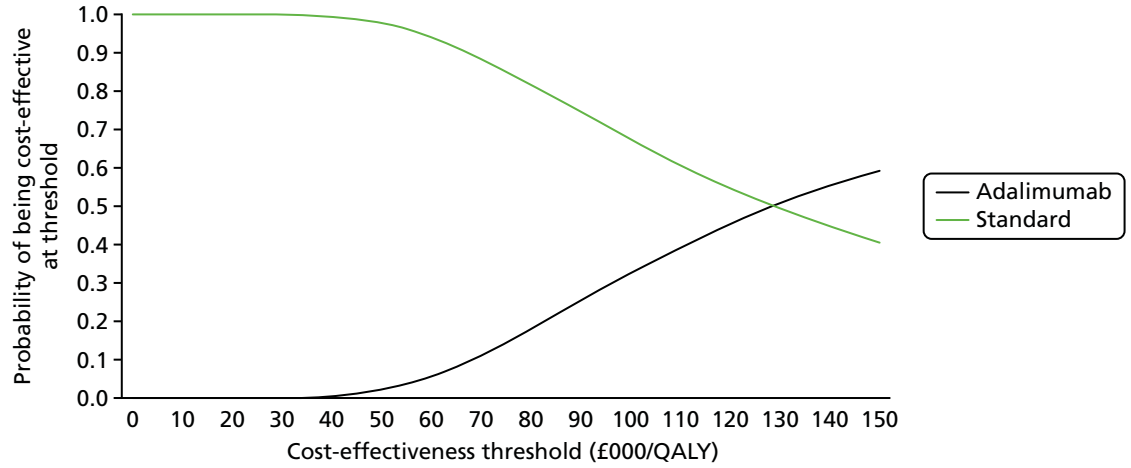

FIGURE 12 Cost-effectiveness acceptability curve.

Scenario analyses

The complete-case analysis was limited by sparse QALY data for participants in the placebo group ($n = 3$) and should be interpreted with caution. For the imputed data, the ICER is robust to a variety of assumptions (*Table 39*). Taking into account the post-trial closure crossover from placebo to adalimumab has little impact on the ICER during the 18-month time horizon, but it has greater effect in the extrapolated phase, as patient benefit associated with adalimumab administered to participants in the placebo group in follow-up is adjusted away from the placebo arm to the adalimumab arm.

TABLE 39 Results of the scenario analyses

Scenario	Costs (£)			QALYs			
	Treatment group			Treatment group			
	Adalimumab	Placebo	Incremental	Adalimumab	Placebo	Incremental	ICER (£)
Complete-case analysis							
18-month time horizon	15,891	5904	9988	1.40	1.45	–0.05	Dominated
+ 10-year time horizon	78,331	45,622	32,710	9.55	9.60	–0.05	Dominated
Imputed data not accounting for crossover							
18-month time horizon	15,891	5904	9988	1.35	1.28	0.07	135,431
+ 10-year time horizon	72,685	39,000	33,685	8.71	8.50	0.21	158,259
Imputed data accounting for crossover							
18-month time horizon	16,336	1962	14,374	1.36	1.25	0.11	136,751
+ 10-year time horizon	70,719	31,403	39,316	8.60	8.29	0.30	129,025

Chapter 9 Discussion

The objectives of SYCAMORE, a randomised, double-blind, placebo-controlled trial were to investigate the clinical efficacy, safety and cost-effectiveness of adalimumab in combination with MTX for the treatment of JIA-associated uveitis in patients who had active uveitis despite having been on MTX for at least 12 weeks (with a stable dose for 4 weeks prior to the screening visit).

A total of 90 participants with active uveitis were randomised from 14 sites in the UK. No participants were excluded from the primary analysis and, therefore, the ITT data set contained all 90 participants. All participants received at least one dose of their allocated treatment and the safety data set also contained all 90 participants.

The majority of participants were female (77.8%) with a mean age of 8.9 years and had one eligible eye (72.2%). All participants had JIA-associated uveitis, with the majority of eligible eyes having mild or moderate uveitis (66.1% had activity of 1+ and 25.2% had activity of 2+); the type of JIA that was most common was persistent oligoarthritis (58.9%). There was no statistical testing of the baseline characteristics but numerically the two groups were very similar.

The primary efficacy outcome was time to treatment failure between the adalimumab and placebo groups. During the blinded phase of the study, the risk of treatment failure was significantly reduced by 75% for participants in the adalimumab group compared with participants in the placebo group (HR 0.25, 95% CI 0.12 to 0.51; $p < 0.0001$ from the log-rank test).

The results of the sensitivity analyses showed that the conclusions of the primary analysis were robust to changes that were made. These results all remained highly statistically significant.

The clinical secondary outcome variables that were both clinically and statistically significant in favour of adalimumab included greater disease control (uveitis) at 3 months and 6 months in at least one eligible eye and in all eligible eyes; greater disease control (uveitis) at 6 months; increased number of participants entering disease (uveitis) remission at 3 months and 6 months in at least one eligible eye and in all eligible eyes; increased duration of inactive disease (uveitis); ability to reduce to fewer than two corticosteroid drops and zero drops; and reduced total oral corticosteroid use.

As expected, the greatest proportion of uveitis patients have the oligoarticular subtype form of JIA. Therefore, measures of disease activity that look at articular disease did not show statistically significant differences.

The AE profile was consistent with the safety profile established across the approved indications of adalimumab. There were no deaths during the course of the trial. There were two AEs in the adalimumab group and one SAE in the placebo group, which led to the withdrawal of the participant.

As adalimumab is a potent immunosuppressive agent, as noted in previous literature,[82] children treated with adalimumab in combination with MTX in this trial (integrated analysis of double-blind and open-label data) had a greater rate of AEs per year than placebo-treated children (9.86 vs. 7.21, respectively). The majority of these AEs were viral infections, which is consistent with published literature.[41] There was also a greater incidence of SAEs in the adalimumab group than the placebo group (21.7% vs. 6.7%, respectively). The most frequently reported SAEs were infections and infestations (11 events in 9 participants in the adalimumab group). The majority of the SAEs were mild or moderate in severity. There were no cases of malignancies, demyelinating events or deaths during the course of this study.

The economic analysis has strength in that it estimates the cost-effectiveness of adalimumab over a time period beyond that of SYCAMORE, up until the participants reach the age of 18 years. However, key limitations included incomplete data on health utilities and crossover effects resulting from early trial closure.

These were addressed using robust methods (multiple imputation and instrumental variable regression) but, nevertheless, might have introduced bias to the analysis. We also deviated from the protocol by using HUI3 [instead of the Health Utility Index Mark 2 (HUI2)] utilities. This was carried out for two justifiable reasons, which had not become apparent (or which we had not appreciated) during the writing of the protocol. First, the attributes of the two HUIs are different, the HUI2 does not include an attribute specific to vision, which, given the context of SYCAMORE, would be a major disadvantage. Second, HUI3 yields more information than HUI2 when there are missing data. Taking the HUI2 sensation attribute as an example, any single missing response to one of the three subattributes (e.g. speech) would result in the whole sensation score being classed as missing in HUI2, whereas in HUI3 it would only affect the speech attribute but vision and hearing could still be counted as they are single attributes. It is acknowledged that one consequence of this change is that although there is UK health state valuation for the HUI2 there is none for HUI3, and so this is based on Canadian values.[73]

A further limitation, related to the outcome measure for the analysis being VI, that differs from the primary outcome measure in SYCAMORE was time to treatment failure. This was necessary in order to model the impact of adalimumab over a time frame valid for JIA-associated uveitis and given the need to link to the Bristol cohort data. Regarding the generalisability of the Bristol cohort, both age and sex were representative of those in SYCAMORE; however, the Bristol cohort included idiopathic uveitis and patients experienced more VI than SYCAMORE participants. Moreover, there were probably differences in treatment plans, such as the choice of DMARDs and thresholds for initiating biologics. Bristol also pioneered combined (ophthalmology and rheumatology) clinics, which needed to be developed during SYCAMORE in many centres or optimised in many others to aid successful delivery of the trial to time and target.

The extrapolation model has several limitations, mainly because of a paucity of data. The structure of the model was limited by the number of participants and the incompleteness of the Bristol data set.[74] The model structure reflects visual acuity in a patient's worst eye, which was deemed to be most clinically relevant. A further stratification of logMAR ≥ 1 as severe VI may have added to the interpretation of the progression of uveitis; however, within SYCAMORE, a logMAR score of 1 was recorded only once in over 900 recorded visits, and transitioning to severe VI from either no VI or VI in the Bristol data set[74] was recorded in $< 3\%$ of transitions.

It was assumed that the transition probabilities in the model were independent of trial arm. Although the longitudinal (Bristol) data set[74] included information on adalimumab prescription, it appeared that adalimumab was only prescribed to those patients in a worse health state (confounding by indication), which would bias the results, hence a single set of transition probabilities were derived based on data from all patients.

A further limitation is acknowledged: 15 participants from the SYCAMORE cohort are included in the longitudinal data set, contributing to 26 out of 268 total recorded transitions. To retain as much power as possible, these participants were not removed; however, this could be considered double counting.

This approach to modelling the long-term costs and consequences of adalimumab might have been structured differently. The model considered the progression of uveitis and associated complications requiring surgery, but does not explicitly reflect the impact of treatment on the progression of JIA. However, health state costs and QALYs determined from the trial implicitly included the benefits of treatment on mobility and pain, which are captured within the HUI3 utilities. The model also did not include the state of severe VI or blindness. A model based on the association between AC cell count and blindness might have offered an alternative approach, although this would not have reduced the need for considerable assumptions relating to the magnitude of long-term treatment benefits. Expected rates of blindness may be low in SYCAMORE participants as they had mild or moderate uveitis, with 91% of participants having AC cell counts of 1+ or 2+ at baseline. It may, alternatively, have been possible to calculate utilities and costs for the states of treatment failure and no treatment failure, and project the survival curves relating to the primary clinical end point of time to treatment failure, with the differences

in costs and QALYs between treatment groups being driven by the survival function. This would have required an assumption that all the health-related quality-of-life benefits and costs (other than those of adalimumab) are driven by treatment success/failure, which might not necessarily be the case.

Despite these limitations, the analysis is robust to several assumptions. In an extreme scenario of every participant randomised to the placebo group moving to the state of VI in the modelled extrapolation, the ICER reduces only to £78,524 per QALY gained, which still exceeds the cost-effectiveness threshold. In order to demonstrate cost-effectiveness, participants receiving adalimumab would need to experience 1.00 additional QALY gain over the 10-year extrapolation, which seems unlikely, given that the QALY gain over the course of the trial was only 0.11.

In summary, this is the first large, randomised, double-blind, placebo-controlled trial of children with MTX-refractory JIA-associated uveitis, which shows that treatment with adalimumab combined with MTX is both effective and safe but, at £129,025 per QALY gained, is unlikely to be cost-effective in the UK NHS setting.

Implications for practice

This trial provides robust evidence regarding the use of adalimumab in the management of children and adolescents with JIA-associated uveitis refractory to MTX. The results show that adalimumab therapy in combination with MTX controlled inflammation and had a lower rate of treatment failure than placebo in this patient group. This finding, taken alongside the expected increased incidence of AEs in the adalimumab group and the economic analysis, can potentially inform current clinical practice with the aim of reducing uveitis-related ocular morbidity, including VI.

Recommendations for research

This trial answered some key questions for the management of JIA-associated uveitis refractory to MTX. However, it also identified a number of crucial next-step research challenges. These include the following:

1. defining the optimum time after control of uveitis to withdraw/stop adalimumab
2. defining the development and clinical utility of testing for antidrug antibodies in patients with waning of response to adalimumab
3. consideration of the option of increasing the frequency of administration of adalimumab for those with a suboptimal response
4. developing biomarkers for predicting early and complete response to adalimumab so that patients can be stratified more quickly to the appropriate treatment.

