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Research Article

Methotrexate versus Ciclosporin in the Treatment of Severe Atopic Eczema in Children: An economic evaluation

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Abstract

Background: Eczema (also known as atopic dermatitis) affects 20% of United Kingdom children, with 16% experiencing moderate-to-severe eczema. Eczema impacts patients' quality of life, mainly through intense itching and sleep disturbance. Most caregivers are able to control their children's eczema with topical treatments, including emollients, topical corticosteroids or calcineurin inhibitors. For those who do not respond to these topical treatments, or who require consistent use of high potency topical corticosteroids to maintain control, systemic therapies should be considered. Ciclosporin is the most commonly used systemic treatment for paediatric patients, but methotrexate is a widely used promising alternative. Currently, there is not enough evidence to inform guidance about which treatment (methotrexate or ciclosporin) should be used to treat severe atopic eczema in children and young people.
Aim: In this study, we sought to compare the cost-effectiveness of two oral drug treatments (methotrexate or ciclosporin) for children and young people who have severe eczema.
Methods: We collected information on resource use and health-related quality of life using data from the TREAT trial. One hundred and three children and young people aged 2–16 years were randomly allocated to receive either oral methotrexate or ciclosporin for a 36-week treatment period with 24 weeks of further follow-up. An economic evaluation was undertaken, as it is currently uncertain which drug represents the best value for money for the United Kingdom National Health Service. The base case consists of a cost–utility analysis undertaken from a partial National Health Service perspective (limited to medication plus adverse event resource use for which complete data were available from clinical report forms) over 60 weeks; and multiple imputation was used to account for the missing utility data, and the analysis adjusted for baseline cost/utility/Objective Scoring Atopic Dermatitis (as appropriate), gender, age and recruiting centre.
Results: In the base-case analysis, usage of methotrexate resulted not only in cost savings compared to ciclosporin of −£489.67 (95% confidence interval −£685.78 to −£293.36) per participant but also in a small decrease in quality-adjusted life-years of −0.0057 (95% confidence interval −0.0384 to 0.0270) per participant; the resulting net monetary benefit at a willingness to pay per quality-adjusted life-year threshold of £20,000 (£30,000) was £375.49 (£38.45).

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The probability of methotrexate being cost-effective was 85.5% (73.1%) for a £20,000 (£30,000) threshold. The results were similar in unadjusted analyses and those analyses taking a wider perspective. However, in the secondary cost-effectiveness analysis, methotrexate was found to dominate ciclosporin as it was both cost saving and resulted in a greater improvement in severity scores.

Limitations: Both wider National Health Service resource use (collected by patient diary) and utility data had missing data, which was taken account of using multiple imputation assuming data was missing at random. Being a within-trial economic evaluation, the long-term cost-effectiveness beyond 60 weeks cannot be inferred from this data set or analysis.

Conclusion and future work: This study extends the findings of the TREAT trial by demonstrating that methotrexate and ciclosporin are similar in terms of costs (for visits/monitoring, adverse events and concomitant medications) and quality-adjusted life-years but that methotrexate drug costs are significantly cheaper than ciclosporin drug costs. This supports the conclusion reached in the randomised controlled trial paper that, where first-line novel systemic biologics and small molecules prescribing is generally restricted by health-funding bodies, as is the case in most jurisdictions, methotrexate provides an effective and low-cost, first-line systemic agent and is thus an alternative to ciclosporin. Given its overall cost-effectiveness, methotrexate now needs to be directly compared with novel systemic therapies.

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Background

Atopic eczema, also known as atopic dermatitis and hereon referred to as eczema, is an inflammatory skin condition leading to inflamed, itchy skin. Around 20% of UK children experience eczema, of whom 16% experience moderate or severe forms.[1] Eczema has a similar impact on health-related quality of life as other common conditions in children.[2] A review of economic evidence for eczema found a paucity of such evidence, although 12 cost-of-illness studies showed that, for children with eczema, costs increased with disease severity.[3] Treatment options for severe childhood eczema are limited, and there are concerns about short- and long-term side effects.[4]

Aims and objectives

This study aimed to increase the value of a trial funded by the National Institute for Health Research Efficacy and Mechanism Evaluation programme comparing two drugs for severe eczema (the TREAT trial, https://treat-trial.org.uk/) by conducting an add-on economic evaluation to estimate the cost-effectiveness of methotrexate (MTX) compared to ciclosporin (CyA) in child and young persons (CYPs) with severe atopic eczema from an NHS perspective.

The four economic objectives were to:

1. estimate resource use and costs for severe eczema in children in the MTX group compared to the CyA group
2. estimate quality-adjusted life-years (QALYs) in the MTX group compared to the CyA group
3. undertake a cost–utility analysis (CUA) and cost-effectiveness analysis (CEA) to assess which treatment represents the best value for money for NHS provision
4. estimate uncertainty levels associated with the decision about treatment provision.

Methods

This study utilises data collected alongside the TREAT trial. TREAT was a parallel group, assessor-blind randomised controlled trial (RCT) conducted in 13 UK and Irish Centres. CYP with moderate-to-severe eczema aged between 2 and 16 years, who did not have an adequate response to potent topical corticosteroid, were randomised to receive either oral CyA (4 mg/kg/day) or oral MTX (0.4 mg/kg/ week) for 36 weeks and were followed up for 24 weeks post treatment cessation. The trial had coprimary outcomes estimating change from baseline to 12 weeks in Objective Scoring of Atopic Dermatitis (o-SCORAD) and the time to first significant flare after treatment cessation. Further details of the trial design can be found in the published protocol.[5]

Overview of economic analysis

The within-trial economic analysis was undertaken using individual patient-level data using the intention-to-treat (ITT) principle. A health economic analysis plan (HEAP) was written, in keeping with published guidelines for the

economic evaluation of healthcare interventions,[6–10] and was signed before analysis began, see *Report Supplementary Material 1*. The primary analytical approach taken was CUA, with secondary analysis taking a CEA approach.

The economic evaluation takes a UK NHS and Personal Social Services (PSS) perspective to reflect the funder and location of the work. The study did include one Irish centre which recruited five (< 5%) participants; however, the process of care for the drugs being considered is not dissimilar between the UK and Ireland and therefore participants' data from the Irish centre were included in the analysis. Data on time off work for parents/carers are presented separately to reflect the broader perspective of these costs.

Identification and measurement of resources

In accordance with National Institute for Health and Care Excellence (NICE) guidance,[9] the data collection tools were designed to capture resource use from the NHS perspective. Clinicians did not feel that this group of patients were likely to incur any PSS because of their eczema. Resource use data were compiled from two sources. Intervention costs, including visits (paediatric dermatologist and hospital admissions related to side effects), safety monitoring (blood tests) and medication [both intervention drugs and concomitant medications (i.e. any drug or substance administered between the screening visit and the visit at week 60)], were sourced from clinical report form (CRF) data. These resources reflect those likely to take place in practice and exclude any visits or procedures undertaken solely for the purposes of the trial. Wider NHS resource use [general practitioner (GP) and practice nurse visits in primary care and secondary care hospital contacts with doctors, nurses or accident and emergency (A&E)] related to the child's eczema was collected via diaries (hereon referred to as diary data) that were completed by the main parent/carer. Some resource use incurred as a result of adverse events (AEs) were collected via CRFs as part of safety monitoring, but because these data might overlap with the diary data, they were not analysed together. Costs of any pregnancy tests undertaken during monitoring were not included because they were not routine in this aged population and represent a very small cost. Parents were asked to record time off work because of their child's eczema (i.e. either to attend appointments or look after them when off school) and their children's time off school due to their eczema as part of the diary data. Study diaries were designed for completion at 4, 8, 12, 20, 28, 36, 48 and 60 weeks (for copies of the pre-36-week and post-36-week diaries for each treatment group, please contact the corresponding author). These diaries were designed to be self-completed and returned to the trial research nurses at clinic visits and were entered into the database by the central research team at the Liverpool Clinical Trials Centre, University of Liverpool. Following an amendment to the protocol, consent was also sought to contact participants' GP practices in order to collect resource use data. *Report Supplementary Material 2* provides a copy of the health resource use GP questionnaire that was designed and sent to practices.

Given the low response and completion rates of diary data and GP questionnaire on wider (non-trial) health resource use data, the resource use data collected as part of the CRF on AEs and serious AEs were used to cost additional healthcare visits. These data were only collected for the duration for which a participant was taking trial treatment and then for the subsequent 4 weeks post treatment cessation, and then the data are analysed together with intervention resource use and concomitant medication to provide what has been termed a partial NHS perspective in the base-case analysis.

Valuation of resources

All unit costs are valued in Great British pounds for 2022. The cost of the intervention medications were valued using published unit costs in the prescription cost analysis.[11] Other resource use was valued using published sources, including prescription cost analysis,[11] unit costs of health and social care[12] and NHS reference costs.[13] A table of unit costs, together with their sources and assumptions, is presented in *Appendix 1*. Assessment appointments were costed using the paediatric dermatology service – consultant-led, non-admitted, face-to-face attendance follow-up rate after the first visit, which was costed using the first visit unit cost. Where more than one product existed for a particular medicine, the unit cost for that most frequently prescribed was used. There were missing data with respect to the formulation of the intervention medication issued to each participant and so, to cost these data, it was assumed that all CYP were issued tablets, as for the data available, this seemed to be the most reasonable assumption.

Parental time off work to look after their child due to appointments or illness as a result of eczema was sought in the participants' diaries and was costed using the human capital approach using published average wages.[14] Time off school due to eczema was captured for the child participants and this is reported in units of time as there is no agreed approach to costing children's time.[15,16]

The cost of all reported resource use (relevant to an NHS perspective) was calculated for each participant. A total cost for each participant was estimated along with a

mean [standard deviation (SD)] cost per participant by treatment group.

