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Short title: The TREatment of severe Atopic eczema Trial (TREAT)
Classification: Clinical trial

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)

A.D. Irvine,[1,2,3] A.P. Jones,[4] P. Beattie,[5] S. Baron,[6] F. Browne,[2] F. Ashoor,[4] L. O'Neill,[7] A. Rosala-Hallas,[4] T. Sach,[8] C. Spowart,[4] L. Taams,[9] C. Walker,[6] M. Wan,[6] N. Webb,[10] P. Williamson[4] and C. Flohr[6] on behalf of the TREAT Trial Investigators

[1]Clinical Medicine, Trinity College Dublin, Ireland

[2]Paediatric Dermatology, Our Lady's Children Hospital Crumlin, Dublin, Ireland
[3]National Children's Research Centre, Crumlin, Dublin, Ireland

[4]Clinical Trials Research Centre, Department of Biostatistics, University of Liverpool, Liverpool, U.K.

[5]Royal Hospital for Children NHS Trust, Glasgow, U.K.

[6]Unit for Population-Based Dermatology Research, St John's Institute of Dermatology, Guy's and St Thomas' NHS Foundation Trust and King's College London, London, U.K.

[7]Biochemistry, Trinity College Dublin, Dublin, Ireland

[8]Health Economics Group, Norwich Medical School, University of East Anglia, Norwich, U.K.

[9]Centre for Molecular and Cellular Biology of Inflammation, King's College London, London, U.K.

[10]Renal Research Laboratories, Manchester Royal Infirmary, Oxford Road, Manchester, U.K.

http://orcid.org/0000-0002-9048-2044 (A.D. Irvine)
http://orcid.org/0000-0003-4884-6286 (C. Flohr; both URLs checked and working)

Correspondence

Carsten Flohr.

E-mail: carsten.flohr@kcl.ac.uk

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Conflicts of interest

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All TREAT investigators are listed in the Appendix.

Summary

Background Oral systemic immunomodulatory medication is regularly used off-licence in children with severe atopic eczema. However, there is no firm evidence regarding the effectiveness, safety, cost-effectiveness and impact on quality of life from an adequately powered randomized controlled trial (RCT) using systemic medication in children.

Objectives To assess whether there is a difference in the speed of onset, effectiveness, side-effect profile and reduction in flares post-treatment between ciclosporin (CyA) and methotrexate (MTX), and, also the cost-effectiveness of the drugs. Treatment impact on quality of life will also be examined in addition to whether *FLG* genotype influences

treatment response. In addition, the trial studies the immune–metabolic effects of CyA and MTX.

Methods Multicentre, parallel group, assessor-masked, pragmatic RCT of 36 weeks' duration with a 24-week follow-up period. In total, 102 children aged 2–16 years with moderate-to-severe atopic eczema, unresponsive to topical treatment will be randomized (1 : 1) to receive MTX (0.4 mg kg^{-1} per week) or CyA (4 mg kg^{-1} per day). *Results* The trial has two primary outcomes: change from baseline to 12 weeks in Objective Severity Scoring of Atopic Dermatitis (o-SCORAD) and time to first significant flare following treatment cessation.

Conclusions This trial addresses important therapeutic questions, highlighted in systematic reviews and treatment guidelines for atopic eczema. The trial design is pragmatic to reflect current clinical practice.

What's already known about this topic?

- Oral systemic immunomodulatory medication is regularly used off-licence in children with severe atopic eczema.
- Ciclosporin is the commonest first-line systemic agent used in this context, but methotrexate has emerged as an important therapeutic alternative.
- There is currently no adequately powered randomized controlled trial that compares both treatments in children.

What does this study add?

- The TREatment of severe Atopic eczema Trial (TREAT) addresses this gap and compares the effectiveness, safety, cost-effectiveness and impact on patient's quality of life of these two drugs.
- TREAT also examines the effects of both drugs using systemic and cutaneous markers of inflammation and the effect of filaggrin (*FLG*) genotype and T-cell cytokine signatures on treatment response.