Overall conclusion

Adalimumab in combination with MTX is safe and effective in the management of JIA-associated uveitis. However, the likelihood of cost-effectiveness is < 1% at the £30,000-per-QALY threshold. Several limitations of the trial are noted. However, overall, this trial is, to our knowledge, the first randomised, double-blind, placebo-controlled, multicentre trial with an integrated economic evaluation comparing the efficacy, safety and cost-effectiveness of adalimumab in combination with MTX versus placebo with MTX alone, with regard to controlling disease activity in refractory uveitis associated with JIA. It also notes important future research priorities, including a future clinical trial to define the most effective time to stop therapy and to identify prognostic biomarkers of early and complete response.

Acknowledgements

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Contributions of authors

Athimalaipet V Ramanan and **Michael W Beresford** were chief investigators of the trial and provided rheumatology expertise for the trial design and throughout the trial period, with input from **Sandrine Compeyrot-Lacassagne** and **Patricia Woo**.

Athimalaipet V Ramanan, **Ashley P Jones**, **Dyfrig A Hughes** and **Michael W Beresford** wrote early versions of the manuscript with significant input from all co-authors. The manuscript was finalised and revisions addressed by **Athimalaipet V Ramanan** and **Michael W Beresford** with all co-authors' consent.

Andrew D Dick and **Clive Edelsten** provided ophthalmology support and expertise during the design of the trial and throughout the trial period.

The study was conceived by **Athimalaipet V Ramanan** and **Michael W Beresford**, and the protocol and design were by **Athimalaipet V Ramanan**, **Clive Edelsten**, **Dyfrig A Hughes**, **Ashley P Jones**, **Ben Hardwick**, **Helen Hickey** and **Michael W Beresford** with support from all co-authors.

The day-to-day management of the trial was undertaken by **Ashley P Jones**, **Andrew McKay**, **Paula R Williamson**, **Ben Hardwick** and **Helen Hickey**, with ongoing support from **Athimalaipet V Ramanan**, **Michael W Beresford** and all co-authors.

Data were gathered and analysed by **Athimalaipet V Ramanan**, **Ashley P Jones**, **Dyfrig A Hughes**, **Andrew McKay**, **Anna Rosala-Hallas**, **Paula R Williamson**, **Naomi Rainford**, **Graeme Hickey**, **Ruwanthi Kolamunnage-Dona**, **Giovanna Culeddu**, **Catrin Plumpton**, **Eifiona Wood** and **Michael W Beresford**, and who vouch for the data and the analyses.

The authors assume responsibility for the accuracy and completeness of the data and vouch for the fidelity of the trial to the protocol.

Publications

Ramanan AV, Dick AD, Jones AP, McKay A, Williamson PR, Compeyrot-Lacassagne S, *et al.* Adalimumab plus methotrexate for uveitis in juvenile idiopathic arthritis. *N Eng J Med* 2017;**376**:1637–46.

Hughes DA, Culeddu G, Plumpton CO, Wood E, Dick AD, Jones AP, *et al.* Cost-effectiveness analysis of adalimumab for the treatment of uveitis associated with juvenile idiopathic arthritis [published online ahead of print 15 October 2018]. *Ophthalmology* 2018.

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to available anonymised data may be granted following review.

University Hospitals Bristol NHS Foundation Trust, as the sponsor of this trial, has a data-sharing agreement with AbbVie Inc. in support of regulatory purposes.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 Trial oversight committees

Trial Steering Committee

Independent members

Professor Ian Bruce (chairperson), Professor of Rheumatology, Arthritis Research UK Centre for Epidemiology, University of Manchester, UK.

Dr Carlos Pavesio, Consultant Ophthalmologist, Moorfields Eye Hospital NHS Foundation Trust, London, UK.

Mr Matt Sydes, Senior Scientist and Senior Medical Statistician, MRC Clinical Trials Unit, London, UK.

Dr Janine Gray, Principal Medical Statistician, Leeds Institute of Clinical Trials Research, University of Leeds, UK (Dr Gray left the TSC on 29 January 2015).

Non-independent members

Professor Athimalaipet Vaidyanathan Ramanan* (Co-Chief Investigator), Consultant Paediatric Rheumatologist, Bristol Royal Hospital for Children & Royal National Hospital for Rheumatic Diseases, UK.

Professor Michael W Beresford* (Co-Chief Investigator), Professor of Child Health, University of Liverpool, Liverpool, UK.

Dr Ashley P Jones, Senior Statistician, CTRC, University of Liverpool, Liverpool, UK.

Professor Andrew Dick, Professor of Ophthalmology, Department of Clinical Sciences, University of Bristol, Bristol, UK.

Dr Clive Edelsten, Consultant Ophthalmologist, Great Ormond Street Hospital for Children, London, UK.

Mr Ben Hardwick, Trial Co-ordinator, CTRC, University of Liverpool, Liverpool, UK.

*Trial management group members eligible to vote. Only one non-independent member was eligible to vote.

Independent Data and Safety Monitoring Committee

Professor John Sparrow (Chairperson), Consultant Ophthalmologist, Bristol Eye Hospital, Bristol, UK.

Professor Justine Smith, Consultant Ophthalmologist, School of Medicine, Adelaide, SA, Australia.

Dr Nico Wulffraat, Paediatric Rheumatologist, UMC Utrecht, Department of Paediatrics, Utrecht, Netherlands.

Professor Steff Lewis, Personal Chair in Medical Statistics, Public Health Sciences section, Centre for Population Health Sciences, The University of Edinburgh, Medical School, Edinburgh, UK.

Trial Management Group

Professor Athimalaipet Vaidyanathan Ramanan (Co-Chief Investigator), Consultant Paediatric Rheumatologist, Bristol Royal Hospital for Children & Royal National Hospital for Rheumatic Diseases, UK.

Professor Michael W Beresford (Co-Chief Investigator), Professor of Child Health, University of Liverpool, Liverpool, UK.

Diana Benton, Research & Innovation, University Hospitals Bristol NHS Foundation Trust, Bristol, UK.

Jessica Bisset, Research & Innovation, University Hospitals Bristol NHS Foundation Trust, Bristol, UK.

Professor Andrew Dick, Professor of Ophthalmology, Department of Clinical Sciences, University of Bristol, Bristol, UK.

Dr Clive Edelsten, Consultant Ophthalmologist, Great Ormond Street Hospital for Children, London, UK.

Mr Ben Hardwick, Trial Co-ordinator, CTRC, University of Liverpool, Liverpool, UK.

Ms Helen Hickey, Head of Trial Management, CTRC, University of Liverpool, Liverpool, UK.

Professor Dyfrig Hughes, Professor of Pharmaeconomics, Centre for Health Economics and Medicines Evaluation, Bangor University, Bangor, UK.

Debbie Janson, patient representative.

Dr Ashley P Jones, Senior Statistician, CTRC, University of Liverpool, Liverpool, UK.

Dr Sandrine Lacassagne, Paediatric Rheumatologist, Great Ormond Street Hospital for Children NHS Trust, London, UK.

Mr Andrew McKay, Trial Statistician, CTRC, University of Liverpool, Liverpool, UK.

Jennifer Oliver, Bristol Children's Vaccine Centre, Bristol, UK.

Emma Stoica, Research & Innovation, University Hospitals Bristol NHS Foundation Trust, Bristol, UK.

Ms Giovanna Culeddu, Research Project Support Officer, Centre for Health Economics and Medicines Evaluation, Bangor University, Bangor, UK.

Professor Paula Williamson, Director, CTRC, University of Liverpool, Liverpool, UK.

Professor Patricia Woo, Emeritus Professor of Paediatric Rheumatology, University College London.

Appendix 2 Differences between *The New England Journal of Medicine* manuscript[63] and *Chapter 5* results of this report

Outcome	NEJM paper[63] results	*Chapter 5* results	Notes
Time to treatment failure	HR 0.25, 95% CI 0.12 to 0.49; $p < 0.0001$	HR 0.25, 95% CI 0.12 to 0.51; $p < 0.0001$	Three participants who were classified as treatment failures in the first snapshot were classified incorrectly and, therefore, should have been withdrawals (participants from the adalimumab group, anonymised identification numbers: 0249031, 0249040; placebo: 0243049). Additionally, in the treatment failure line listings, 0133058's further details changed from 'No follow up, consent to use collected data' to 'Continue follow up' and 0116008's first of the consecutive visits changed from 'Visit 3 – 3 months' treatment: 2+ on 31 May 2012' to 'Unscheduled visit: 2+ on 12 July 2012'
Number of participants failing treatment	RR 0.40, 95% CI 0.22 to 0.73; $p = 0.002$	RR 0.40, 95% CI 0.23 to 0.72; $p = 0.002$	See above for an explanation of the reclassification of the three treatment failures
AEs	588 AEs in 53 participants in the adalimumab group and 103 AEs in 25 participants in the placebo group Rate (95% CI) in the adalimumab group 10.07, 95% CI 9.26 to 10.89 Rate in the placebo group 6.51, 95% CI 5.26 to 7.77	619 AEs in 59 participants in the adalimumab group and 114 AEs in 26 participants in the placebo group Rate (95% CI) in the adalimumab group 10.60, 95% CI 9.77 to 11.44 Rate in the placebo group 7.21, 95% CI 5.89 to 8.53	The number of AEs increased owing to responses to data queries that were received in relation to concomitant medications. When concomitant medications were queried, extra rows of concomitant medications that were not expected were submitted, which then indicated that there were further AEs (as they had AE numbers indicated on the form that had not been received)

Outcome	NEJM paper[63] results	*Chapter 5* results	Notes
SAEs	17 SAEs in 13 participants in the adalimumab group and 3 SAEs in two participants in the placebo group Rate (95% CI) in the adalimumab group 0.29, 95% CI 0.15 to 0.43 Rate in the placebo group 0.19, 95% CI 0.00 to 0.40	No change	N/A
Compliance	Participant diaries: IMP – Adalimumab, 82.87%; placebo, 74.11% MTX – Adalimumab, 60.46%; placebo, % Accountability logs: IMP – Adalimumab, 94.00%; placebo, 90.24%	Participant diaries: IMP – Adalimumab, 84.00%; placebo, 74.00% MTX – Adalimumab, 62.50%; placebo, % Accountability logs: IMP – Adalimumab, 94.00%; placebo, 90.00%	Minor differences between two sets of result
Total oral corticosteroid dose	The analysis of this outcome was not reported in the NEJM manuscript or supplementary table	N/A	N/A
Reduction in systemic corticosteroid dose from entry dose to 0 mg	Analyses of these data were not possible owing to the statistical algorithm not converting	No change	N/A
Reduction in systemic corticosteroid dose from entry dose to < 5 mg	Analyses of these data were not possible owing to the statistical algorithm not converting	No change	N/A
Time to reduction to fewer than two drops in topical corticosteroid	HR 3.72, 95% CI 1.09 to 12.71; $p = 0.04$	HR 3.99, 95% CI 1.18 to 25.20; $p = 0.03$	00243049: originally failure code 2 and now failure code 1. Changed from 49 days to 147 days owing to incorrect treatment failure. Placebo participant 00249040: originally failure code 2 and now failure code 1. Changed from 202 days to 343 days owing to incorrect treatment failure. Adalimumab participant