Outcome measurement

Health-related quality of life

Measurement of health status in children for use in economic evaluations is challenging, and currently, there is no agreed approach.[16–21] In this study, QALYs were estimated using utility scores obtained using the Child Health Utility Nine Dimension (CHU-9D) instrument.[22,23] The CHU-9D is a generic, preference-based measure of health-related quality of life that asks how a child is today based on nine questions (worries, sad, pain, tired, annoyed, schoolwork/homework, sleep, daily routine and activities), where each has five response levels (ranging from no difficulty through to a lot or cannot do).[22,23] Additional guidance, providing extra wording to help parents of younger children understand how to answer questions for a child of pre-school age, given to us by the developer of the CHU-9D, was used. Utility ranges from 0.33 (worst health) through to 1 (best health).[24] The CHU-9D was completed by parental/carer proxy for all participants aged < 7 years and was self-completed by children aged ≥ 7. Utility measurements were collected via paper-based questionnaires at baseline, 12, 24, 36, 48 and 60 weeks post study initiation. In the base-case CUA, the responses received on the CHU-9D were converted to utility scores using the valuation set published by Stevens.[24] Following this, the utility values were used to calculate the number of QALYs generated over the trial period of 60 weeks, using both linear interpolation and area under the curve analysis with and without baseline adjustment.[25]

Objective Scoring Atopic Dermatitis

The Objective Scoring Atopic Dermatitis (o-SCORAD) measure was one of the coprimary outcomes in the TREAT trial, where the study sought to detect a difference of eight points. o-SCORAD is one of only three validated severity outcome measures for eczema. It measures the extent and intensity of eczema, and the score can range from 0 to 83 (where scores of 0–14 are considered to be mild, 15–39 are moderate and 40–83 are severe).[26] The o-SCORAD score at 60 weeks was subtracted from the baseline score to estimate the change in o-SCORAD score for use in the CEA.

Flares

The number of participant-reported flares experienced across the 60 weeks was collected in diaries. A CEA was planned using number of flares.

Economic analysis

The economic base-case analysis was undertaken using the ITT principle so that all 103 children were included in the analysis. The analysis is a within-trial analysis of 60-week time horizon. The benefits were discounted between weeks 53 and 60 using a discount rate of 3.5%.[9] It was not possible to discount the costs in week 53–60 because the start and/or end date for concomitant medications was often missing, meaning it was unclear for which weeks the medication was related to. The cost-effectiveness threshold (λ) of £20,000 (£30,000) per QALY was used.[9]

Analysis of resource use and costs

Mean (SD) resource use and cost per participant were estimated for each treatment group. Mean difference [95% confidence interval (CI)] in resource use and cost per participant between groups (MTX vs. CyA) are estimated. This analysis fulfils objective 1.

Analysis of outcomes

The primary economic outcome was the CHU-9D.[22–24] Mean (SD) utility at each time point and mean (SD) QALYs per participant per treatment group are presented along with the mean difference (95% CI) in utility and QALYs between groups (MTX vs. CyA).

Secondary outcomes, including change in eczema severity measured using the o-SCORAD and number of flares, were elicited and used in CEAs. Mean (SD) change in o-SCORAD score between baseline and 60 weeks per participant per treatment group was estimated along with the mean difference (95% CI) in the change in o-SCORAD score between groups (MTX vs. CyA). We also planned to estimate the mean (SD) number of flares between baseline and 60 weeks per participant per randomised group along with the mean difference (95% CI) in the number of flares between groups (MTX vs. CyA). This analysis fulfils objective 2.

Dealing with missing data

Missing economic data is common in RCTs and can result in bias and lack of precision.[27] In line with recommendations for within-trial analysis of cost-effectiveness the amount of missing data, missing data patterns and association between missing data and baseline/observed variables were explored to infer the assumed missing data mechanism. A complete case analysis did not represent the base-case analysis.[27] The base-case analysis was undertaken using multiple imputation by means of the 'mi impute' command in Stata® SE 17 (StataCorp LP, College Station, TX, USA) to generate multiple data sets (the number reflecting the percentage of missing data[28]) to be pooled using Rubin

rules.[29] In addition, to the costs (week 4, 8, 12, 20, 28, 36, 48 and 60 diary data costs) and outcomes (baseline and 12, 36, 48 and 60 weeks utility), the multiple imputation model included baseline variables and variables associated with missing data, costs or outcomes (including site, age, sex and ethnic group). Individual domain sores of the CHU-9D were not included, because where CHU-9D data were missing, it was generally missing across the whole nine domains. Diary data costs were imputed for each time point rather than at an individual resource use level within each time point, given the level of missing data, number of time points and resource items involved.

Economic evaluation analysis

Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA) was used for exploratory analysis and Stata SE 17 was used for the main analysis. Incremental cost and outcome data (QALYs in the base-case CUA) were combined for the trial to estimate both incremental cost-effectiveness ratios (ICERs) and net monetary benefit (NMB) from the NHS perspective comparing MTX to CyA. In secondary CEA, incremental cost and outcome data (change in o-SCORAD score/number of flares) were combined just as ICERs (since the willingness-to-pay threshold for a unit change on the o-SCORAD is unknown but needed to estimate a NMB). The ICER is estimated by dividing incremental costs by incremental benefits and is compared to a willingness-to-pay threshold to decide if MTX is cost-effective compared to CyA. The NMB is estimated as the willingness-to-pay threshold multiplied by incremental benefit minus incremental costs; a positive NMB denotes that the costs of a QALY achieved by MTX compared to CyA are less than the cost society would be willing to pay for the QALY and thus the intervention is deemed to be cost-effective. The interpretation of ICERs depends on which quadrant of the cost-effectiveness plane they fall (see *Appendix 1*, *Figure 1* for further explanation) such that it can be easier to interpret NMBs, which have the same interpretation regardless of location on the cost-effectiveness plane. For instance, an intervention which has negative incremental costs (cost savings) and negative incremental QALYs (forgone QALYs) would have a positive ICER, but because it lies in the southwest quadrant of the cost-effectiveness plane, it would be interpreted differently as ICERs need to be higher than the threshold value, rather than lower, for the new intervention to be considered as cost-effective compared to the standard intervention.[30]

The original aim was to conduct a full NHS perspective as the base-case analysis capturing intervention costs (medications, visits and safety monitoring), concomitant medications and wider NHS resource use related to the child's eczema (primary and secondary care), which was assumed would include resource use associated with AEs as the respondents were not asked to exclude these. In the event of significant amounts of missing data, a narrower partial perspective was planned to take the place as the base-case analysis, covering intervention costs (medications, visits and safety monitoring), concomitant medications and AE data as captured in the trial CRFs but not including wider NHS resource use due to eczema. This partial perspective does not capture any wider NHS resource use due to the eczema in the period when AE data stopped being collected (4 weeks after the treatment was stopped) to the end of follow-up (60 weeks).

A bivariate regression-based approach using seemingly unrelated regression equations[31] was used in all analyses.

The adjusted analyses represent the main base-case analysis, adjusting for baseline cost/utility/o-SCORAD (as appropriate), gender, age and recruiting centre. Unadjusted analyses are also presented for comparison. This analysis fulfils objective 3.

The level of uncertainty associated with the decision regarding cost-effectiveness was estimated using non-parametric bootstrapping to calculate the probability of the treatment being cost-effective at the £20,000 and £30,000 willingness-to-pay threshold values.[9] This analysis fulfils objective 4.

Subgroup analysis and sensitivity analyses

No subgroup analyses were planned, given the sample size. Sensitivity analysis was planned to explore the impact of including parental productivity costs in the analysis. The HEAP specified that, if appropriate, the impact of missing data would be explored by comparing base-case results using multiple imputation to a complete case analysis. It also stated that if the intervention was found to be effective but not cost-effective, a threshold analysis would be used to explore at what drug cost the result would switch to being cost-effective.

Patient and public involvement or community engagement and involvement

This study addresses one of the treatment uncertainties identified by a James Lind Alliance group of patients, carers and health professionals: 'What is the best and safest way of using drugs that suppress the immune system when treating eczema?',[32] complementing the recently published findings of the TREAT trial ITT analysis.[33] A public contributor (AA) with lived experience of looking after a child with eczema was a member of the trial management group and was involved in all aspects of the trial, including design and review of patient-facing materials such as questionnaires and diaries. AA is a coauthor on this report.

Equality, diversity and inclusion

We recruited from 13 sites nationally and in Ireland, in a broad range of settings across the UK, not only including highly specialised centres but also district general hospitals, with some hospitals having a catchment area with a very diverse set of ethnicities and social backgrounds.

Study/trial registration details

The TREAT trial was registered on 9 March 2016 with Trial registration number: ISRCTN15837754. The EudracCT number was 2015-002013-29.

Results

The TREAT trial recruited 103 children out of 333 children screened between 26 May 2016 and 5 February 2019, with 51 randomised to receive MTX and 52 randomised to CyA. All 103 children were included in the ITT economic analysis. *Table 1* shows the baseline demographics of the sample. The MTX and CyA groups were reasonably balanced in terms of sex, age (ranging between 2 and 16 years), ethnicity, o-SCORAD and recruiting centre (see *Table 1*). The clinical study demonstrated that both CyA and MTX

TABLE 1 Demographic and baseline characteristics

	MTX *N* = 51	CyA *N* = 52
Age in years, mean (SD)	9.82 (4.01)	10.34 (4.21)
Sex, n (%)		
Female	28 (55%)	21 (40%)
Male	23 (45%)	31 (60%)
Ethnicity, n (%)		
White	30 (59%)	31 (60%)
Black	4 (8%)	7 (13%)
Asian	12 (24%)	11 (21%)
Other	5 (10%)	3 (6%)
Recruiting centre, n (%)		
Site 1	21 (41%)	22 (42%)
Site 2	6 (12%)	5 (10%)
Site 3	5 (10%)	4 (8%)
Site 4	4 (8%)	5 (10%)
Site 5	4 (8%)	4 (8)
Site 6	2 (4%)	3 (6%)
Site 7	2 (4%)	3 (6%)
Site 8	1 (2%)	2 (4%)
Site 9	1 (2%)	1 (2%)
Site 10	2 (4%)	0 (0%)
Site 11	1 (2%)	1 (2%)
Site 12	1 (2%)	1 (2%)
Site 13	1 (2%)	1 (2%)
o-SCORAD [mean (SD)]	45.25 (9.60)	48.34 (11.35)

Note
All variables have complete data.

were effective and largely well-tolerated treatments for CYP with severe atopic eczema. It found that CyA acted more quickly, while MTX induced better disease control after treatment discontinuation.[33]

Resource use and costs

Appendix 1, *Table 6* shows the proportion of participants with complete cost data collected via CRF and diary. There were complete resource use data, where the data were collected via CRFs, but there were high levels of missing data for resource use data which were collected via participant diaries. Only nine (< 20%) per treatment group had complete resource use data collected via the diaries across the whole 60-week period, and this was achieved only after imputing the return date for some diaries and making assumptions necessary to clean the data ready for use. It was not always clear when the diaries were returned such that the date of completion had to be imputed. Using this date, the number of days post randomisation was calculated so that the questionnaire could be assigned to a data point (4, 8, 12, 30, 28, 36, 48 or 60 weeks) based on which it was closest to. Some participants had multiple diaries that could have related to the same data point. Where this occurred, the one that was most completed was used and the others were discarded to avoid the potential for double counting. Where a diary entry had positive resource use recorded, any other items left blank were assumed to be of zero use. Diary completion fluctuated between 49% and 73% at different time points but was broadly similar between treatment groups over time. The pattern of missingness for the diary data can be seen in *Appendix 1*, *Figures 2* and *3* for MTX and CyA, respectively. The missing data do not follow a monotonic pattern, as *Appendix 1*, *Figures 2* and *3* show some participants did not complete the diary at one time point but completed at subsequent points. Logistic regressions to explore the association between baseline variables and the likelihood of data being missing for the total cost and the individual resource items (data not presented) collected in the diary were undertaken. The former is reported in *Appendix 1*, *Table 10* and shows that only sex was associated with the missing cost data.