Atopic eczema (synonymous with 'atopic dermatitis, 'eczema') is a chronic, pruritic inflammatory skin disease, affecting around 20% of U.K. children, 16% of whom have moderate-to-severe disease.[1] It comes at a high cost, for patients and families in addition to society.[2,3] Severe atopic eczema is often accompanied by significant sleep disturbance, poor school attendance and social withdrawal, in addition to attention-

deficit hyperactivity disorder, anxiety and clinical depression.[4] Skin infections are also common in poorly controlled atopic eczema and a reason for hospital admission.[4]

Although most cases of atopic eczema are adequately controlled with emollients, topical anti-inflammatory treatments and/or ultraviolet (UV) therapy, around 2% of children require oral immunosuppressive treatment to induce and maintain disease control.[5] There are, however, only limited systemic treatment options available and there is concern about their potential short- and long-term side-effects.[5] The European TREatment of severe Atopic eczema in children Taskforce survey in 765 consultant dermatologists and paediatricians from eight European countries was conducted to establish which systemic treatment options are available.[6] This showed that the first-choice systemic immunosuppressive agent was overall ciclosporin (CyA) with 43%, compared with the U.K. where 39% use azathioprine (AZA) and 35% use CyA.[6] Although methotrexate (MTX) was only the third most commonly used systemic treatment in the survey in the U.K., it is increasingly being used as a first-line systemic agent in children, as shown by our most recent treatment survey in the U.S.A.[7] Furthermore, while there is significant concern about the long-term prescribing of CyA (renal toxicity) and AZA (in particular lymphoma and progressive multifocal leucoencephalopathy), MTX is generally considered well tolerated and safe in the long term.[5,8] In addition, two randomized controlled trials (RCTs) and their follow-up studies suggested no significant difference in efficacy between MTX and AZA in adults and MTX and CyA in children, even if CyA appears to show its treatment effect more quickly.[8–11] However, these studies were statistically underpowered.[12]

There is therefore a clear need to compare MTX with the most established immunosuppressive medication, CyA, which has also been highlighted in a systematic review.[13] Both drugs have demonstrated a reduction in atopic eczema severity and improve quality of life.[4,5,14] The protocol for the trial is presented here and has been written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.[15]

The primary objectives are to compare the safety and efficacy of MTX vs. CyA, in recalcitrant atopic eczema in children, during 36 weeks of treatment and to compare disease control post-treatment cessation (time to return to baseline disease severity) over the 24-week follow-up period. Secondary objectives are to examine (i) the number of

flares during the trial period as well disease severity throughout follow-up; (ii) the impact on quality of life; (iii) the effects of both drugs using novel systemic and cutaneous markers of inflammation during treatment; (iv) the effect of filaggrin (*FLG*) genotype and T-cell cytokine signatures on treatment efficacy; (v) the side-effect profiles of both drugs, and (vi) a comparison of the cost-effectiveness of both drugs in a health economic evaluation.

Patients and methods

Trial design and study setting

The TREatment of severe Atopic eczema Trial (TREAT) is a phase III multicentre, parallel group, assessor-masked, pragmatic RCT aiming to recruit 102 children (Current Controlled Trials: ISRCTN15837754 (registered 09/03/2016); EudraCT Number 2015-002013-29 REC reference 15/EE/0328, sponsor reference TREAT). Study sites are in 13 secondary and tertiary care paediatric dermatology departments across the U.K. and Ireland (Table S1; see Supporting Information).

Children are identified in the paediatric dermatology clinics at the study sites. Inclusion criteria include (see full criteria in Table 1): (i) age 2–16 years; (ii) severe recalcitrant atopic eczema, defined as an inadequate clinical response to moderate (face) and to potent (body) topical corticosteroids and an Objective Severity Scoring of Atopic Dermatitis (o-SCORAD) severity score ≥ 30, and (iii) residence within travelling distance of the recruiting centre. Exclusion criteria include (see full criteria in Table 2): (i) a serious underlying medical condition; (ii) previous exposure to systemic immunosuppressive or biological agent(s); and (iii) recent use of oral corticosteroids, phototherapy or live vaccines.