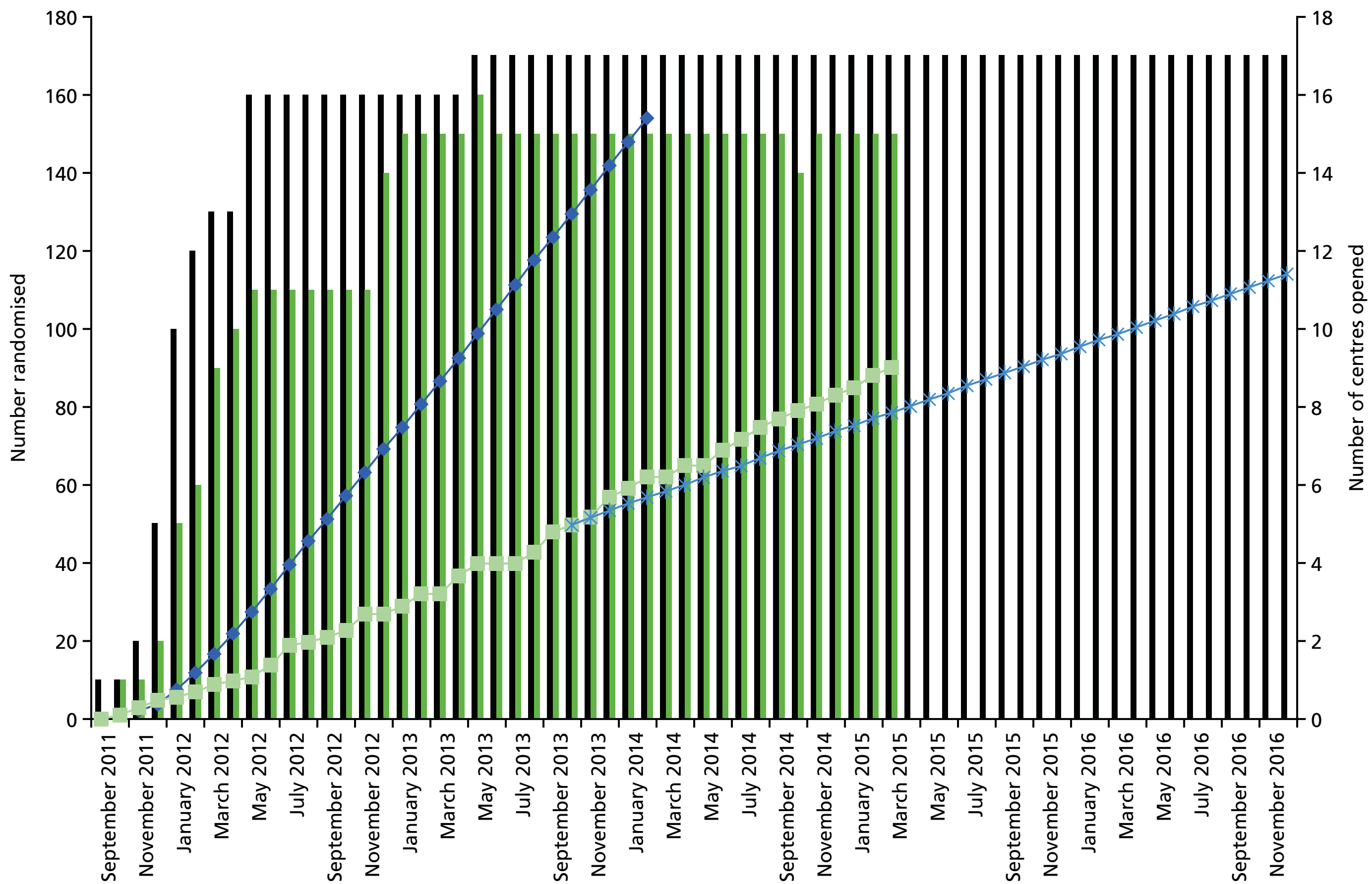
Outcome	NEJM paper[63] results	*Chapter 5* results	Notes
Time to reduction to zero drops in topical steroid (post hoc analysis)	HR 3.58, 95% CI 1.24 to 10.32; $p = 0.02$	HR 4.02, 95% CI 1.40 to 11.50; $p = 0.01$	00243049: originally failure code 2 and now failure code 1. Changed from 49 days to 147 days owing to incorrect treatment failure. Placebo participant 00249040: originally failure code 2 and now failure code 1. Changed from 202 days to 475 days owing to incorrect treatment failure. Adalimumab participant 00249048: originally failure code 0 and now failure code 1. Changed from 504 days to 483 days. One concomitant medication added. Originally, the last entry had a missing end date, so this was imputed as the PO date, but now one concomitant medication has been added, which has an end date and so the participant reached zero drops before their PO date. Adalimumab participant
Number of participants requiring pulsed therapy	RR 0.50, 95% CI 0.03 to 7.72; $p > 0.99$	RR 1.00, 95% CI 0.09 to 10.59, $p > 0.99$	Two participants required pulsed therapy during the blinded phase in the adalimumab group; only one was reported in the NEJM manuscript
Number of participants having uveitis disease flares following 3 months of disease control	The analysis of this outcome was not reported in the NEJM manuscript or supplementary table	N/A	
Number of participants having disease flares within the first 3 months	RR 0.07, 95% CI 0.00 to 1.36	No change	N/A
Visual acuity measured by age-appropriate logMAR assessment	Best case: –0.01, 95% CI –0.06 to 0.03; $p = 0.59$ Worst case: –0.02, 95% CI –0.07 to 0.03; $p = 0.53$	Best case: –0.01, 95% CI –0.07 to 0.02; $p = 0.51$ Worst case: –0.02, 95% CI –0.07 to 0.02; $p = 0.36$	An incorrect assumption had been made with regard to how premature discontinuations were handled in the analysis. In the NEJM manuscript, these were incorrectly handled as treatment failures
Number of participants with resolution of associated optic nerve or macular oedema	Analysis of the optic nerve data was not possible owing to the low number of participants who had this Macular oedema: RR 5.00, 95% CI 0.34 to 74.52	No changes	N/A

Outcome	NEJM paper[63] results	*Chapter 5* results	Notes
Number of participants with disease control (in all eligible eyes)	3 months: RR 11.00, 95% CI 1.56 to 77.74; $p < 0.001$ 6 months: RR 8.50, 95% CI 1.19 to 60.87; $p = 0.005$	3 months: RR 5.75, 95% CI 1.45 to 22.78; $p = 0.001$ 6 months: no change	One more participant in the adalimumab arm had disease control for 3 months
Number of participants entering disease remission (in all eligible eyes)	3 months: RR 7.50, 95% CI 1.04 to 54.12; $p = 0.02$ 6 months: RR 13.72, 95% CI 0.84 to 223.26; $p = 0.004$	3 months: no change 6 months: no change	N/A
Duration of sustaining inactive disease	MD 164.79, 95% CI 104.41 to 225.16; $p < 0.0001$	MD 164.55, 95% CI 104.41 to 224.69; $p < 0.0001$	Very minor difference in MD
CHQ	PsS 2.69, 95% CI –0.26 to 5.86; $p = 0.06$ PhS 1.36, 95% CI –2.28 to 5.05; $p = 0.49$	PsS 2.31, 95% CI –0.44 to 5.40; $p = 0.15$ PhS 1.16, 95% CI –2.41 to 5.05; $p = 0.55$	An incorrect assumption had been made with regard to how premature discontinuations were handled in the analysis. In the NEJM manuscript, these were incorrectly handled as treatment failures
CHAQ	–0.14, 95% CI –0.32 to 0.01; $p = 0.08$	–0.14, 95% CI –0.31 to 0.02; $p = 0.09$	An incorrect assumption had been made with regard to how premature discontinuations were handled in the analysis. In the NEJM manuscript these were incorrectly handled as treatment failures
ACR	ACR30: –0.70, 95% CI –1.86 to 0.52; $p = 0.23$ ACR50: –0.65, 95% CI –1.74 to 0.44; $p = 0.25$ ACR70: –0.61, 95% CI –1.89 to 0.74; $p = 0.34$ ACR90: –0.46, 95% CI –3.38 to 2.46; $p = 0.76$ ACR100: –1.23, 95% CI –2.34 to –0.14; $p = 0.03$	ACR30: –0.04, 95% CI –1.37 to 1.59; $p = 0.98$ ACR50: –0.70, 95% CI –2.15 to 0.77; $p = 0.37$ ACR70: –1.08, 95% CI –2.70 to 0.46; $p = 0.16$ ACR90: –0.33, 95% CI –2.22 to 1.39; $p = 0.72$ ACR100: –0.32, 95% CI –1.85 to 1.17; $p = 0.65$	An incorrect assumption had been made with regard to how premature discontinuations were handled in the analysis. In the NEJM manuscript, these were incorrectly handled as treatment failures The significance of ACR100 did change, but this is not regarded as clinically important because there were such small numbers in the analysis
Number of participants undergoing arthritis disease flare, in remission on and/or off medication for their JIA, and with minimum disease activity	Disease flare: RR 0.07, 95% CI 0.00 to 1.36; $p = 0.03$ Remission: this outcome was only reportable during the follow-up phase and, therefore, was not reported in the NEJM paper Minimum disease activity: RR 2.33, 95% CI 0.87 to 6.24; $p = 0.08$	Disease flare: no change Remission: N/A Minimum disease activity: no change	N/A

Outcome	NEJM paper[63] results	*Chapter 5* results	Notes
Number of participants requiring change in biologics or DMARD therapy owing to failure to respond from arthritis	RR 1.00, 95% CI 0.20 to 5.09; $p = 0.99$	No change	N/A
JADAS	JADAS10: –0.35, 95% CI –0.79 to –0.01; $p = 0.07$ JADAS27: –0.34, 95% CI –0.78 to 0.03; $p = 0.08$ JADAS71: –0.36, 95% CI –0.80 to –0.0004; $p = 0.07$	JADAS10: –0.35, 95% CI –0.78 to 0.01; $p = 0.07$ JADAS27: –0.34, 95% CI –0.76 to 0.03; $p = 0.08$ JADAS71: –0.36, 95% CI –0.78 to 0.004; $p = 0.07$	An incorrect assumption had been made with regard to how premature discontinuations were handled in the analysis. In the NEJM manuscript these were incorrectly handled as treatment failures

MD, mean difference; N/A, not applicable; NEJM, *New England Journal of Medicine*; PO, primary outcome.
Parts of this table are from *The New England Journal of Medicine*, Ramanan AV, Dick AD, Jones AP, McKay A, Williamson PR, Compeyrot-Lacassagne S, Hardwick B, *et al.* for the SYCAMORE Study Group. Adalimumab plus methotrexate for uveitis in juvenile idiopathic arthritis, vol. 376, pp. 1637–46.[63] Copyright © (2017) Massachusetts Medical Society. Reprinted with permission.

Appendix 3 Additional clinical effectiveness data



	September 2011	October 2011	November 2011	December 2011	January 2012	February 2012	March 2012	April 2012	May 2012	June 2012	July 2012	August 2012	September 2012	October 2012	November 2012	December 2012
Centres expected	1	1	2	5	10	12	13	13	16	16	16	16	16	16	16	16
Centres opened	0	1	1	2	5	6	9	10	11	11	11	11	11	11	11	14
Expected	0.5	1.0	1.8	3.5	7.3	11.8	16.7	21.6	27.5	33.4	39.4	45.5	51.2	57.1	65.1	69.0
Actual	0	1	3	5	6	7	9	10	11	14	19	20	21	23	27	27
Revised target																

	January 2013	February 2013	March 2013	April 2013	May 2013	June 2013	July 2013	August 2013	September 2013	October 2013	November 2013	December 2013	January 2014	February 2014	March 2014	April 2014
Centres expected	16	16	16	16	17	17	17	17	17	17	17	17	17	17	17	17
Centres opened	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15
Expected	74.9	80.8	86.8	92.7	98.8	104	111	117	123	129	135	141	147	154		
Actual	29	32	32	37	40	40	40	43	48	50	52	57	59	62	62	65
Revised target										50	51.7	53.4	55.1	56.7	58.4	60.4

	May 2014	June 2014	July 2014	August 2014	September 2014	October 2014	November 2014	December 2014	January 2015	February 2015	March 2015	April 2015	May 2015	June 2015	July 2015	August 2015
Centres expected	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17
Centres opened	15	15	15	15	15	14	15	15	15	15	15					
Expected																
Actual	65	69	72	75	77	79	81	83	85	88	90					
Revised target	61.1	63.5	65.2	66.3	68.5	70.2	71.9	73.4	75.3	76.9	78.6	80.3	82	83.7	85.4	87.1

	September 2015	October 2015	November 2015	December 2015	January 2016	February 2016	March 2016	April 2016	May 2016	June 2016	July 2016	August 2016	September 2016	October 2016	November 2016	December 2016
Centres expected	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17
Centres opened																
Expected																
Actual																
Revised target	88.7	90.4	92.1	93.8	95.5	97.2	98.8	101	102	104	106	107	109	111	112	114

FIGURE 13 Overall recruitment graph.