The issue of low diary completion was picked up during routine monitoring while the trial was ongoing and mitigation factors were taken (e.g. encouraging sites to provide reminders to participants). In addition, consent was sought to contact participants' GP practices in order to collect resource use data. However, the timing of the COVID-19 pandemic and resultant disruption to health services meant that this means of data collection did not prove to be successful despite offering a £50 reimbursement for the GP's time to return the requested data [10 (9.7%) GP questionnaires were returned (7 in the MTX group and 3 for the CyA)], but all these participants had complete or partially complete diary data. Given this and the low response rate, these data are not analysed in this report.

The unit costs used to value resources are detailed in *Appendix 1*, *Table 7* along with any assumptions made. All costs are reported in Great British pounds for the year 2022. *Table 2* shows the resource use data by treatment group, and *Table 3* shows the mean cost per participant by treatment group as well as the mean difference (95% CI) in cost. The diary data in these tables only include those participants with complete data at all time points. *Appendix 1*, *Table 8* presents the mean costs by treatment group and mean difference (95% CI) in costs for all available data broken down by data point. The available data show that there were similar levels of missing data in both arms and that resource use and costs were similar between treatment groups except for the intervention drug costs.

Outcomes

The proportion of participants with complete utility data is shown in *Table 4* and that by age is shown in *Appendix 1*, *Table 9*. It shows that 26 (51%) MTX and 29 (56%) CyA participants had utility data at all time points. An additional 14 participants had utility at baseline and 60 weeks. Rather than use this to estimate QALYs using linear interpolation, these were treated in the same way as participants who had missing data at any time point (see *Dealing with missing data*). The pattern of missingness for the utility data can be seen in *Appendix 1*, *Figures 4* and *5* for MTX and CyA, respectively. The missing data do not follow a monotonic pattern, as *Appendix 1*, *Figures 4* and *5* show, some participants did not complete the CHU-9D at one time point but completed at subsequent points. All participants had some utility data reported except one MTX participant who had no utility data at any of the time points.

At baseline, 21 (20.6%) participants had missing utility data. This in part reflects that the economic study was funded separately to TREAT. As a consequence, by the time approvals were in place, the opportunity to elicit baseline utility had passed for some participants. The amount of missingness at different time points was fairly constant around 80% and this was similar between treatment groups. *Appendix 1*, *Table 10* shows the odds ratios from a logistic regression of indicators of missing QALY data for the treatment group and various baseline variables. This shows that the missing QALY data were associated with participants who recorded their ethnic group as Black across all sites and for participants from two specific sites. While it is not possible to be definitive,

TABLE 2 Mean (SD) resource use and mean (95% CI) difference in resource use at 60 weeks (available case data)

Resource item	MTX (*n* = 51) Mean (SD)	*n*	CyA (*n* = 52) Mean (SD)	*n*	Mean difference (95% CI)
Intervention (case report form data)					
MTX (doses)	33.95 (7.71)	51	0.00 (0.00)	52	33.95 (31.83 to 36.07)
Folic acid (doses)	203.71 (46.29)	51	0.00 (0.00)	52	203.71 (190.98 to 216.45)
CyA (doses)	0.00 (0.00)	51	412.54 (107.96)	52	−412.54 (−442.53 to −382.55)
Paediatric dermatologist (number of visits)	9.24 (2.30)	51	8.23 (1.71)	52	1.00 (0.21 to 1.80)
Blood tests[a] (number)	10.12 (2.37)	51	9.29 (2.30)	52	0.83 (−0.08 to 1.74)
Total AEs	8.12 (9.68)	51	7.19 (6.45)	52	0.93 (−2.28 to 4.13)
GP visit for AE	0.41 (0.73)	51	0.52 (0.92)	52	−0.11 (−0.43 to 0.22)
Admission for AE	0.14 (0.40)	51	0.06 (0.24)	52	0.08 (−0.05 to 0.21)
A&E visit for AE	0.14 (0.45)	51	0.06 (0.24)	52	0.08 (−0.06 to 0.22)
All medications (number of)	13.35 (6.30)	51	14.98 (8.28)	52	−1.63 (−4.51 to 1.25)
NHS primary care (diary data)					
GP (number of visits)	0.89 (1.36)	9	0.44 (0.53)	9	0.44 (−0.59 to 1.48)
Practice nurse (number of visits)	0.11 (0.33)	9	0.00 (0.00)	9	0.11 (−0.12 to 0.35)
NHS secondary care (diary data)					
Hospital doctor (number of visits)	1.33 (1.80)	9	0.11 (0.33)	9	1.22 (−0.07 to 2.52)
Hospital nurse (number of visits)	0.56 (1.33)	9	0.00 (0.00)	9	0.56 (−0.39 to 1.50)
A&E visit (number of visits)	0.00 (0.00)	9	0.11 (0.33)	9	−0.11 (−0.35 to 0.12)
Time off work (number of hours)	1.89 (3.76)	9	0.00 (0.00)	9	1.89 (−0.77 to 4.54)
Time off school (number of hours)	5.67 (6.40)	9	3.78 (7.05)	9	1.89 (−4.84 to 8.62)

a Includes any taken for AEs.

TABLE 3 Mean (SD) cost and mean (95% CI) difference in cost at 60 weeks (£2022) (available case data)

Cost item	MTX (*n* = 51) Mean (SD)	*n*	CyA (*n* = 52) Mean (SD)	*n*	Mean difference (95% CI)
Total intervention	**1761.24 (421.31)**	**51**	**2314.07 (469.99)**	**52**	**−552.83 (−727.41 to −378.25)**
MTX + folic acid	27.09 (8.69)	51	0.00 (0.00)	52	27.09 (24.70 to 29.48)
MTX alone	14.86 (7.16)	51	0.00 (0.00)	52	14.86 (12.89 to 16.83)
Folic acid alone	12.22 (2.78)	51	0.00 (0.00)	52	12.22 (11.46 to 12.99)
CyA	0.00 (0.00)	51	765.12 (316.14)	52	−765.12 (−852.94 to −677.30)
Paediatric dermatologist	1686.60 (415.66)	51	1505.29 (308.74)	52	181.31 (38.38 to 324.26)
Blood tests[a]	47.55 (11.15)	51	43.66 (10.83)	52	3.90 (−0.40 to 8.19)
Total AEs	**123.98 (292.32)**	**51**	**66.30 (142.50)**	**52**	**57.67 (−31.95 to 147.30)**
GP visit for AE	16.88 (29.77)	51	21.29 (37.64)	52	−4.41 (−17.69 to 8.87)
Admission for AE	73.88 (215.83)	51	31.05 (126.73)	52	42.83 (−26.20 to 111.85)

TABLE 3 Mean (SD) cost and mean (95% CI) difference in cost at 60 weeks (£2022) (available case data) (*continued*)

	MTX (*n* = 51)		CyA (*n* = 52)		
Cost item	**Mean (SD)**	***n***	**Mean (SD)**	***n***	**Mean difference (95% CI)**
A&E visit for AE	33.22 (108.44)	51	13.96 (56.98)	52	19.25 (−14.51 to 53.02)
All medications	**159.70 (152.72)**	**51**	**153.79 (108.49)**	**52**	**5.91 (−45.79 to 57.61)**
NHS primary care (diary data)					
GP	36.44 (55.93)	9	18.22 (21.61)	9	18.22 (−24.15 to 60.59)
Practice nurse	1.93 (5.78)	9	0.00 (0.00)	9	1.93 (−2.16 to 6.01)
NHS secondary care (diary data)					
Hospital doctor	240.65 (325.38)	9	20.05 (60.16)	9	220.60 (−13.23 to 454.43)
Hospital nurse	19.17 (46.00)	9	0.00 (0.00)	9	19.17 (−13.34 to 51.67)
A&E visit	0.00 (0.00)	9	26.89 (80.68)	9	−26.89 (−83.90 to 30.12)
Total NHS cost (excluding diary data)	**2044.92 (580.59)**	**51**	**2534.16 (500.85)**	**52**	**−489.25 (−701.06 to −277.43)**
Cost of time off work (diary data)	35.34 (70.29)	9	0.00 (0.00)	9	35.34 (−14.32 to 85.01)

a Includes any taken for AEs.

TABLE 4 Mean (SD) outcomes and mean (95% CI) difference in outcomes over 60 weeks (available case data)

	MTX (*n* = 51)		CyA (*n* = 52)		
	Mean (SD)	***n***	**Mean (SD)**	***n***	**Mean difference (95% CI)**
Child participants (all ages n = 103)					
CHU-9D baseline	0.7264 (0.1505)	41	0.7242 (0.1434)	41	0.0022 (−0.0624 to 0.0668)
CHU-9D at 12 weeks	0.8374 (0.1341)	41	0.8738 (0.1183)	44	−0.0364 (−0.0909 to 0.0181)
CHU-9D at 36 weeks	0.8642 (0.1084)	42	0.8567 (0.1120)	46	0.0075 (−0.0393 to 0.0543)
CHU-9D at 48 weeks	0.8300 (0.1412)	42	0.8292 (0.1410)	41	0.0004 (−0.0616 to 0.0624)
CHU-9D at 60 weeks	0.8754 (0.1040)	41	0.8274 (0.1479)	45	0.0480 (−0.0073 to 0.1033)
QALYs[a] (undiscounted, all ages)	0.9848 (0.0951)	26	0.9691 (0.1008)	29	0.0157 (−0.0375 to 0.0689)
QALYs[a] (discounted, all ages)	0.9803 (0.0947)	26	0.9648 (0.1004)	29	0.0155 (−0.0374 to 0.0685)
QALYs with missing[b] (discounted, all ages)	0.9166 (0.1768)	32	0.9560 (0.1142)	37	−0.0393 (−0.1100 to 0.0313)
Child participants (all ages n = 103) (lower o-SCORAD score indicates milder severity)					
o-SCORAD at baseline	45.25 (9.60)	51	48.34 (11.35)	52	−3.09 (−7.20 to 1.02)
o-SCORAD at 60 weeks	21.55 (10.89)	44	28.00 (12.76)	46	−6.45 (−11.43 to −1.47)
Change in o-SCORAD	23.04 (14.39)	44	20.86 (15.96)	46	2.18 (−4.19 to 8.56)[c]
Child participants (all ages n = 103)					
Number of flares over 60 weeks[d]	12.71 (9.03)	7	34.5 (17.68)	2	−21.79 (−42.08 to −1.49)

a QALYs estimated for only those with utility data at all five time points.
b QALYs estimated for those with at least utility data at baseline and 60 weeks.
c The reduction in o-SCORAD is greater for MTX, which means the severity of symptoms reduced more for MTX participants.
d Number of flares over 60 weeks estimated for those with complete data only.

based on the above, we believe that missing at random is likely to be the mechanism of missingness and that multiple imputation is appropriate.