TABLE 40 Screening overview (by centre)

Site	Patients, *n* (*n* visits)					
	Screened	Eligible	Non-eligible	Eligibility unclear	Not consented (*n*)	Randomised (*n*)
University Hospitals Bristol NHS Foundation Trust	43 (59)	28 (28)	26 (30)	1 (1)	0	28
Great Ormond Street Hospital for Children NHS Trust	26 (34)	22 (24)	10 (10)		2	22
Alder Hey Children's NHS Foundation Trust Hospital	30 (33)	12 (13)	20 (20)		6	7
The Newcastle upon Tyne Hospitals NHS Foundation Trust	18 (23)	9 (9)	13 (14)		4	5
Norfolk and Norwich University Hospitals NHS Foundation Trust	25 (49)	7 (8)	24 (41)		3	5
Central Manchester University Hospitals NHS Foundation Trust	8 (15)	6 (6)	6 (9)		2	4
University Hospital Southampton NHS Foundation Trust	8 (13)	6 (6)	3 (6)	1 (1)	2	4
Sheffield Children's NHS Foundation Trust	33 (52)	11 (13)	25 (39)		9	3
Royal Belfast Hospital for Sick Children	11 (37)	4 (4)	10 (33)		1	3
University Hospitals of Leicester NHS Trust	5 (5)	3 (3)	2 (2)		0	2
The Leeds Teaching Hospitals NHS Trust	17 (29)	9 (9)	13 (20)		7	1
Birmingham Children's Hospital NHS Foundation Trust	90 (151)	8 (11)	87 (137)	3 (3)	10	1
Hull and East Yorkshire Hospitals NHS Trust	3 (4)	1 (1)	3 (3)		0	1
Royal Hospital for Sick Children Edinburgh – NHS Lothian	6 (6)	2 (2)	4 (4)		1	0
Royal Hospital for Sick Children, Glasgow – NHS Greater Glasgow and Clyde	9 (9)	2 (2)	7 (7)		2	2
Total	332 (519)	130 (139)	253 (375)	5 (5)	49	90

TABLE 41 Reasons for receiving no consent

Site	Total (*N*)	Reason	*n*	Percentage of total
The Leeds Teaching Hospitals NHS Trust	7	Does not like injections	1	14.3
		Wanted alternative treatment	3	42.9
		Could not comply with trial	1	14.3
		Clinician did not think appropriate	1	14.3
		Wanted to start adalimumab outside trial	1	14.3
Norfolk and Norwich University Hospitals NHS Foundation Trust	3	Other family commitments	2	66.7
		Declined; no reason	1	33.3
The Newcastle upon Tyne Hospitals NHS Foundation Trust	4	Declined; no reason	4	100.0
University Hospital Southampton NHS Foundation Trust	2	Declined; no reason	1	50.0
		Did not want placebo	1	50.0
Birmingham Children's Hospital	10	Declined; no reason	3	30.0
		Did not want placebo	2	20.0
		Does not like injections	1	10.0
		Wanted to start adalimumab outside trial	1	10.0
		Other	3	30.0
Alder Hey Children's NHS Foundation Trust Hospital	6	Declined; no reason	3	50.0
		Did not want placebo	1	16.7
		Does not like injections	1	16.7
		Other	1	16.7
Central Manchester University Hospitals NHS Foundation Trust	2	Did not want placebo	1	50.0
		Could not comply with trial	1	50.0
Sheffield Children's NHS Foundation Trust	9	Other family commitments	4	44.4
		Declined; no reason	3	33.3
		Did not want placebo	1	11.1
		Other	1	11.1
Great Ormond Street Hospital for Children NHS Trust	2	Other	2	100.0
Royal Hospital for Sick Children Edinburgh – NHS Lothian	1	Did not want placebo	1	100.0
Royal Hospital for Sick Children, Glasgow – NHS Greater Glasgow and Clyde	2	Declined; no reason	1	50.0
		Did not want placebo	1	50.0
Royal Belfast Hospital for Sick Children	1	Does not like injections	1	100.0

TABLE 42 Reasons for treatment failure

Participant ID	Site	Treatment	Date of randomisation	Date of treatment failure	Time to fail (days/months)	Reason for treatment failure	Further details	Participant unblinded at time of treatment failure (date)	Eye treatment failure occurred in
0116003	Bristol Children's Hospital	Placebo	23 November 2011	19 January 2012	57/1.87	Intermittent or continuous suspension of trial treatment (placebo)	Continue follow-up	No	Right
0116008	Bristol Children's Hospital	Placebo	15 March 2012	16 August 2012	154/5.06	Sustained scores as recorded at entry grade, measured over two consecutive readings (grades 1 to 2) still present after 6 months of therapy	Continue follow-up: Baseline visit – (1+) Previous visit = SYCAMORE Unscheduled visit – (2+ on 12 July 2012) Failure visit = SYCAMORE Premature withdrawal – (1+ on 16 August 2012)	No	Left
0249019	Great Ormond Street Hospital	Placebo	27 July 2012	27 September 2012	62/2.04	Non-permitted used	No follow-up, consent to use collected data	Yes; 1 October 2012	Left
0114011	Southampton General Hospital	Adalimumab	11 April 2012	2 January 2013	266/8.74	Permitted concomitant medications used against acceptable criteria	Continue follow-up	Yes; 3 January 2013	Left
0036018	Norfolk and Norwich University Hospitals	Placebo	17 July 2012	21 January 2013	188/6.18	Sustained scores as recorded at entry grade, measured over two consecutive readings (grades 1 to 2) still present after 6 months of therapy	Continue follow-up: Baseline visit – (2+) Previous visit = SYCAMORE Treatment visit 3 – 3-months' treatment (3+ on 16 October 2012) Failure visit = SYCAMORE Premature withdrawal – (2+ on 21 January 2013)	Yes; 11 March 2013	Right
0249025	Great Ormond Street Hospital	Placebo	2 November 2012	13 February 2013	103/3.38	Non-permitted concomitant medications used	No follow-up, consent to use collected data	Yes; 20 November 2013	Both
0116006	Bristol Children's Hospital	Adalimumab	26 January 2012	14 March 2013	413/13.57	Permitted concomitant medications used against acceptable criteria	Continue follow-up	Yes; 15 March 2013	Left
0114033	Southampton General Hospital	Placebo	13 February 2013	11 April 2013	57/1.87	Permitted concomitant medications used against acceptable criteria	Continue follow-up	Yes; 17 April 2013	Left
0246030	Royal Manchester Children's Hospital	Placebo	29 January 2013	24 April 2013	85/2.79	Non-permitted concomitant medications used	Continue follow-up	Yes; 26 April 2013	Both

continued

TABLE 42 Reasons for treatment failure (*continued*)

Participant ID	Site	Treatment	Date of randomisation	Date of treatment failure	Time to fail (days/months)	Reason for treatment failure	Further details	Participant unblinded at time of treatment failure (date)	Eye treatment failure occurred in
0116026	Bristol Children's Hospital	Adalimumab	8 November 2012	25 April 2013	168/5.52	Permitted concomitant medications used against acceptable criteria	Continue follow-up	Yes; 5 April 2013	Both
0243023	Alder Hey Children's Hospital	Adalimumab	12 October 2012	19 October 2013	250/8.21	Non-permitted concomitant medications used	Continue follow-up	Yes; 19 June 2013	Left
0249024	Great Ormond Street Hospital	Adalimumab	16 October 2012	21 June 2013	248/8.15	Permitted concomitant medications used against acceptable criteria	Continue follow-up	No	Right
0116005	Bristol Children's Hospital	Placebo	15 December 2011	4 July 2013	567/18.63	Sustained scores as recorded at entry grade, measured over two consecutive readings (grades 1 to 2) still present after 6 months of therapy	Continue follow-up: Baseline visit – (1+) Previous visit = SYCAMORE End of treatment – follow-up visit 2 (1+ on 2 May 2013) Failure visit = SYCAMORE Unscheduled visit – (2+ on 4 July 2013)	Yes; 16 November 2012	Right
0243032	Alder Hey Children's Hospital	Placebo	11 February 2013	17 July 2013	156/5.13	Non-permitted concomitant medications used	Continue follow-up	No	Right
0540037	Royal Belfast Hospital for Sick Children	Placebo	30 April 2013	24 July 2013	85/2.79	Non-permitted concomitant medications used	Continue follow-up	Yes; 24 July 2013	Both
0249043	Great Ormond Street Hospital	Adalimumab	16 August 2013	28 October 2013	73/2.4	Non-permitted concomitant medications used	Continue follow-up	No	Right
0249029	Great Ormond Street Hospital	Placebo	25 January 2013	20 December 2013	329/10.81	Sustained scores as recorded at entry grade, measured over two consecutive readings (grades 1 to 2) still present after 6 months of therapy	Continue follow-up: Baseline visit – (1+) Previous visit = SYCAMORE Treatment visit 5 – 9 months' treatment (2+ on 27 September 2013) Failure visit = SYCAMORE Treatment visit 6 – 12 months' treatment (1+ on 20 December 2013)	Yes; 26 June 2014	Left

Participant ID	Site	Treatment	Date of randomisation	Date of treatment failure	Time to fail (days/months)	Reason for treatment failure	Further details	Participant unblinded at time of treatment failure (date)	Eye treatment failure occurred in
0069039	Great North Children's Hospital	Adalimumab	2 May 2013	27 January 2014	270/8.87	Intermittent or continuous suspension of study treatment (adalimumab)	Continue follow-up	Yes; 16 January 2014	Right
0249047	Great Ormond Street Hospital	Placebo	12 September 2013	28 February 2014	169/5.55	Sustained scores as recorded at entry grade, measured over two consecutive readings (grades 1 to 2) still present after 6 months of therapy	Continue follow-up: Baseline visit – (1+) Previous visit = SYCAMORE Treatment visit 2 – 2 months' treatment (1+ on 15 November 2013) Failure visit = SYCAMORE End of treatment – follow-up visit 1 (3+ on 28 February 2014)	Yes; 18 November 2013	Right
0133058	Birmingham Children's Hospital	Adalimumab	31 December 2013	24 February 2014	83/2.73	Non-permitted concomitant medications used	Continue follow-up	Yes; 30 May 2014	Right
0116051	Bristol Children's Hospital	Placebo	31 October 2013	17 April 2014	168/5.52	Sustained scores as recorded at entry grade measured over two consecutive readings (grades 1 to 2) still present after 6 months of therapy	Continue follow-up: Baseline visit – (1+) Previous visit = SYCAMORE Treatment visit 3 – 3 months of treatment (1+ on 23 January 2014) Failure visit = SYCAMORE Treatment visit 4 – 6 months of treatment (1+ on 17 April 2014)	No	Left
0246055	Royal Manchester Children's Hospital	Adalimumab	5 December 2013	23 April 2014	139/4.57	Sustained scores as recorded at entry grade measured over two consecutive readings (grades 1 to 2) still present after 6 months of therapy	Continue follow-up: Baseline visit – (2+) Previous visit = SYCAMORE End of treatment – follow-up visit 1 (1+ on 7 March 2014) Failure visit = SYCAMORE Unscheduled visit (1+ on 23 April 2014)	No	Left

continued

TABLE 42 Reasons for treatment failure (*continued*)