Table 4 shows the mean (SD) outcomes and mean difference (95% CI) in outcomes over 60 weeks. CHU-9D results are presented for the whole sample and in *Appendix 1*, *Table 9*, these are broken down by age, for those < 7 years for whom the CHU-9D was proxy completed by the main parent/carer and for those ≥ 7 years who self-completed the questionnaire. It can be seen that there was a small improvement in mean (SD) utility for both treatment groups across the 60 weeks, although not in a linear way, but QALYs were marginally higher for those with complete data in the MTX group, 0.9803 (0.0947) compared to 0.9648 (0.1004) for CyA, with a mean difference (95% CI) of 0.0155 (−0.0374 to 0.0685) over the 60-month period.

The o-SCORAD was available for 86.3% in the MTX group and for 88.5% in the CyA group at both baseline and 60 weeks. o-SCORAD improvement was slightly better in the MTX group than in the CyA group, with mean difference of 2.18 (95% CI −4.19 to 8.56), though this was not significant (see *Table 4*).

The quantity of missing data for patient-reported flares was large; just 13.7% in the MTX group and 3.8% in the CyA group had complete data. This can be seen in *Table 4*, where the CyA group had a greater number of flares than the MTX group, mean difference of −21.79 (95% CI −42.08 to −1.49). Given the level of missing data, there are significant limitations as to the conclusions that can be inferred from this result.

Incremental analysis

The results of all incremental analyses for both the CUA, CEA and sensitivity analyses can be found in *Table 5*.

TABLE 5 Cost–utility analyses and CEAs' results, including sensitivity analyses

CUA (Nm, Nc)	Incremental cost (95% CI)	Incremental QALYs (95% CI)	ICER (cost-effectiveness if threshold of £30,000 per QALY)	NMB £20,000 (£30,000) threshold	Probability MTX cost-effective at £20,000 (£30,000) threshold
Partial NHS perspective, multiple imputation, adjusted[a] (51, 52)	−489.67 (−685.78 to −293.36)	−0.0057 (−0.0384 to 0.0270)	85,828[b] (MTX cost-effective)	375.49 (318.45)	85.5% (73.1%)
Partial NHS perspective, multiple imputation, unadjusted (51, 52)	− 489.25 (−696.48 to −282.01)	−0.0019 (−0.0435 to 0.0396)	254,722[b] (MTX cost-effective)	450.83 (431.62)	84.2% (74.4%)
Full NHS perspective, multiple imputation, adjusted[a] (51, 52)	−522.13 (−717.01 to −327.25)	−0.0034 (−0.0361 to 0.0292)	152,301[b] (MTX cost-effective)	453.57 (419.29)	90.2% (79.4%)
Full NHS perspective, multiple imputation, unadjusted (51, 52)	− 530.32 (−734.94 to −325.70)	−0.0020 (−0.0427 to 0.0386)	261,463[b] (MTX cost-effective)	489.76 (469.47)	87.0% (76.9%)
CEA analysis (*N* s, *N* p)	**Incremental cost (95% CI)**	**Incremental o-SCORAD change (95% CI)**	**Incremental cost per unit change**		
Secondary analysis, multiple imputation, adjusted[a] (51, 52)	−492.20 (−688.40 to −296.00)	5.67[c] (1.52 to 9.82)	MTX dominant	NMB and probability of cost-effectiveness are not estimated for the CEA because the decision-makers' willingness to pay per unit change on the o-SCORAD is unknown	
Secondary analysis, multiple imputation, unadjusted (51, 52)	−489.25 (−696.48 to −282.01)	3.09[c] (−2.76 to 8.94)	MTX dominant		

Nc, number of participants allocated to CyA; Nm, number of participants allocated to MTX.

a In adjusted analyses, costs were adjusted for treatment group, sex, age, site, ethnic group and baseline o-SCORAD and outcomes were adjusted for treatment group, sex, age, site, ethnic group and baseline utility (CUA) or baseline o-SCORAD (CEA).

b The ICERs from the CUAs are in the southwest quadrant of the cost-effectiveness plane, where an ICER larger than £20,000 (£30,000) means that MTX is cost-effective compared to CyA.[30]

c The reduction in o-SCORAD is greater for MTX, which means that the severity of symptoms reduced more for MTX participants.

Note

The partial NHS perspective captured intervention drug use, concomitant medication, safety monitoring and AEs resource use collected via CRFs in the trial, since these data were complete, multiple imputation was used for utility only. The full NHS perspective captured intervention costs (medications, visits and safety monitoring), concomitant medications and wider NHS resource use related to the child's eczema and any AE to treatment. The wider NHS resource use data were collected via diaries; given the low data completion rates, multiple imputation was used for both costs and outcomes in these analyses.

Cost–utility analysis for partial National Health Service perspective (base-case, imputed analysis)

Given the poor quality and quantity of diary data on wider resource use, a partial NHS perspective was undertaken as the base-case analysis, imputing missing utility data at each time point. The adjusted analyses estimated an incremental cost per participant of −£489.67 (95% CI −£685.78 to −£293.36) (MTX cost saving and statistically significant) and incremental QALYs of −0.0057 (95% CI −0.0384 to 0.0270) per participant (a loss equivalent of just over 2 days of perfect health, where 1 day of perfect health equals 0.0027; this was not statistically significant). The ICER was £85,828 per QALY, given this is in the southwest quadrant of the cost-effectiveness plane; this means that MTX would be considered as cost-effective at £20,000 and £30,000 thresholds as the ICER is higher than these. The NMB at a threshold of £20,000 (£30,000) per QALY was £375.49 (£318.45); given this is positive, it can be interpreted to mean that MTX is cost-effective, that is for the level of cost savings, the loss of QALYs estimated would be considered to be acceptable. It should, however, be noted that there is debate about whether the threshold value is the same in the southwest quadrant as the northeast quadrant since theory and evidence suggest that the threshold will be higher where willingness to accept is concerned.[34] Given the very small and non-significant incremental QALYs which are close to zero, and the probability of cost-effectiveness at £20,000 (£30,000) per QALY was estimated as 85.5% (73.1%), respectively, there is high confidence that MTX is cost-effective compared to CyA. *Table 5* also shows the unadjusted analysis for this perspective, which differs mainly in that the loss of incremental QALYs is smaller and even closer to zero, resulting in a much higher ICER and NMB, again showing that MTX is likely to be cost-effective.

Cost–utility analysis for full National Health Service perspective (imputed analysis)

Given the poor quality and quantity of diary data capturing wider NHS resource use related to eczema over the 60 weeks, this analysis is presented, but this is not the base case as planned. Given the sample size to start with costs could only be imputed at the level of time point (total costs at 4, 8, 12, 20, 28, 36, 48 and 60 weeks) rather than at the individual resource use level (GP, practice nurse, hospital doctor, hospital nurse and A&E at each of the time points) which would have been desirable. However, as *Table 5* shows, the conclusions reached from this analysis are similar to that of the partial perspective. The adjusted analysis estimated an incremental cost per participant of −£522.13 (95% CI −717.01 to −327.25) (MTX cost saving and statistically significant) and incremental QALYs of −0.0034 (95% CI −0.0361 to 0.0292) per participant. The ICER was £152,301 per QALY; given this is in the southwest quadrant of the cost-effectiveness plane, this means that MTX is likely to be considered to be cost-effective if the willingness-to-pay threshold was either £20,000 or £30,000 per QALY as the ICER is higher. The NMB at a threshold of £20,000 (£30,000) per QALY was £453.57 (£419.29); given this is positive, it can be interpreted to mean that MTX is cost-effective.

Secondary analysis: cost-effectiveness analysis (Objective Scoring Atopic Dermatitis) (imputed analysis)

This secondary analysis was undertaken for the partial NHS perspective using multiple imputation to estimate the incremental cost of a point change on the o-SCORAD. In the adjusted analysis, the estimated incremental costs were −£492.20 (95% CI −688.40 to −296.00) per participant and the incremental change in o-SCORAD was 5.67 points (95% CI 1.52 to 9.82); thus, MTX was both cost saving and resulted in improved outcomes compared to CyA such that MTX can be said to be dominant (Southeast quadrant of the cost-effectiveness plane). A similar result was found for the unadjusted analysis, see *Table 5*.

Secondary analysis: cost-effectiveness analysis (flares)

This analysis was not conducted as planned because of the level of missingness for the flare data in the diaries. Only 9 of the 103 participants had complete data over the whole 60 weeks for flares. The reason for missing data is unknown as is whether the reason may be linked to whether the child had a flare or not.

Sensitivity analysis

See *Appendix 2* for the results of the sensitivity analyses.

Discussion

This study shows that the mean drug cost per participant for MTX is significantly less than CyA, but all other therapy-associated cost categories are similar between treatment groups. The finding for outcomes is less clear cut, with most analyses finding marginally negative QALYs for MTX compared to CyA; thus, MTX fell in the southwest quadrant of the cost-effectiveness plane in many analyses. In this quadrant, ICERs higher than the willingness-to-pay threshold for a QALY are likely to be considered as cost-effective, but theory and evidence suggest that the threshold in this quadrant may be higher than that of the northeast quadrant, though how much higher is unclear. If the same threshold is used, MTX appears to be cost-effective compared to CyA, and the threshold would have to increase significantly to change this finding. At the same time, the secondary CEAs estimating the incremental cost

per point change on the o-SCORAD found outcomes improved more for MTX compared to CyA, suggesting MTX is dominant (cheaper and more effective) at 60 weeks. The NMBs in all imputed analyses were positive for MTX, suggesting that the size of the cost saving is likely to be considered as sufficient to make the small loss (equivalent to around 1 or 2 days of perfect health over 60 weeks) in QALYs acceptable. However, NMBs are specific to the threshold value used, and if society has a loss aversion, the threshold may well be higher in the southwest quadrant than that used in this analysis.