Participant ID	Site	Treatment	Date of randomisation	Date of treatment failure	Time to fail (days/months)	Reason for treatment failure	Further details	Participant unblinded at time of treatment failure (date)	Eye treatment failure occurred in
0249059	Great Ormond Street Hospital	Placebo	2 January 2014	20 June 2014	169/5.55	Sustained scores as recorded at entry grade measured over two consecutive readings (grades 1 to 2) still present after 6 months of therapy	No follow-up, consent to use collected data: Baseline visit – (1+) Previous visit = SYCAMORE Unscheduled visit – (2+ on 16 May 2014) Failure visit = SYCAMORE Treatment visit 4 – 6 months of treatment (3+ on 20 June 2014)	No	Left
0116067	Bristol Children's Hospital	Placebo	5 June 2014	24 July 2014	49/1.61	Permitted concomitant medications used against acceptable criteria	Continue follow-up	No	Both
0030035	Leeds General Infirmary	Adalimumab	19 April 2013	5 September 2014	504/16.56	Permitted concomitant medications used against acceptable criteria and intermittent or continuous suspension of study treatment (adalimumab)	Continue follow-up	Yes; 28 August 2014	Both
0393075	Royal Hospital for Sick Children (Edinburgh)	Placebo	21 August 2014	16 October 2014	56/1.84	Non-permitted concomitant medications used	Continue follow-up	No	Right
0030073	Leeds General Infirmary	Adalimumab	30 July 2014	17 November 2014	110/3.61	Permitted concomitant medications used against acceptable criteria	Continue follow-up	Yes; 3 December 2014	Both
0069076	Great North Children's Hospital	Adalimumab	28 August 2014	17 February 2015	173/5.68	Sustained scores as recorded at entry grade measured over two consecutive readings (grades 1 to 2) still present after 6 months of therapy	Continue follow-up: Baseline visit – (1+) Previous visit = SYCAMORE Unscheduled visit (1+ on 6 January 2015) Failure visit = SYCAMORE Treatment visit 4 – 6 months of treatment (1+ on 17 February 2015)	Yes; 25 February 2015	Right

Participant ID	Site	Treatment	Date of randomisation	Date of treatment failure	Time to fail (days/months)	Reason for treatment failure	Further details	Participant unblinded at time of treatment failure (date)	Eye treatment failure occurred in
0249086	Great Ormond Street Hospital	Placebo	5 January 2015	2 April 2015	87/2.86	Non-permitted concomitant medications used	Continue follow-up	Yes; 8 May 2015	Left
0116062	Bristol Children's Hospital	Adalimumab	17 February 2014	9 April 2015	416/13.67	Intermittent or continuous suspension of study treatment (adalimumab)	Continue follow-up	Yes; 10 April 2015	Right
0116066	Bristol Children's Hospital	Adalimumab	25 April 2014	9 April 2015	349/11.47	Intermittent or continuous suspension of study treatment (adalimumab)	Continue follow-up	Yes; 30 March 2015	Right

ID, identification.

TABLE 43 Line listings of SAEs

Subject number	Age at onset (years)/sex	Onset date	Resolution date	MedDRA PT	Severity	Relationship to adalimumab/ placebo (per the investigator)
Adalimumab						
0114011	4.89/female	9 June 2012	13 June 2012	Varicella	Moderate	Possibly/possibly
0114016	3.56/female	23 July 2012	15 August 2012	Streptococcal infection	Moderate	Possibly/possibly
0249021	7.63/male	21 October 2012	25 October 2012	Diarrhoea	Moderate	Possibly/possibly
				Syncope	Moderate	Possibly/possibly
0116015	5.14/female	14 November 2012	15 November 2012	Viral infection	Moderate	Possibly/possibly
0116004	9/male	24 March 2013	3 April 2013	Scarlet fever	Moderate	Possibly/possibly
0246022	9.22/female	9 August 2013	20 August 2013	Cellulitis	Mild	Possibly/possibly
				Infected bites	Mild	Possibly/possibly
0116015	5.85/female	1 August 2013	1 September 2013	Lower respiratory tract infection	Moderate	Probably/possibly
0116026	9.43/female	24 April 2013	1 May 2013	Cataract	Moderate	Unrelated/unrelated
0243056	5.05/female	25 January 2014	28 January 2014	Varicella	Moderate	Possibly/possibly
0116044	14.37/male	27 February 2014	15 June 2014	Testes exploration	Moderate	Unrelated/unrelated
0248064	6.17/male	7 July 2014	9 July 2014	Streptococcal infection	Moderate	Probably/possibly
0030035	7.47/female	25 August 2014	27 August 2014	Viral infection	Mild	Possibly/possibly
0116068	8.31/female	18 October 2014	18 October 2014	Antiviral prophylaxis	Mild	Unrelated/unrelated
0116052	7.56/male	9 November 2014	17 November 2014	Food poisoning	Moderate	Unrelated/unrelated
0248064	6.76/male	6 February 2015	7 February 2015	Tonsillar hypertrophy	Moderate	Possibly/possibly
0116061[a]	5.34/female	30 June 2015	1 July 2015	Tonsillitis	Mild	Possibly/possibly
0540060[b]	12.82/female	13 May 2015	14 May 2015	Joint swelling	Mild	Unlikely/unlikely
Placebo						
0249025	7.07/female	13 February 2013	13 February 2013	Anterior chamber flare	Mild	Possibly/unrelated
				Anterior chamber flare	Mild	Possibly/unrelated
0248070	6.24/male	7 July 2014	20 August 2014	Uveitis	Severe	Possibly/unrelated

MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term.
a A SAE that occurred during the open-label phase.
b A SAE that occurred during follow-up (i.e. outside the reporting timelines as stated in the SYCAMORE protocol).

TABLE 44 Study drug compliance data for participants in the adalimumab group

				Treatment diaries				Accountability logs					
Participant ID	Date of first dose	Date of expected last dose	Reason for expected last dose	Expected number of study drug doses	Recorded number of study drug doses	Compliance (%)	Missing entry in diary (*n*)	Number of vials issued	Number of vials returned used	Number of vials returned unused	Missing vials (*n*)	Compliance (%)	Additional information on vials returned unused
0030035	19 April 2013	5 September 2014	Failed treatment: permitted concomitant medications used against acceptable criteria and intermittent or continuous suspension of study treatment (adalimumab)	37	32	86.49	5	36	31	4	1	88.89	
0030073	1 August 2014	17 November 2014	Failed treatment: permitted concomitant medications used against acceptable criteria	8	7	87.50	1	8	7	0	1	100.00	
0031078	1 October 2014	15 September 2015	Last treatment visit in blinded phase	25	25	100.00	0	30	0	0	30	100.00	
0031079	16 October 2014	26 November 2015	Last treatment visit in blinded phase	30	26	86.67	4	38	0	0	38	100.00	
0036038	2 May 2013	13 October 14	Completed 18 months of treatment	38	34	89.47	4	38	26	2	10	94.74	
0036053	11 November 2013	7 April 2014	Withdrew	11	11	100.00	0	14	11	3	0	78.57	
0036081	21 November 2014	11 January 2016	Last treatment visit in blinded phase	30	24	80.00	6	30	20	0	10	100.00	
0069020	30 July 2012	10 February 2014	Completed 18 months of treatment	41	40	97.56	1	42	20	0	22	100.00	
0069039	8 May 2013	27 January 2014	Failed treatment: intermittent or continuous suspension of study treatment (adalimumab)	19	13	68.42	6	18	0	6	12	66.67	
0069076	2 September 2014	17 February 2015	Failed treatment: sustained scores as recorded at entry grade, measured over two consecutive readings (grades 1 to 2) still present after 6 months of therapy	13	13	100.00	0	18	13	5	0	72.22	Four vials were issued on 10 February 2015. One vial was used prior to the participant failing treatment on 17 February 2015. The remaining three were returned unused
0078071	3 July 2014	21 August 2014	Withdrew	4	2	50.00	2	4	0	0	4	100.00	
0114011	11 April 2012	2 January 2013	Failed treatment	20	19	95.00	1	22	9	1	12	95.45	
0114016	4 July 2012	15 August 2012	Withdrew	4	1	25.00	3	4	0	0	4	100.00	
0114041	22 May 2013	13 February 2014	Withdrew	20	19	95.00	1	24	20	0	4	100.00	

continued

TABLE 44 Study drug compliance data for participants in the adalimumab group (*continued*)

				Treatment diaries				Accountability logs					
Participant ID	Date of first dose	Date of expected last dose	Reason for expected last dose	Expected number of study drug doses	Recorded number of study drug doses	Compliance (%)	Missing entry in diary (*n*)	Number of vials issued	Number of vials returned used	Number of vials returned unused	Missing vials (*n*)	Compliance (%)	Additional information on vials returned unused
0116001	27 October 2011	14 March 2013	Completed 18 months of treatment	37	34	91.89	3	36	19	0	17	100.00	
0116002	10 November 2011	28 March 2013	Completed 18 months of treatment	37	33	89.19	4	36	32	0	4	100.00	
0116004	15 December 2011	2 May 2013	Completed 18 months of treatment	37	35	94.59	2	36	0	0	36	100.00	
0116006	26 January 2012	14 March 2013	Failed treatment	30	30	100.00	0	30	0	0	30	100.00	
0116007	8 February 2012	27 June 2013	Completed 18 months of treatment	37	36	97.30	1	36	33	0	3	100.00	
0116013	21 June 2012	7 November 2013	Completed 18 months of treatment	37	36	97.30	1	38	2	0	36	100.00	
0116014	28 June 2012	14 November 2013	Completed 18 months of treatment	37	36	97.30	1	36	33	0	3	100.00	
0116015	28 June 2012	14 November 2013	Completed 18 months of treatment	37	34	91.89	3	42	17	0	25	100.00	
0116026	8 November 2012	25 April 2013	Failed treatment	13	11	84.62	2	14	0	0	14	100.00	
0116034	18 April 2013	11 September 2014	Completed 18 months of treatment	37	36	97.30	1	36	1	0	35	100.00	
0116044	23 August 2013	15 January 2015	Completed 18 months of treatment	37	24	64.86	13	36	0	0	36	100.00	
0116052	7 November 2013	18 November 2014	Withdrew	27	23	85.19	4	30	20	3	7	90.00	
0116061	14 February 2014	18 June 2015	Completed 18 months of treatment	35	34	97.14	1	38	30	2	6	94.74	
0116062	18 February 2014	9 April 2015	Failed treatment: intermittent or continuous suspension of study treatment (adalimumab)	30	27	90.00	3	32	24	4	4	87.50	
0116066	28 April 2014	9 April 2015	Failed treatment: intermittent or continuous suspension of study treatment (adalimumab)	25	15	60.00	10	28	21	6	1	78.57	
0116068	5 June 2014	30 July 2015	Last treatment visit in blinded phase (unscheduled)	31	17	54.84	14	32	13	3	16	90.63	
0116069	5 June 2014	17 September 2015	Last treatment visit in blinded phase (unscheduled)	34	29	85.29	5	36	0	0	36	100.00	

				Treatment diaries				Accountability logs					
Participant ID	Date of first dose	Date of expected last dose	Reason for expected last dose	Expected number of study drug doses	Recorded number of study drug doses	Compliance (%)	Missing entry in diary (*n*)	Number of vials issued	Number of vials returned used	Number of vials returned unused	Missing vials (*n*)	Compliance (%)	Additional information on vials returned unused
0116072	10 July 2014	26 November 2015	Completed 18 months of treatment	37	36	97.30	1	36	2	0	34	100.00	
0116088	5 February 2015	15 October 2015	Last treatment visit in blinded phase	19	12	63.16	7	24	3	0	21	100.00	
0133058	31 December 2013	24 March 2014	Failed treatment: non-permitted concomitant medications used	6	1	16.67	5	12	2	0	10	100.00	
0243009	26 March 2012	31 July 2013	Completed 18 months of treatment	36	34	94.44	2	36	35	1	0	97.22	
0243023	12 October 2012	19 June 2013	Failed treatment: non-permitted concomitant medications used	18	17	94.44	1	18	18	0	0	100.00	
0243042	17 August 2013	17 December 2014	Completed 18 months of treatment	35	28	80.00	7	36	36	0	0	100.00	
0243056	16 December 2013	6 May 2015	Completed 18 months of treatment	37	34	91.89	3	36	36	0	0	100.00	
0243089	11 February 2015	13 January 2016	Last treatment visit in blinded phase	25	23	92.00	2	24	24	0	0	100.00	
0246022	11 September 2012	14 February 2014	Completed 18 months of treatment	38	34	89.47	4	38	22	0	16	100.00	
0246054	4 December 2013	8 May 2015	Completed 18 months of treatment	38	36	94.74	2	38	34	1	3	97.37	
0246055	10 December 2013	19 February 2014	Withdrew	6	3	50.00	3	4	3	1	0	75.00	
0248050	10 October 2013	9 March 2015	Completed 18 months of treatment	37	15	40.54	22	36	33	1	2	97.22	
0248064	10 April 2014	16 March 2015	Withdrew	25	22	88.00	3	26	23	3	0	88.46	
0248087	5 January 2015	7 December 2015	Last treatment visit in blinded phase	25	13	52.00	12	24	18	0	6	100.00	
0249021	24 August 2012	10 January 2014	Completed 18 months treatment	37	35	94.59	2	36	36	0	0	100.00	
0249024	18 October 2012	21 June 2013	Failed treatment: permitted concomitant medications used against acceptable criteria	18	16	88.89	2	24	16	8	0	66.67	On 11 June 2013, six vials were issued; all were returned unused as the participant withdrew on 21 June 2013
0249028	23 November 2012	28 March 2014	Completed 18 months of treatment	36	34	94.44	2	36	36	0	0	100.00	

continued

TABLE 44 Study drug compliance data for participants in the adalimumab group (*continued*)