The primary RCT[33] found that both MTX and CyA were clinically effective for eczema. CyA had a quicker initial response, while MTX had a more sustained effect. It is unclear whether the CHU-9D is sensitive enough to pick these different response patterns up. The RCT also showed that blood monitoring can be rationalised in this age group. This is likely to make use of these drugs more acceptable to CYP in addition to saving money, although these costs were small in comparison to the cost of CyA.

The NICE clinical guidance on the diagnosis and management of atopic eczema in the under 12-year-olds[35] was originally written in 2007 and was updated in June 2023 for new evidence on emollients. It currently recommends using systemic treatments only when all other options have failed, but it provides no guidance on which systemic agent to use because they found no evidence to inform such a recommendation. This study, therefore, contributes evidence to help inform future updates on this section of the guidance. It is argued that resource allocation decisions should be based only on the estimates of mean net benefit even where incremental differences are statistically insignificant, as this makes the best use of available evidence.[36]

Strengths and limitations

This economic evaluation was undertaken using data collected alongside a multicentre RCT in children with atopic eczema (the only adequately powered RCT in this age group with conventional systemic therapy). The study had sites across the UK and Ireland, enhancing representativeness of the sample; the trial outcomes followed the core outcome set recommended by the Harmonising Outcome Measures for Eczema initiative,[37] and it studied not only active treatment for a relatively long time (36 weeks) but also a 24-week follow-up to assess disease control after treatment cessation. A strength of the study was that there were a good level of complete data collected via CRF, including intervention drug use, concomitant medication, safety monitoring and AEs, which enabled the costs of the partial NHS perspective to be robustly estimated. The unit cost for CyA was based on the neoral brand since this was the brand used in TREAT. In practice, the use of generic brands might be expected and these are sometimes cheaper, but this is unlikely to be enough to change the conclusions reached in this study both because the cost difference between generic and branded CyA is not large (in 2022, price of a 100-mg capsule of CyA was £2.28 for neoral compared to £1.39 for a capsorin capsule, the cheapest alternative at the time) and because CyA is used daily compared to the weekly use of MTX.

There were significant amounts of missing diary data about wider NHS resource use related to eczema. This meant that the base-case analysis was undertaken using a narrower health sector perspective than originally planned. The narrower health sector perspective included intervention costs for the 36-week treatment period, consultations for weeks 0–40 and concomitant medications for the whole 60-week period, but it assumes zero costs for primary and secondary healthcare consultations in weeks 41–60 because these data were not available via CRF data. Given the missing data with respect to the formulation of the intervention medication issued to each participant, we assumed all CYP were issued tablets/capsules. While based on the data available for formulation, this seemed to be the most reasonable assumption, verbal feedback from centres suggests that some of the youngest participants were issued liquid formulations that are more expensive than tablets/capsules, particularly for MTX. For instance, a weekly dose of MTX for a child weighing 19 kg would cost £0.24 in tablet form and £9.84 for the oral solution per week. The weekly cost of daily dosing for CyA for a child weighing 19 kg would cost around £12.68 for capsules and £14.32 for oral liquid formulation. The weekly cost of the oral solution of MTX is still cheaper than CyA such that the conclusions reached in the analysis are likely to hold. The missing utility data mean that there is some uncertainty around the QALY estimates presented, which is a limitation. However, missingness was similar for both treatment groups, and patterns of missingness were explored to ensure that the data were analysed appropriately. Nevertheless, missing not at random (i.e. the missing data depend on the unobserved variables) can never completely be ruled out as the mechanism of missingness and thus the estimates based on the missing at random assumption may be biased.

Being a within-trial economic evaluation, the results are limited to concluding that MTX is likely to be more cost-effective than CyA over the 60-week time frame of the trial. Long-term (cost-) effectiveness cannot be inferred from this data set or analysis.

The appropriateness of the CHU-9D for use with CYP with severe eczema might be worth exploring as might

the validity of using the CHU-9D in children younger than 5 years of age, where there is currently limited evidence. Systemic therapies are, however, rarely indicated at very young ages, for instance in TREAT only 13 (12.6%) children were aged under five on entry to this study.

Given the paucity of economic evidence for these drugs for use in children with atopic eczema, the results of this study provide an important evidence base.

Lessons learnt

As a trial with frequent face-to-face follow-up, the collection of data alongside these visits had been anticipated to be good. However, in practice, diary completion was low, particularly for the resource use questions which were at the end of the diary. It may be that the ordering of questionnaires mattered and may be worth investigating in future as a study within a trial. The time between visits varied throughout the trial, and this, together with the quantity/frequency of diary and questionnaire completion required, may have caused fatigue in families. In hindsight, completion rates for the health resource use questions ought to have been monitored earlier in the trial so that the issue could have been observed earlier and attempts could have been made to remedy the issue quicker. As it was by the time our alternative approach (eliciting wider NHS resource use data from GP practices) was adopted, it fell at a time when GP practices were struggling with the pressures of COVID, meaning that the timing meant this approach also failed and contributed to delays in conducting the analysis. Particularly in light of the COVID pandemic, it might have been better to use an electronic data capture system such as an app, with inbuilt reminders for families to complete the diaries.

Future research

Novel therapies for atopic eczema, such as novel biologics and small molecules,[38] including dupilumab (for 6 months and over), abrocitinib (for 12 years and over), upadacitinib (12 years and over), lebrikizumab (available in European Union for 12 years and over) and tralokinumab (for 12 years and over), for example, are increasingly available. The cost of treatment with these drugs is significantly more than that seen for conventional systemic treatments[39] in this study, and for this reason, technology appraisal guidance has tended to limit their use to those with severe atopic eczema for whom conventional systemic treatment has stopped working or is not well tolerated by the patient.[40] A recent systematic review of economic evaluations for these newer drugs in atopic eczema[41] found a quarter of studies compared the novel strategy only to dupilumab and the majority to standard or usual care, where this sometimes included topical corticosteroids or topical calcineurin inhibitors in addition to emollients but not to systemic therapies. In this study, MTX was found to have a sustained effect in the RCT,[33] and given its overall cost-effectiveness, it now needs to be directly compared with novel systemic therapies, such as biologics and small molecules,[38] the use of which is already strictly curtailed in many jurisdictions due to cost. Such evidence would be particularly useful for resource-constrained settings.

Conclusions

This study extends the findings of the primary TREAT RCT by demonstrating that MTX and CyA are similar in terms of costs (for visits/monitoring, AEs and concomitant medications) and QALYs but that MTX drug costs are significantly cheaper than CyA drug costs in terms of the mean per participant cost. MTX also involved less administration time for parents since it was taken weekly rather than twice daily as was CyA. These findings support the conclusion reached in the clinical paper that, where novel systemic biologics and small molecules prescribing is restricted by health-funding bodies, as is the case in most settings, MTX provides an effective and low-cost first-line systemic agent and is thus an alternative to CyA.

Additional information

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TREAT Trial Laboratory Investigations: Nicholas Webb (Manchester Royal Infirmary) – provision of expertise on measurement and assessment of renal function relating to study drug administration; Leonie Taams (King's College London)

– immunology work; Luke O'Neil (Trinity College Dublin) – metabolomics; Irwin Mclean (University of Dundee) – *FLG* mutation analyses.

Data-sharing statement

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

Ethics statement

The study was approved by the East of England – Cambridge Central Research Ethics Committee, REC number: 15/EE/0328, date of REC opinion: 16 January 2016.

Information governance statement

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Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/GJCF0407.

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This article was published based on current knowledge at the time and date of publication. NIHR is committed to being inclusive and will continually monitor best practice and guidance in relation to terminology and language to ensure that we remain relevant to our stakeholders.

Publications

Irvine AD, Jones AP, Beattie P, Baron S, Browne F, Ashoor F, *et al.*; TREAT Trial Investigators. A randomized controlled trial protocol assessing the effectiveness, safety and cost-effectiveness of methotrexate vs. ciclosporin in the treatment of severe atopic eczema in children: the TREatment of severe Atopic eczema Trial (TREAT). *Br J Dermatol* 2018;**179**:1297–306. https://doi.org/10.1111/bjd.16717

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About this article

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List of supplementary material

Report Supplementary Material 1
Health economic analysis plan for the TREAT trial

Report Supplementary Material 2
TREAT Form 22: GP health economic data

Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/GJCF0407).

Supplementary material has been provided by the authors to support the article and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

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List of abbreviations

AE	adverse event
A&E	accident and emergency
CEA	cost-effectiveness analysis
CHU-9D	Child Health Utility Nine Dimensions
CI	confidence interval
CRF	clinical report form
CUA	cost–utility analysis
CYA	ciclosporin
CYP	child and young person
GP	general practitioner
HEAP	health economic analysis plan
ICER	incremental cost-effectiveness ratio
ITT	intention to treat
MTX	methotrexate
NICE	National Institute for Health and Care Excellence
NMB	net monetary benefit

o-SCORAD	Objective Scoring Atopic Dermatitis
PSS	Personal Social Services
QALY	quality-adjusted life-year
RCT	randomised controlled trial

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Appendix 1

TABLE 6 Number and proportion of participants with complete data by treatment group

Complete at	MTX (*n* = 51)	CyA (*n* = 52)
CRF resource use data[a]	103 (100%)	103 (100%)
Diary resource use data		
Week 4	29 (57%)	32 (62%)
Week 8	28 (55%)	27 (52%)
Week 12	29 (57%)	37 (71%)
Week 20	37 (73%)	35 (67%)
Week 28	35 (69%)	35 (67%)
Week 36	35 (68%)	34 (65%)
Week 48	36 (71%)	35 (67%)
Week 60	25 (49%)	28 (54%)
All time points	9 (18%)	9 (17%)
Utility data (CHU-9D)		
Utility at baseline	41 (80%)	41 (79%)
Utility at 12 weeks	41 (80%)	44 (85%)
Utility at 36 weeks	42 (82%)	46 (88%)
Utility at 48 weeks	42 (82%)	41 (79%)
Utility at 60 weeks	41 (80%)	45 (87%)
QALYs	26 (51%)	29 (56%)

a Some dnce, but enough information was provided to apply a cost using consistent assumptions.

Note
This is after the data were cleaned and assumptions were applied to make the data useable. The quality of the diary data, in particular, was quite poor and the figures in this table do not fully reflect this.