				Treatment diaries				Accountability logs					
Participant ID	Date of first dose	Date of expected last dose	Reason for expected last dose	Expected number of study drug doses	Recorded number of study drug doses	Compliance (%)	Missing entry in diary (*n*)	Number of vials issued	Number of vials returned used	Number of vials returned unused	Missing vials (*n*)	Compliance (%)	Additional information on vials returned unused
0249031	1 February 2013	9 May 2014	Failed treatment: permitted concomitant medications used against acceptable criteria	34	4	11.76	30	36	29	5	2	86.11	On 19 March 2014, six vials were issued. One vial was used prior to the participant failing treatment on 9 May 2016; the rest were returned unused
0249036	26 April 2013	12 September 2014	Completed 18 months of treatment	37	34	91.89	3	36	36	0	0	100.00	
0249040	17 May 2013	5 December 2013	Failed treatment: permitted concomitant medications used against acceptable criteria	15	12	80.00	3	18	12	6	0	66.67	On 28 October 2013, six vials were issued. All six vials were returned unused
0249043	16 August 2013	28 October 2013	Failed treatment: non-permitted concomitant medications used	6	4	66.67	2	12	6	6	0	50.00	On 18 October 2013, six vials were issued. All six vials were returned unused
0249046	12 September 2013	30 January 2015	Completed 18 months of treatment	37	36	97.30	1	40	35	3	2	92.50	
0249048	13 September 2013	30 January 2015	Completed 18 months of treatment	37	32	86.49	5	36	36	0	0	100.00	
0249065	25 April 2014	11 September 2015	Completed 18 months of treatment	37	35	94.59	2	36	36	0	0	100.00	
0249077	5 September 2014	16 January 2015	Last treatment visit in blinded phase (unscheduled)	10	5	50.00	5	12	9	0	3	100.00	
0249083	5 December 2014	6 November 2015	Last treatment visit in blinded phase	25	18	72.00	7	28	9	0	19	100.00	
0249091	27 March 2015	4 December 2015	Last treatment visit in blinded phase	19	18	94.74	1	18	12	0	6	100.00	
0540060	31 January 2014	7 January 2015	Withdrew	25	14	56.00	11	24	0	5	19	79.17	On 7 October 2014, six vials were issued. Five of these vials were returned unused. Participant withdrew as a result of missing MTX doses before failing treatment for missing adalimumab doses
0540080	21 October 2014	9 December 2015	Last treatment visit in blinded phase	30	29	96.67	1	28	0	0	28	100.00	
Mean compliance				81.01%				93.91%					

ID, identification.

TABLE 45 Study drug compliance data for participants in the placebo group

Participant ID	Date of first dose	Date of expected last dose	Reason for expected last dose	Treatment diaries				Accountability logs					
				Expected number of study drug doses	Recorded number of study drug doses	Compliance (%)	Missing entry in diary (*n*)	Number of vials issued	Number of vials returned used	Number of vials returned unused	Compliance (%)	Missing vials (*n*)	Additional information on vials returned unused
0031074	14 August 2014	5 May 2015	Last treatment visit in blinded phase (unscheduled)	19	18	94.74	1	20	0	0	100.00	20	
0036018	18 July 2012	21 January 2013	Failed treatment: sustained scores as recorded at entry grade measured over two consecutive readings (grades 1 to 2), still present after 6 months of therapy	14	15	107.14	0	14	13	1	92.86	0	
0036057	16 December 2013	31 March 2014	Withdrew	8	8	100.00	0	12	8	4	66.67	0	Six vials were issued on 6 March 2014. Two vials were used prior to the participant withdrawing on 31 March 2014. The remaining four vials were returned unused
0069017	5 July 2012	13 January 2014	Completed 18 months of treatment	40	39	97.50	1	44	6	2	95.45	36	
0069092	31 March 2015	5 May 2015	Last treatment visit in blinded phase (unscheduled)	3	2	66.67	1	4	2	0	100.00	2	
0114033	13 February 2013	11 April 2013	Failed treatment	5	3	60.00	2	6	4	0	100.00	2	
0116003	24 November 2011	19 January 2012	Failed treatment	5	1	20.00	4	6	0	0	100.00	6	
0116005	15 December 2011	15 November 2012	Withdrew	25	22	88.00	3	30	16	0	100.00	14	
0116008	15 March 2012	16 August 2012	Failed treatment: sustained scores as recorded at entry grade measured over two consecutive readings (grades 1 to 2), still present after 6 months of therapy	12	11	91.67	1	16	1	6	62.50	9	Six vials were issued on 16 August 2012 prior to the participant failing treatment (on the same day). These vials were all returned unused
0116012	17 May 2012	10 October 2013	Completed 18 months of treatment	37	35	94.59	2	36	27	1	97.22	8	

continued

TABLE 45 Study drug compliance data for participants in the placebo group (*continued*)

				Treatment diaries				Accountability logs					
Participant ID	Date of first dose	Date of expected last dose	Reason for expected last dose	Expected number of study drug doses	Recorded number of study drug doses	Compliance (%)	Missing entry in diary (*n*)	Number of vials issued	Number of vials returned used	Number of vials returned unused	Compliance (%)	Missing vials (*n*)	Additional information on vials returned unused
0116027	8 November 2012	17 January 2013	Withdrew	6	2	33.33	4	4	0	0	100.00	4	
0116051	31 October 2013	17 April 2014	Failed treatment	13	12	92.31	1	14	9	0	100.00	5	
0116063	27 February 2014	12 February 2015	Withdrew	26	24	92.31	2	34	19	9	73.53	6	Two vials were issued on 6 May 2014 and a further six were issued on 21 May 2014. The extra two vials issued in error were returned unused Six vials were issued on 28 January 2015 and all six were returned unused; one of these vials should have been used
0116067	5 June 2014	24 July 2014	Failed treatment: permitted concomitant medications used against acceptable criteria	4	4	100.00	0	6	1	2	66.67	3	
0116085	18 December 2014	29 January 2015	Withdrew	4	2	50.00	2	4	2	0	100.00	2	
0243032	12 February 2013	18 December 2013	Withdrew	23	22	95.65	1	26	22	4	84.62	0	Two extra vials issued on 3 December 2013 were returned unused
0243049	24 September 2013	6 November 2013	Failed treatment: permitted concomitant medications used against acceptable criteria	4	3	75.00	1	4	3	1	75.00	0	
0246030	30 January 2013	24 April 2013	Failed treatment: non-permitted concomitant medications used	7	6	85.71	1	12	0	0	100.00	12	
0248070	10 June 2014	7 July 2014	Withdrew	2	2	100.00	0	4	2	2	50.00	0	
0249019	2 August 2012	27 September 2012	Failed treatment: non-permitted concomitant medications used	5	4	80.00	1	6	4	2	66.67	0	
0249025	2 November 2012	13 February 2013	Failed treatment: non-permitted concomitant medications used	8	5	62.50	3	12	4	4	66.67	4	On 29 January 2013, six vials were issued; two were used prior to participant failing treatment on 13 February 2013 and the remaining four were returned unused

Participant ID	Date of first dose	Date of expected last dose	Reason for expected last dose	Treatment diaries				Accountability logs					
				Expected number of study drug doses	Recorded number of study drug doses	Compliance (%)	Missing entry in diary (*n*)	Number of vials issued	Number of vials returned used	Number of vials returned unused	Compliance (%)	Missing vials (*n*)	Additional information on vials returned unused
0249029	25 January 2013	20 December 2013	Failed treatment: sustained scores as recorded at entry grade measured over two consecutive readings (grades 1 to 2), still present after 6 months of therapy	24	9	37.50	15	30	22	6	80.00	2	On 16 December 2013, six vials were issued, all were returned unused as participant failed treatment on 20 December 2013
0249045	13 September 2013	30 January 2015	Completed 18 months of treatment	37	14	37.84	23	40	35	1	97.50	4	
0249047	12 September 2013	15 November 2013	Withdrew	5	2	40.00	3	6	3	2	66.67	1	
0249059	3 January 2014	20 June 2014	Failed treatment: sustained scores as recorded at entry grade measured over two consecutive readings (grades 1 to 2), still present after 6 months of therapy	13	1	7.69	12	18	12	6	66.67	0	On 16 June 2014, six vials were issued. All six vials were returned unused
0249082	28 November 14	31 July 2015	Last treatment visit in blinded phase (unscheduled)	18	20	111.11	0	20	9	0	100.00	11	
0249086	5 January 2015	2 April 2015	Failed treatment: non-permitted concomitant medications used	7	6	85.71	1	10	6	4	60.00	0	On 5 February 2015, six vials were issued; a further two vials were issued on 6 March 2015. Four vials were used prior to the participant failing treatment on 2 April 2014. The remaining four vials were returned unused
0249090	13 February 2015	8 May 2015	Last treatment visit in blinded phase	7	6	85.71	1	6	4	0	100.00	2	
0393075	21 August 2014	16 October 2014	Failed treatment: non-permitted concomitant medications used	5	3	60.00	2	6	1	1	83.33	4	
0540037	1 May 2013	24 July 2013	Failed treatment: non-permitted concomitant medications used	7	6	85.71	1	12	0	6	50.00	6	On 24 July 2013, six vials were issued prior to the participant failing treatment. All six vials were returned unused
Mean compliance				74.61%				83.40%					

ID, identification.

TABLE 46 The logMAR score by treatment group at each time point

	Treatment group																	
	Adalimumab						Placebo						Total					
	Best score			Worst score			Best score			Worst score			Best score			Worst score		
Visit	*n*	Mean (SD)	Median (range)	*n*	Mean (SD)	Median (range)	*n*	Mean (SD)	Median (range)	*n*	Mean (SD)	Median (range)	*n*	Mean (SD)	Median (range)	*n*	Mean (SD)	Median (range)
Baseline	60	0.04 (0.15)	0.00 (–0.23 to 0.56)	60	0.05 (0.16)	0.00 (–0.23 to 0.56)	30	0.06 (0.12)	0.05 (–0.13 to 0.40)	30	0.08 (0.12)	0.06 (–0.10 to 0.40)	90	0.04 (0.14)	0.00 (–0.23 to 0.56)	90	0.06 (0.14)	0.03 (–0.23 to 0.56)
1 month	60	0.03 (0.17)	0.00 (–0.30 to 0.80)	60	0.04 (0.18)	0.00 (–0.30 to 0.80)	30	0.02 (0.16)	0.00 (–0.28 to 0.38)	30	0.06 (0.17)	0.04 (–0.28 to 0.38)	90	0.02 (0.17)	0.00 (–0.30 to 0.80)	90	0.05 (0.18)	0.00 (–0.30 to 0.80)
2 months	57	0.02 (0.17)	0.00 (–0.20 to 0.56)	57	0.04 (0.19)	0.00 (–0.20 to 0.75)	25	0.05 (0.18)	0.00 (–0.15 to 0.76)	25	0.06 (0.18)	0.02 (–0.15 to 0.76)	82	0.03 (0.17)	0.00 (–0.20 to 0.76)	82	0.05 (0.19)	0.00 (–0.20 to 0.76)
3 months	56	0.00 (0.16)	0.00 (–0.20 to 0.80)	56	0.02 (0.20)	0.00 (–0.20 to 0.88)	19	0.01 (0.11)	0.00 (–0.13 to 0.24)	19	0.03 (0.12)	0.00 (–0.13 to 0.28)	75	0.00 (0.14)	0.00 (–0.20 to 0.80)	75	0.02 (0.18)	0.00 (–0.20 to 0.88)
6 months	47	0.02 (0.20)	–0.02 (–0.20 to 0.88)	47	0.03 (0.20)	0.00 (–0.20 to 0.88)	12	0.05 (0.16)	0.02 (–0.18 to 0.30)	12	0.07 (0.19)	0.02 (–0.18 to 0.38)	59	0.03 (0.19)	0.00 (–0.20 to 0.88)	59	0.03 (0.19)	0.00 (–0.20 to 0.88)
9 months	42	–0.01 (0.14)	0.00 (–0.25 to 0.40)	42	–0.01 (0.14)	0.00 (–0.25 to 0.40)	7	0.00 (0.17)	–0.08 (–0.10 to 0.36)	7	0.04 (0.20)	–0.08 (–0.10 to 0.36)	49	–0.01 (0.14)	0.00 (–0.25 to 0.40)	49	0.00 (0.15)	0.00 (–0.25 to 0.40)
12 months	34	–0.01 (0.14)	–0.01 (–0.23 to 0.34)	34	0.00 (0.14)	0.00 (–0.23 to 0.34)	5	0.03 (0.14)	0.02 (–0.10 to 0.26)	5	0.08 (0.17)	0.03 (–0.10 to 0.26)	39	–0.01 (0.14)	0.00 (–0.23 to 0.34)	39	0.01 (0.14)	0.00 (–0.23 to 0.34)
15 months	27	0.00 (0.14)	0.00 (–0.25 to 0.40)	27	0.00 (0.13)	0.00 (–0.25 to 0.40)	3	0.00 (0.26)	–0.10 (–0.20 to 0.30)	3	0.00 (0.26)	–0.10 (–0.20 to 0.30)	30	0.00 (0.15)	–0.02 (–0.25 to 0.40)	30	0.00 (0.15)	–0.02 (–0.25 to 0.40)
18 months	23	0.02 (0.13)	0.00 (–0.20 to 0.28)	23	0.04 (0.11)	0.02 (–0.20 to 0.28)	3	0.02 (0.21)	–0.10 (–0.10 to 0.26)	3	0.02 (0.21)	–0.10 (–0.10 to 0.26)	26	0.02 (0.13)	0.00 (–0.20 to 0.28)	26	0.04 (0.12)	0.01 (–0.20 to 0.28)

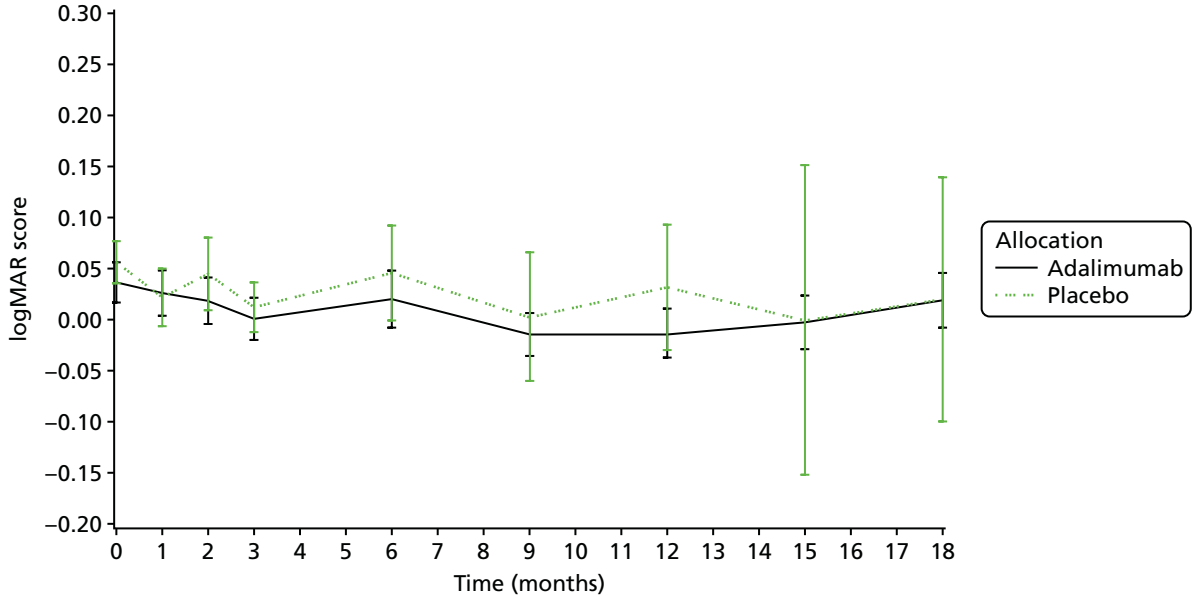


FIGURE 14 Mean profile plot for logMAR best score.

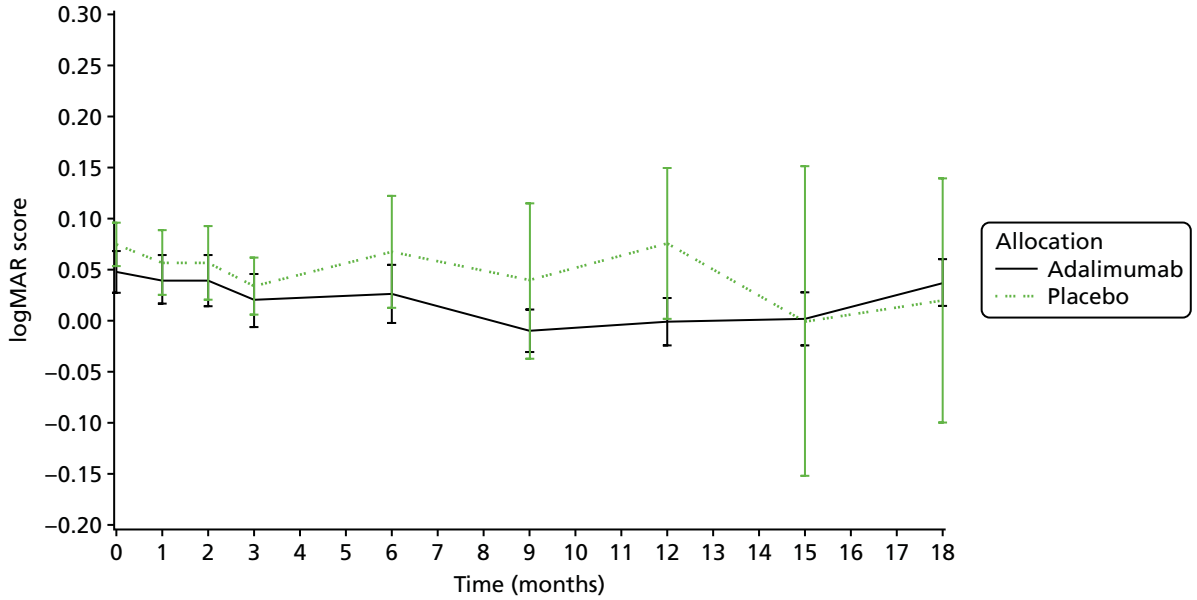


FIGURE 15 Mean profile plot for logMAR worst score.

TABLE 47 The CHQ PsS: summary statistics by treatment by time point

	Treatment group											
	Adalimumab				Placebo				Total			
Visit	*n*	Missing	Mean (SD)	Median (range)	*n*	Missing	Mean (SD)	Median (range)	*n*	Missing	Mean (SD)	Median (range)
Baseline	53	7	51.17 (9.53)	52.74 (30.69–65.85)	22	8	49.48 (7.55)	49.67 (37.25–60.76)	75	15	50.68 (8.98)	51.99 (30.69–65.85)
1 month	53	7	51.06 (10.36)	53.41 (18.72–65.19)	27	3	50.01 (10.27)	50.58 (20.75–63.60)	80	10	50.71 (10.28)	53.24 (18.72–65.19)
2 months	49	9	53.02 (10.00)	54.62 (24.01–64.52)	19	6	50.20 (10.75)	52.42 (30.57–64.29)	68	15	52.23 (10.21)	54.47 (24.01–64.52)
3 months	50	6	54.12 (9.02)	57.52 (26.86–64.30)	16	3	54.21 (8.57)	55.38 (38.63–64.47)	66	9	54.14 (8.85)	57.32 (26.86–64.47)
6 months	40	8	53.94 (9.79)	57.00 (15.14–65.20)	11	1	49.68 (11.56)	54.18 (23.16–61.32)	51	9	53.02 (10.23)	56.19 (15.14–65.20)
9 months	35	7	55.82 (6.84)	58.04 (39.68–65.82)	7	0	50.26 (13.72)	56.14 (25.06–62.08)	42	7	54.89 (8.41)	56.93 (25.06–65.82)
12 months	33	1	54.08 (9.22)	57.61 (27.32–65.30)	4	1	54.18 (8.83)	55.36 (42.61–63.39)	37	2	54.09 (9.06)	57.61 (27.32–65.30)
15 months	25	2	53.56 (7.76)	53.61 (36.75–65.35)	3	0	53.27 (11.83)	55.45 (40.50–63.87)	28	2	53.53 (8.00)	54.53 (36.75–65.35)
18 months	20	3	53.58 (11.71)	55.14 (10.02–64.60)	3	0	47.25 (18.64)	55.49 (25.91–60.35)	23	3	52.76 (12.44)	55.49 (10.02–64.60)

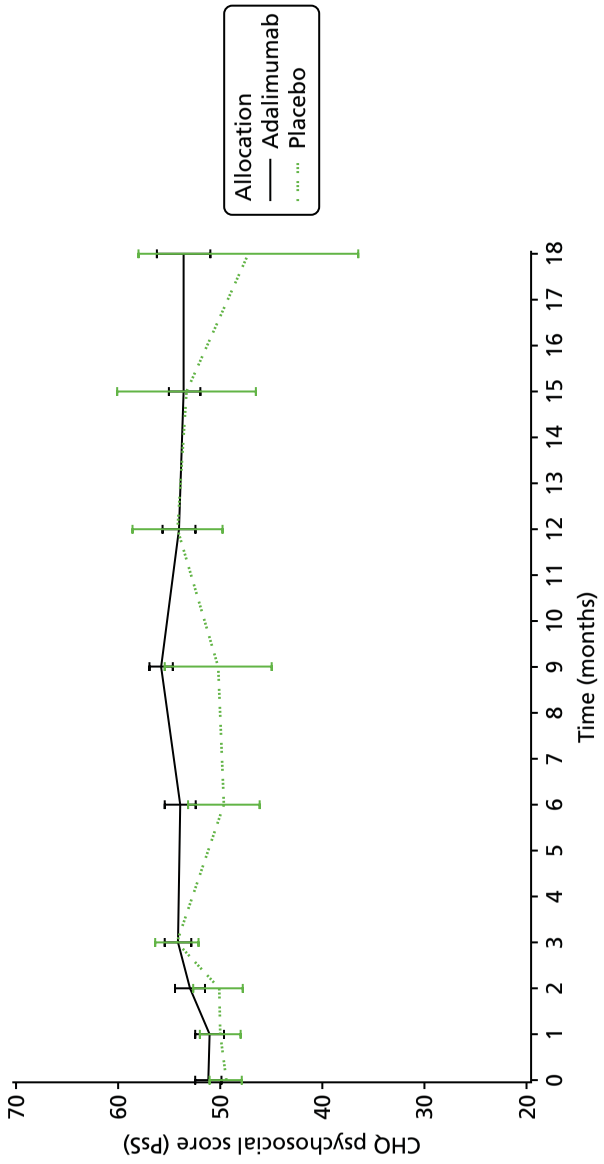


FIGURE 16 The PsS mean profile plot.