TABLE 7 Unit costs table (Great British pounds, 2022)

Cost item	Unit cost (£)	Assumption	Source
Intervention			
MTX	0.08 per 2.5-mg tablet	Doses made up of 2.5-mg tablets as per protocol	PCA, 2022[11]
Folic acid	0.06 per ml	1 ml per day except day of MTX administration	PCA, 2022[11]
CyA	0.30 per 10 mg up to 2.28 per 100-mg capsule	Neoral used as per protocol	PCA, 2022[11]
Paediatric dermatologist first visit	200.21	Paediatric Dermatology Service – consultant-led non-admitted face-to-face attendance, first visit	NHS reference costs, 2022[13]
Paediatric dermatologist follow-up visit	180.49	Paediatric Dermatology Service – consultant led non-admitted face-to-face attendance, follow-up	NHS reference costs, 2022[13]
Blood test	4.70		NHS reference costs, 2022[13]

continued

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TABLE 7 Unit costs table (Great British pounds, 2022) (*continued*)

Cost item	Unit cost (£)	Assumption	Source
AE – hospital admission	538.26	Non-Elective Inpatient – short stay, currency code PJ35D, paediatric skin disorders with CC score 0	NHS reference costs, 2022[13]
Medication	Various		PCA 2022[11]
NHS primary care			
GP	41.00	Including direct care staff costs with qualification costs for a 9.22-minute appointment	Jones *et al.*, 2022[12]
Practice nurse	17.33	Assumes 20-minute appointment (£52/3) and including qualification costs	Jones *et al.*, 2022[12]
NHS secondary care			
Hospital doctor	180.49	Paediatric Dermatology Service – consultant-led non-admitted face-to-face attendance, follow-up	NHS reference costs, 2022[13]
Hospital nurse	34.50	Assumed band 7 nurse for 30-minute consultation	Jones *et al.*, 2022[12]
A&E visit	242.03	Weighted average of total costs across all attendances in the emergency care section divided by total number of attendances	NHS reference costs, 2022[13]
Time off work (parents)	18.71	Mean gross hourly pay for all employee jobs	ASHE, 2022[14]

ASHE, Annual Survey of Hours and Earnings; CC, Complication/Comorbidity Score; PCA, prescription cost analysis.

TABLE 8 Mean (SD) cost and mean (95% CI) difference for cost using diary data by time point (Great British pounds 2022) (available case data)

	MTX (*n* = 51)		CyA (*n* = 52)		
Cost item (diary data)	**Mean (SD)**	***n***	**Mean (SD)**	***n***	**Mean difference (95% CI)**
4 weeks					
GP	1.41 (7.61)	29	0.00 (0.00)	32	1.41 (−1.28 to 4.10)
Practice nurse	0.60 (3.22)	29	0.00 (0.00)	32	0.60 (−0.54 to 1.74)
Hospital doctor	37.34 (147.73)	29	22.56 (99.92)	32	14.75 (−49.30 to 78.86)
Hospital nurse	4.76 (25.63)	29	0.00 (0.00)	32	4.76 (−4.30 to 13.82)
A&E visit	0.00 (0.00)	29	0.00 (0.00)	32	0.00 (0.00 to 0.00)
Cost of time off work (parent)	5.16 (27.80)	29	3.51 (19.85)	32	1.65 (−10.63 to 13.94)
8 weeks					
GP	5.86 (21.51)	28	4.56 (17.37)	27	1.30 (−9.29 to 11.90)
Practice nurse	0.00 (0.00)	28	0.00 (0.00)	27	0.00 (0.00 to 0.00)
Hospital doctor	12.89 (47.34)	28	0.00 (0.00)	27	12.89 (−5.39 to 31.17)
Hospital nurse	1.23 (6.52)	28	1.28 (6.64)	27	−0.05 (−3.60 to 3.51)
A&E visit	0.00 (0.00)	28	0.00 (0.00)	27	0.00 (0.00 to 0.00)
Cost of time off work (parent)	6.68 (25.06)	28	44.30 (113.19)	27	−37.61 (−81.58 to 6.35)
12 weeks					
GP	1.41 (7.61)	29	3.32 (14.90)	37	−1.91 (−7.98 to 4.16)
Practice nurse	0.00 (0.00)	29	0.00 (0.00)	37	0.00 (0.00 to 0.00)
Hospital doctor	24.90 (79.62)	29	19.51 (70.98)	37	5.38 (−31.72 to 42.48)
Hospital nurse	0.00 (0.00)	29	2.80 (12.54)	37	−2.80 (−7.46 to 1.86)

TABLE 8 Mean (SD) cost and mean (95% CI) difference for cost using diary data by time point (Great British pounds 2022) (available case data) (*continued*)

	MTX (*n* = 51)		CyA (*n* = 52)		
Cost item (diary data)	**Mean (SD)**	***n***	**Mean (SD)**	***n***	**Mean difference (95% CI)**
A&E visit	0.00 (0.00)	29	0.00 (0.00)	37	0.00 (0.00 to 0.00)
Cost of time off work (parent)	12.56 (37.18)	29	17.98 (65.09)	37	−5.72 (−32.81 to 21.36)
20 weeks					
GP	3.32 (14.90)	37	5.56 (14.56)	35	−2.53 (−9.46 to 4.40)
Practice nurse	0.00 (0.00)	37	0.00 (0.00)	35	0.00 (0.00 to 0.00)
Hospital doctor	4.88 (29.67)	37	0.00 (0.00)	35	4.88 (−5.13 to 14.89)
Hospital nurse	0.00 (0.00)	37	0.00 (0.00)	35	0.00 (0.00 to 0.00)
A&E visit	6.54 (39.79)	37	0.00 (0.00)	35	6.54 (−6.88 to 19.96)
Cost of time off work (parent)	3.03 (18.46)	37	10.69 (51.80)	35	−7.66 (−25.74 to 10.42)
28 weeks					
GP	3.51 (15.31)	35	1.17 (6.93)	35	2.34 (−3.33 to 8.01)
Practice nurse	0.50 (2.93)	35	0.00 (0.00)	35	0.50 (−0.50 to 1.48)
Hospital doctor	5.16 (30.51)	35	5.16 (30.51)	35	0.00 (−14.55 to 14.55)
Hospital nurse	0.00 (0.00)	35	0.00 (0.00)	35	0.00 (0.00 to 0.00)
A&E visit	6.92 (40.91)	35	0.00 (0.00)	35	6.92 (−6.88 to 20.71)
Time off work (parent)	23.52 (121.12)	35	0.00 (0.00)	35	25.52 (−17.33 to 64.38)
36 weeks					
GP	7.03 (21.06)	35	14.47 (33.30)	34	−7.44 (−20.79 to 5.91)
Practice nurse	0.00 (0.00)	35	0.51 (2.97)	34	−0.51 (−1.51 to 0.49)
Hospital doctor	5.16 (30.51)	35	21.23 (73.88)	34	−16.08 (−43.10 to 10.94)
Hospital nurse	0.00 (0.00)	35	0.00 (0.00)	34	0.00 (0.00 to 0.00)
A&E visit	0.00 (0.00)	35	0.00 (0.00)	34	0.00 (0.00 to 0.00)
Cost of time off work (parent)	0.00 (0.00)	35	550.87 (2919.92)	34	−550.87 (−1535.80 to 434.06)
48 weeks					
GP	10.25 (30.01)	36	5.86 (14.56)	35	4.39 (−6.83 to 15.61)
Practice nurse	0.00 (0.00)	36	0.50 (2.92)	35	−0.50 (−1.47 to 0.48)
Hospital doctor	5.01 (30.08)	36	5.16 (30.51)	35	−0.14 (−14.49 to 14.20)
Hospital nurse	1.92 (8.01)	36	0.00 (0.00)	35	1.92 (−0.79 to 4.62)
A&E visit	6.72 (40.34)	36	0.00 (0.00)	35	6.72 (−6.88 to 20.33)
Cost of time off work (parent)	5.20 (23.50)	36	0.00 (0.00)	35	5.20 (−2.73,13.12)
60 weeks (undiscounted)					
GP	1.64 (8.20)	25	1.46 (7.75)	28	0.18 (−4.22 to 4.58)
practice nurse	0.00 (0.00)	25	0.62 (3.28)	28	−0.62 (−1.94 to 0.70)
hospital doctor	0.00 (0.00)	25	0.00 (0.00)	28	0.00 (0.00 to 0.00)

continued

This article should be referenced as follows:
Sach TH, Jones A, Rosala-Hallas A, Spowart C, Ashoor F, Irvine AD, *et al.* Methotrexate versus Ciclosporin in the Treatment of Severe Atopic Eczema in Children: An economic evaluation. *Efficacy Mech Eval* 2026;**13**(1):51–78. https://doi.org/10.3310/GJCF0407

TABLE 8 Mean (SD) cost and mean (95% CI) difference for cost using diary data by time point (Great British pounds 2022) (available case data) (*continued*)

	MTX (*n* = 51)		CyA (*n* = 52)		
Cost item (diary data)	**Mean (SD)**	***n***	**Mean (SD)**	***n***	**Mean difference (95% CI)**
hospital nurse	0.00 (0.00)	25	1.23 (6.52)	28	−1.23 (−3.85 to 1.39)
A&E visit	0.00 (0.00)	25	8.64 (45.74)	28	−8.64 (−27.03 to 9.74)
Cost of time off work (parent)	0.00 (0.00)	25	0.00 (0.00)	28	0.00 (0.00 to 0.00)
60 weeks[a] (discounted)					
GP	1.68 (8.39)	25	1.50 (7.93)	28	0.18 (−4.32 to 4.68)
practice nurse	0.00 (0.00)	25	0.63 (3.35)	28	−0.63 (−1.98 to 0.71)
hospital doctor	0.00 (0.00)	25	0.00 (0.00)	28	0.00 (0.00 to 0.00)
hospital nurse	0.00 (0.00)	25	1.26 (6.67)	28	−1.26 (−3.94 to 1.42)
A&E visit	0.00 (0.00)	25	8.85 (46.81)	28	−8.85 (−27.66 to 9.97)
Cost of time off work (parent)	0.00 (0.00)	25	0.00 (0.00)	28	0.00 (0.00 to 0.00)

a The cost from week-60 diary was divided by 12 weeks, and 8 weeks of this were discounted and added to the undiscounted 4 weeks, as date the resource was incurred was unknown within this period.

TABLE 9 Mean (SD) outcomes and mean (95% CI) difference in utility and QALYs over 60 weeks by age (available case data)

	MTX (*n* = 51)		CyA (*n* = 52)		
	Mean (SD)	***n***	**Mean (SD)**	***n***	**Mean difference (95% CI)**
Child participants (aged < 7 years, proxy completed, n = 26)					
CHU-9D (under 7) baseline	0.6891 (0.1198)	10	0.6748 (0.1443)	9	0.0143 (−0.1135 to 0.1422)
CHU-9D (under 7) at 12 weeks	0.8115 (0.1171)	11	0.8483 (0.1423)	9	−0.0368 (−0.1585 to 0.0850)
CHU-9D (under 7) at 36 weeks	0.8479 (0.1004)	10	0.8675 (0.0924)	9	−0.0196 (−0.1134 to 0.0741)
CHU-9D (under 7) at 48 weeks	0.8801 (0.0999)	9	0.9089 (0.1296)	8	−0.0288 (−0.1476 to 0.0900)
CHU-9D (under 7) at 60 weeks	0.8810 (0.0944)	11	0.8399 (0.1589)	10	0.0411 (−0.0769 to 0.1591)
QALYs (< 7 years)	**0.9644 (0.0821)**	**6**	**0.9909 (0.0648)**	**5**	**−0.0266 (−0.1292 to 0.0760)**
Child participants (aged ≥ 7 years, participant completed, n = 77)					
CHU-9D (over 7) baseline	0.7384 (0.1590)	31	0.7381 (0.1423)	32	0.0003383 (−0.0756 to 0.0763)
CHU-9D (over 7) at 12 weeks	0.8469 (0.1407)	30	0.8804 (0.1127)	35	−0.0335 (−0.0964 to 0.0293)
CHU-9D (over 7) at 36 weeks	0.8693 (0.1119)	32	0.8560 (0.1183)	36	0.0134 (−0.0426 to 0.0693)
CHU-9D (over 7) at 48 weeks	0.8158 (0.1488)	33	0.8117 (0.1424)	32	0.0041 (−0.0681 to 0.0764)
CHU-9D (over 7) at 60 weeks	0.8734 (0.1087)	30	0.8212 (0.1482)	34	0.0522 (−0.0136 to 0.1179)
QALYs (7+ years)	**0.9851 (0.0996)**	**20**	**0.9594 (0.1066)**	**24**	**0.0257 (−0.0375 to 0.0890)**

TABLE 10 Logistic regression for missingness of costs and QALYs on baseline variables

	Odds ratio in logistic regression for missing data (95% CI)	
	Missing data on costs (diary data)	**Missing data on QALYs**
Treatment group	2.99 (0.57 to 15.58)	1.64 (0.50 to 5.31)
Sex (reference group female)	0.08 (0.01 to 0.71)[a]	0.43 (0.13 to 1.48)
Age	1.22 (0.93 to 1.60)	0.88 (0.76 to 1.03)
Ethnic group (reference group White)		
Black	0.27 (0.2 to 4.86)	7.78 (1.09 to 55.46)[a]
Asian	0.21 (0.03 to 1.38)	1.40 (0.24 to 8.26)
Other	0.08 (0.003 to 1.91)	2.38 (0.21 to 26.26)
Site		
2	–	–
3	–	8.22 (0.31 to 218.55)
4	–	6.90 (0.22 to 215.47)
5	–	9.66 (0.31 to 303.04)
6	0.82 (0.05 to 13.17)	12.38 (1.47 to 103.94)[a]
7	0.46 (0.02 to 9.13)	8.17 (0.71 to 93.68)
8	–	–
9	–	4.68 (0.56 to 39.28)
10	0.34 (0.03 to 4.12)	–
11	0.45 (0.03 to 6.32)	3.26 (0.49 to 21.70)
12	0.18 (0.01 to 3.71)	1.57 (0.08 to 29.50)
13		3.57 (0.15 to 87.71)
CHU-9D at baseline	6.34 (0.02 to 1783.54)	0.60 (0.01 to 40.79)
o-SCORAD at baseline	(0.94 to 1.14)	1.03 (0.97 to 1.10)

a Indicates statistical significance at 0.05.

Note
Not all sites have estimates because there either were not enough observations at the site or the site predicts missingness perfectly.

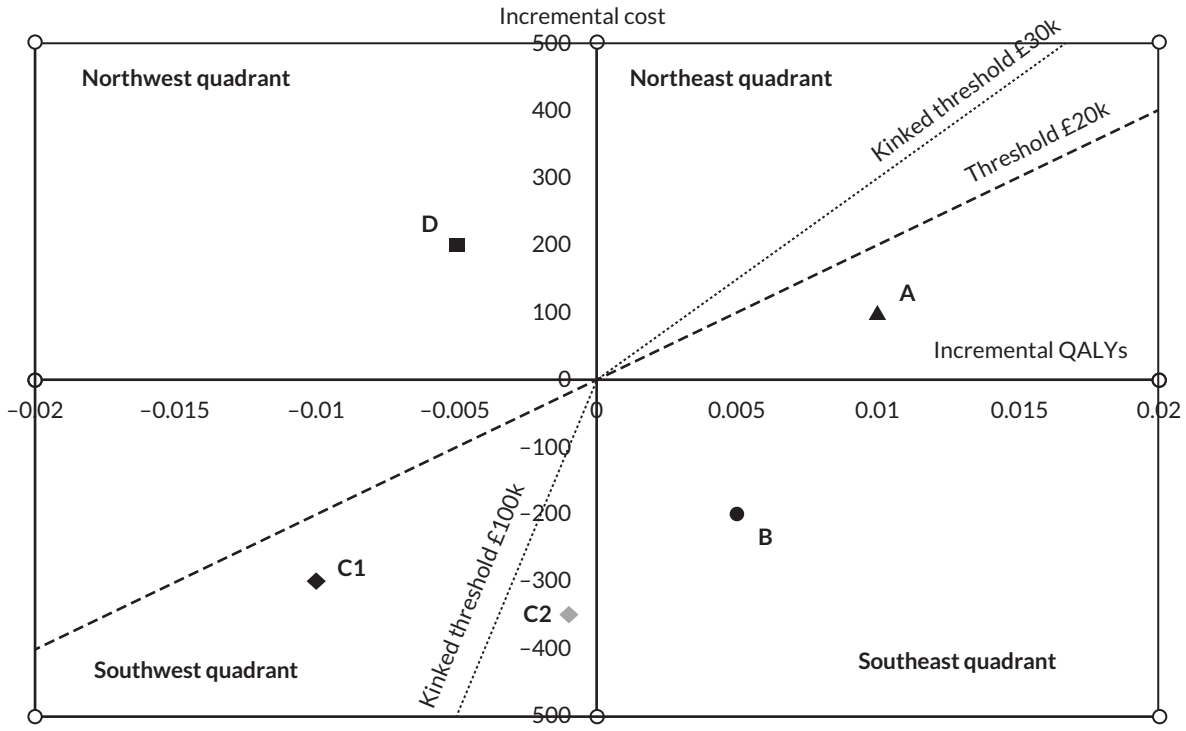

FIGURE 1 The cost-effectiveness plane.

Figure 1 shows the cost-effectiveness plane, with incremental costs on the *y*-axis and incremental QALYs on the *x*-axis.

In the southeast quadrant, the new interventions are both cheaper and more effective, so it can be said to dominate usual care or the comparator. In this case, an ICER is not informative and is not usually estimated.

In the northwest quadrant, the opposite is true; the new intervention is more costly and less effective than usual care or the comparator and is said to be dominated by usual care/comparator. Again, an ICER is not informative and is not usually estimated.

In the northeast quadrant, the new intervention is more costly and more effective, meaning that a judgement has to be made about whether the additional benefit is worth the additional cost. An ICER can be estimated as the incremental cost divided by the incremental benefivt and compared to the willingness to pay per QALY threshold, which, in the UK context, the NICE has indicated lies between £20,000 and £30,000. If the ICER lies below this threshold, then the new intervention is likely to be considered as cost-effective compared to usual care/comparator. In the example on *Figure 1*, intervention A costs £100 more than usual care and results in 0.01 additional QALYs, giving an ICER of £10,000 per QALY as this is below the threshold value; intervention A is likely to be considered as cost-effective.

In the southwest quadrant, the new intervention is cheaper than usual care/comparator, but it is also less effective. Again, an ICER can be estimated and compared to the willingness to pay per QALY threshold. However, there are a few things to note. Consider intervention C1, which is £300 cheaper than usual care/comparator but also produces less QALYs, −0.01 compared to usual care/comparator. The ICER is £30,000; note that a positive ICER does not therefore tell you which quadrant of the cost-effectiveness plane an ICER lies. Note also that this lies below the £20,000 threshold line shown in *Figure 1*, suggesting that the new intervention would likely be considered as cost-effective. However, note this assumes that decision-makers have the same threshold for how much they are willing to pay to gain a QALY (northeast quadrant) as they do for how much they are willing to accept (in terms of cost savings) to lose a QALY. It has been noted in the literature that the threshold may be kinked at the origin due to loss aversion and other factors (O'Brien *et al.*),[42] although it is not clear what size the kink takes. In *Figure 1*, an example is shown where the threshold is £100,000 in the southwest quadrant. In this case, intervention C1 would not be considered to be cost-effective compared to usual care/comparator, but intervention C2 would be considered to be cost-effective (high cost savings and very low QALY loss).