TABLE 48 The CHQ PhS: summary statistics by treatment by time point

	Treatment group											
	Adalimumab				Placebo				Total			
Visit	*n*	Missing	Mean (SD)	Median (range)	*n*	Missing	Mean (SD)	Median (range)	*n*	Missing	Mean (SD)	Median (range)
Baseline	53	7	43.20 (11.84)	46.39 (–3.81 to 59.97)	22	8	40.48 (16.36)	43.54 (6.44 to 58.87)	75	15	42.40 (13.26)	46.28 (–3.81 to 59.97)
1 month	53	7	45.54 (11.29)	47.61 (1.97 to 61.07)	27	3	44.73 (12.10)	49.02 (7.47 to 59.60)	80	10	45.27 (11.50)	47.69 (1.97 to 61.07)
2 months	49	9	47.54 (10.69)	52.06 (10.96 to 59.65)	19	6	43.65 (15.56)	46.85 (–2.61 to 59.65)	68	15	46.46 (12.25)	51.81 (–2.61 to 59.65)
3 months	50	6	46.50 (13.13)	50.76 (3.62 to 60.76)	16	3	47.35 (7.97)	48.89 (31.61 to 59.65)	66	9	46.70 (12.03)	49.70 (3.62 to 60.76)
6 months	40	8	47.16 (11.84)	52.06 (9.30 to 58.64)	11	1	41.95 (15.79)	43.69 (1.20 to 59.65)	51	9	46.03 (12.80)	50.40 (1.20 to 59.65)
9 months	35	7	47.50 (11.26)	51.57 (11.12 to 59.00)	7	0	45.20 (14.77)	51.67 (22.56 to 57.01)	42	7	47.12 (11.74)	51.62 (11.12 to 59.00)
12 months	33	1	47.29 (13.06)	52.92 (3.54 to 59.53)	4	1	53.09 (4.79)	54.07 (46.83 to 57.40)	37	2	47.92 (12.53)	52.92 (3.54 to 59.53)
15 months	25	2	42.85 (15.88)	48.98 (6.03 to 60.05)	3	0	55.75 (2.48)	54.86 (53.83 to 58.55)	28	2	44.23 (15.53)	49.97 (6.03 to 60.05)
18 months	20	3	45.92 (12.06)	51.93 (17.26 to 55.79)	3	0	53.77 (9.71)	59.09 (42.56 to 59.65)	23	3	46.94 (11.89)	52.78 (17.26 to 59.65)

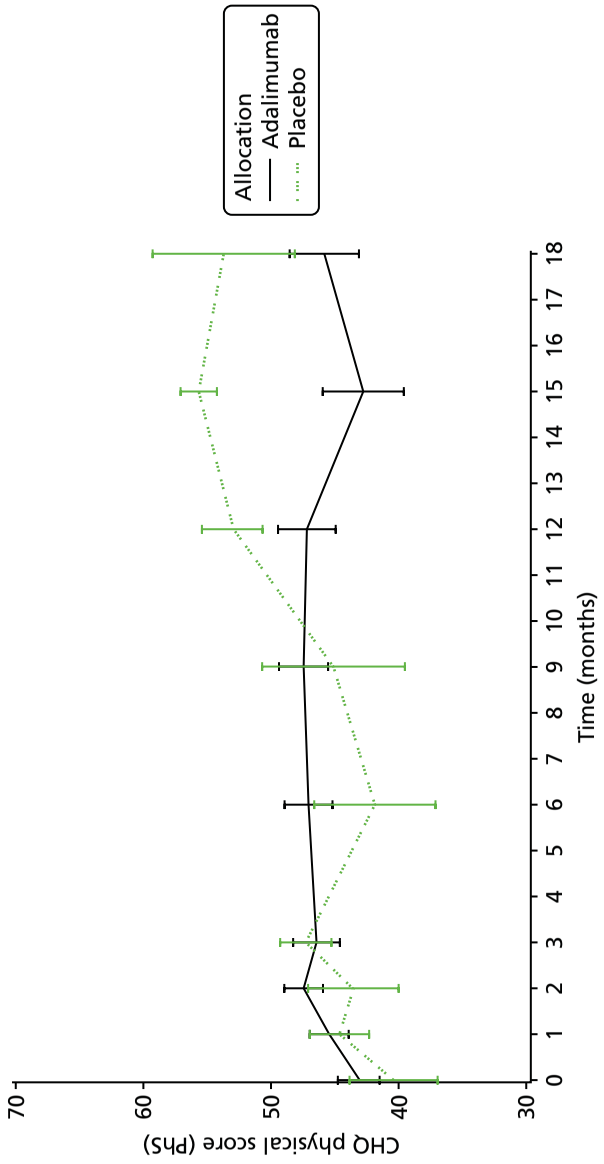


FIGURE 17 The PhS mean profile plot.

TABLE 49 The CHAQ score by treatment group, by time point

	Treatment group											
	Adalimumab				Placebo				Total			
Visit	*n*	Missing	Mean (SD)	Median (range)	*n*	Missing	Mean (SD)	Median (range)	*n*	Missing	Mean (SD)	Median (range)
Baseline	59	1	0.52 (0.64)	0.21 (0.00–2.49)	28	2	0.48 (0.49)	0.45 (0.00–1.57)	87	3	0.51 (0.59)	0.33 (0.00–2.49)
1 month	59	1	0.41 (0.56)	0.13 (0.00–2.29)	30	0	0.60 (0.55)	0.55 (0.00–1.61)	89	1	0.47 (0.56)	0.22 (0.00–2.29)
2 months	57	1	0.38 (0.53)	0.11 (0.00–1.96)	24	1	0.54 (0.59)	0.45 (0.00–2.32)	81	2	0.43 (0.55)	0.20 (0.00–2.32)
3 months	54	2	0.36 (0.58)	0.03 (0.00–2.49)	18	1	0.37 (0.47)	0.19 (0.00–1.50)	72	3	0.36 (0.55)	0.05 (0.00–2.49)
6 months	45	3	0.36 (0.61)	0.02 (0.00–2.49)	12	0	0.46 (0.63)	0.11 (0.00–2.00)	57	3	0.38 (0.61)	0.05 (0.00–2.49)
9 months	39	3	0.35 (0.63)	0.06 (0.00–2.28)	7	0	0.36 (0.57)	0.09 (0.00–1.58)	46	3	0.35 (0.62)	0.06 (0.00–2.28)
12 months	34	0	0.33 (0.60)	0.02 (0.00–2.04)	4	1	0.09 (0.15)	0.02 (0.00–0.31)	38	1	0.31 (0.57)	0.02 (0.00–2.04)
15 months	26	1	0.43 (0.58)	0.11 (0.00–2.00)	3	0	0.03 (0.04)	0.01 (0.00–0.07)	29	1	0.39 (0.56)	0.10 (0.00–2.00)
18 months	22	1	0.30 (0.48)	0.02 (0.00–1.55)	3	0	0.03 (0.05)	0.01 (0.00–0.09)	25	1	0.27 (0.46)	0.02 (0.00–1.55)

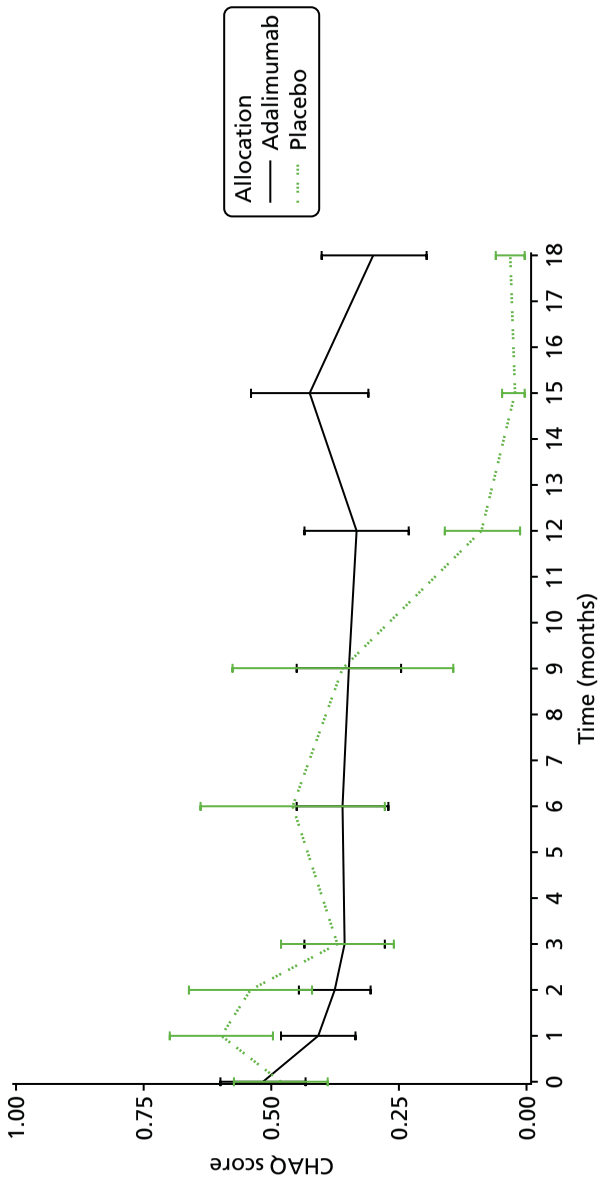


FIGURE 18 Mean profile plots for CHAQ score by treatment group.

TABLE 50 Treatment failures during the open-label phase

Participant ID	Site	Date of randomisation	Date of treatment failure	Time to failure (days/months)	Reason for treatment failure	Further details	Patient unblinded at time of treatment failure (date)	Eye failed
0116068	Bristol Children's Hospital	5 June 2014	18 June 2015	378/12.42	Permitted concomitant medications used against acceptable criteria	Continue follow-up	Already in open-label phase	Left
0116069	Bristol Children's Hospital	5 June 2014	20 August 2015	441/14.49	Sustained scores as recorded at entry grade measured over two consecutive readings (grades 1 to 2), still present after 6 months of therapy	Continue follow-up: Base – (1+) Previous = SYCAMORE Treatment visit 7 – 15 months' treatment (1+ on 30 July 2015) Fail = SYCAMORE Unscheduled visit – (1+ on 20 August 2015)	Already in open-label phase	Right
0249091	Great Ormond Street Hospital	27 March 2015	11 September 2015	168/5.52	Sustained scores as recorded at entry grade measured over two consecutive readings (grades 1 to 2), still present after 6 months of therapy	Continue follow-up: Base – (2+) Previous = SYCAMORE Treatment visit 3 – 3 months' treatment (1+ on 19 June 2015) Fail = SYCAMORE Treatment visit 4 – 6 months' treatment (2+ on 11 September 2015)	Already in open-label phase	Left

Appendix 4 Trial management team

All trial management was conducted by the CTRC, University of Liverpool, Liverpool, UK.

Senior statisticians

Professor Paula Williamson.

Dr Ashley P Jones.

Head of trial management

Ms Helen Hickey.

Senior data manager

Mrs Clare Jackson.

Information systems manager

Dr Duncan Appelbe.

Trial co-ordinator

Mr Ben Hardwick.

Statisticians, database developers and administration

Mrs Anna Rosala-Hallas.

Miss Naomi Rainford.

Dr Graeme Hickey.

Dr Ruwanthi Kolamunnage-Dona.

Miss Elizabeth Conroy.

Dr Kerry Dawn.

Mrs Michaela Brown.

Mr Meirion Thomas.

Mrs Janet Harrison.

Miss Catherine Forrest.

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