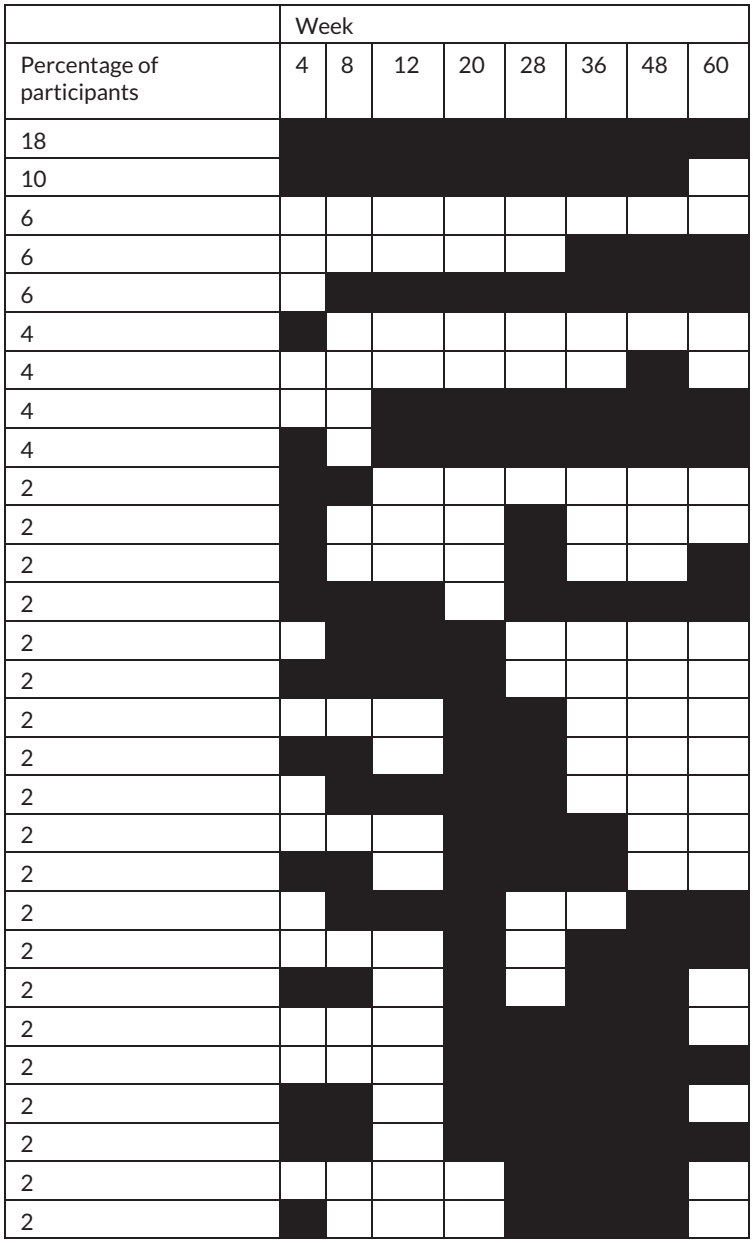

FIGURE 2 Missing data patterns for the resource use diary data for MTX group (n = 51). Note: Black cells represent complete data, and white cells indicate missing data.

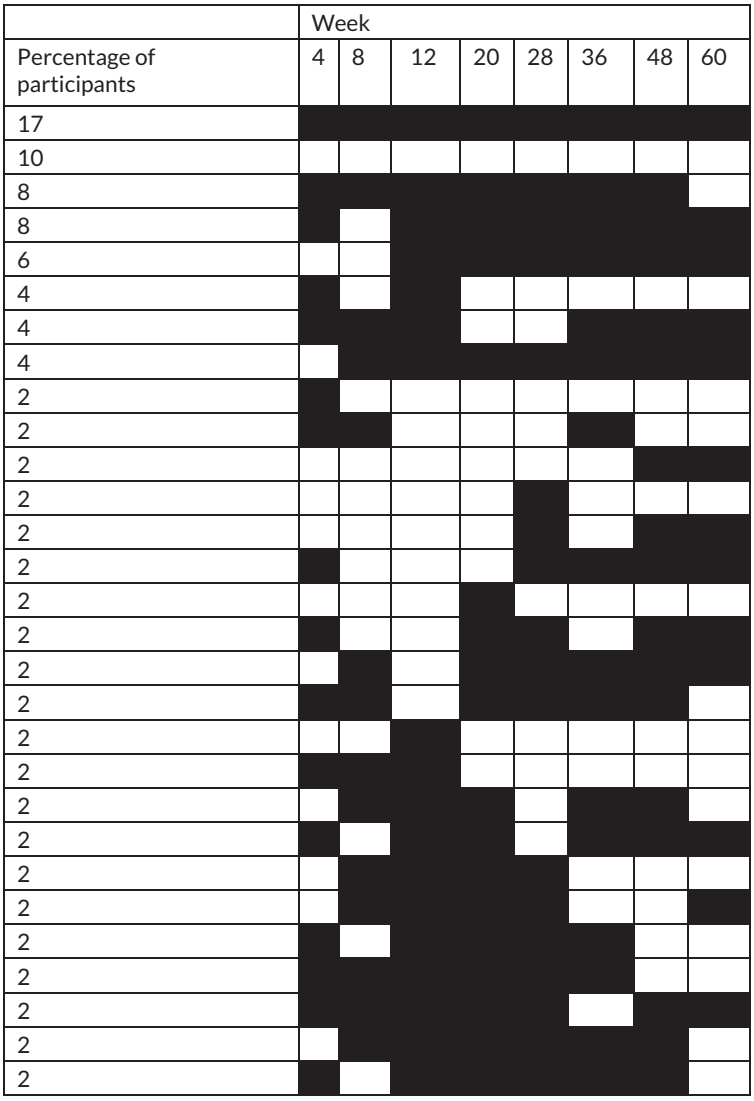

FIGURE 3 Missing data patterns for the resource use diary data for CyA group (n = 52). Note: Black cells represent complete data, and white cells indicate missing data.

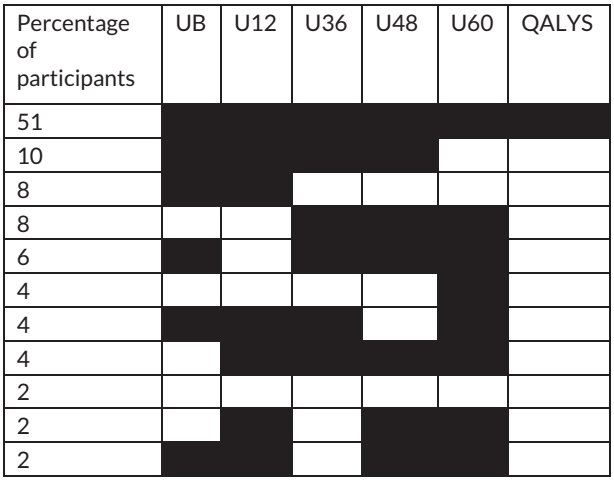

FIGURE 4 Missing data patterns for the CHU-9D for MTX group (n = 51). Note: Black cells represent complete data, and white cells indicate missing data. UB, baseline utility; U12, utility at 12 weeks; U36, utility at 36 weeks; U48, utility at 48 weeks; U60, utility at 60 weeks.

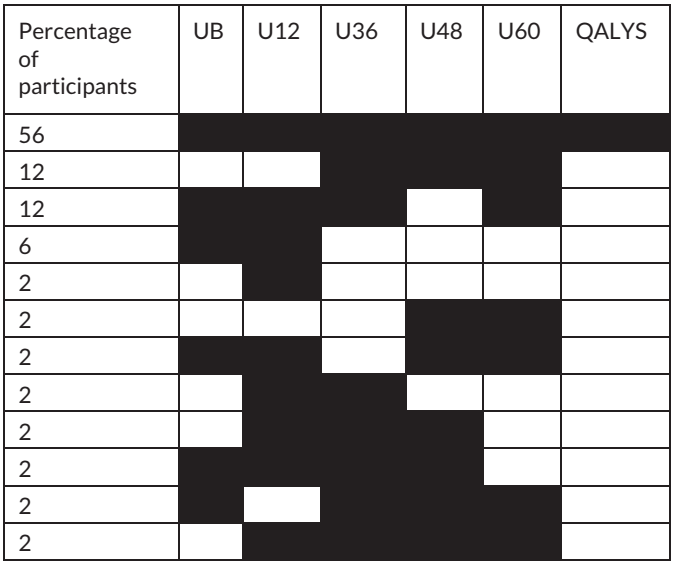

FIGURE 5 Missing data patterns for the CHU-9D for CyA group (n = 52). Note: Black cells represent complete data, and white cells indicate missing data.

Appendix 2 Results of sensitivity analyses

Cost–utility analysis for partial National Health Service + parent time off work (productivity) cost perspective (imputed analysis)

Sensitivity analysis was not undertaken to explore the impact of including parental productivity costs since the total cost of parental time off work over the whole 60 weeks would have had to be imputed due to the low number of responses and reports of positive costs to this question. *Table 3* shows that there were only complete data for time off work for 18 participants, and for these, none in the CyA incurred any such cost. However, available case data in *Appendix 1*, *Table 8* show that when broken down by data point, these costs were incurred by both arms.

Cost–utility analysis for partial National Health Service perspective (complete case analysis)

A complete case analysis for the partial NHS perspective was undertaken, as it was stated in the HEAP. The sample size for this analysis was 53% of the total sample reflecting the amount of missing QALY data. The adjusted analysis estimated incremental costs of −£282.32 (95% CI −511.41 to −53.24) and incremental QALYs of −0.0104 (95% CI −0.0578 to 0.0369), producing an ICER of £27,102 per QALY and NMB of £73.98 (−£30.19) at £20,000 and £30,000 thresholds. This suggests that MTX is likely cost-effective at £20,000, but not at £30,000, if the threshold is the same in the southwest quadrant as the northeast quadrant of the cost-effectiveness plane. The probability of cost-effectiveness is lower at 55.7% (48.4%) at a £20,000 (£30,000) threshold, suggesting that there is greater uncertainty about the decision to recommend MTX in this analysis. The unadjusted analysis of the complete case found cost savings and gains to QALYs, suggesting that MTX dominates CyA, but this likely reflects that factors associated with QALYs were not adjusted for; see *Appendix 2*, *Table 11*.

Cost–utility analysis for partial National Health Service perspective (threshold analysis)

No threshold analysis was undertaken on drug cost because MTX was found to be effective and cost-effective. It is clear from the results that the weekly cost of CyA would need to be similar or less than that to MTX to appear cost-effective, given all other cost categories and outcomes are not significantly different between treatment groups.

TABLE 11 Sensitivity analyses results

CUA (Nm, Nc)	Incremental cost (95% CI)	Incremental QALYs (95% CI)	ICER (cost-effectiveness if threshold £30,000 per QALY)	NMB £20,000 (£30,000) threshold	Probability that MTX is cost-effective at £20,000 (£30,000) threshold
Partial NHS perspective complete case, adjusted[a] (26, 29)	−282.32 (−511.41 to −53.24)	−0.0104 (−0.0578 to 0.0369)	27,102 (MTX cost-effective at £20k but not at £30K)	73.98 (−30.19)	55.7% (48.4%)
Partial NHS perspective, complete case, unadjusted (26, 29)	−404.02 (−638.93 to −169.12)	0.0155 (−0.0353 to 0.0663)	MTX dominant	714.32 (869.47)	90.9% (86.4%)

Nc, number of participants allocated to CyA; Nm, number of participants allocated to MTX.
a In adjusted analyses, costs were adjusted for treatment group, sex, age, site, ethnic group and baseline o-SCORAD, and outcomes were adjusted for treatment group, sex, age, site, ethnic group and baseline utility (CUA) or baseline o-SCORAD (CEA).

Note
The partial NHS perspective captured intervention drug use, concomitant medication, safety monitoring and AEs resource use collected via CRFs in the trial; since these data were complete, multiple imputation was used for utility only.