Interventions

Participants are randomized to either oral/subcutaneous MTX or oral CyA using an allocation ratio of 1 : 1 and will receive the trial drug for a period of 36 weeks and are followed up for a further 24 weeks following treatment cessation.

CyA and MTX are commonly used in children for other chronic inflammatory conditions. For instance, for severe paediatric psoriasis a dose of 0.4 mg kg^{-1} per week MTX (max 25 mg per week) is used, as in TREAT (Children's British National Formulary).[16] The Children's British National Formulary stipulates a maximum dose for

CyA for severe atopic eczema of 5 mg kg^{-1} per day, but a dose of 4 mg kg^{-1} per day is used in TREAT based on the European TREatment of severe Atopic eczema in children Taskforce survey results.[6] Table S2 (see Supporting Information) summarizes the formulations of MTX and CyA used in the study. The assessor who will perform the severity assessments will be masked to the trial allocation.

Ciclosporin

Participants are prescribed 4 mg kg^{-1} per day given in two divided doses for the treatment period of 36 weeks. After 12 weeks, dose increases (to a maximum of 5 mg kg^{-1} per day) or decreases are allowed, dependent on treatment response. Dose modifications according to blood pressure and blood test results are detailed in Table S3 (see Supporting Information). As Neoral® (Novartis Pharmaceuticals UK Ltd, Frimley, UK) is the only brand with both liquid and capsule preparations it was selected for TREAT.

Methotrexate

Participants are prescribed an initial test dose of 0.1 mg kg^{-1} at week 0 and then the therapeutic dose of 0.4 mg kg^{-1} per week (maximum dose 25 mg per week) until week 12, providing there are no significant side-effects and safety blood tests results (Table S4; see Supporting Information). After week 12, dose modifications according to treatment response are allowed (maximum dose 25 mg per week). Only the 2.5 mg strength of MTX tablet will be prescribed and dispensed. Subcutaneous administration is available to those who experience significant gastrointestinal intolerance. Participants on the MTX arm will also be prescribed folic acid 1 mg once daily apart from on the day of MTX administration. Dose modifications according to blood pressure and blood test results are detailed in Table S5 (see Supporting Information).

Adherence

Participants are instructed to return unused medication, which will be counted and recorded on the accountability log prior to being disposed of/destroyed according to local National Health Service (NHS) policy. If for any reason a participant misses a treatment dose, this will be documented in the participant diary.

Potential side-effects

CyA's main potential side-effect is an increase in blood pressure and nephrotoxicity. Regular blood pressure and renal function measurements are therefore mandatory in routine clinical care. To assess renal function more carefully both plasma creatinine and cystatin C levels are measured in TREAT (at baseline, 2, 8, 12, 36 and 60 weeks) in addition to urinary tubular *N*-acetyl-beta-D-glucosaminidase (at baseline, 2, 12, 36 and 60 weeks), a sensitive marker of renal tubular function.[17]

As for MTX, gastrointestinal disturbance (e.g. nausea), liver function abnormalities and bone-marrow suppression are the main potential side-effects. However, based on both paediatric dermatology and rheumatology experience, MTX appears to be generally well tolerated and safe in children, even in settings where higher doses are used, often for prolonged time periods and in combination with biologics.[4,5,18–21] In TREAT, safety bloods are taken 1 week after the MTX test dose to capture rare idiosyncratic reactions. In addition, children in both study arms have safety bloods every 2 weeks for the first month, then monthly until week 12 and then 8-weekly thereafter while on treatment, in keeping with the American Academy of Dermatology guidelines for the use MTX and CyA in children with severe atopic eczema.[22]

Drugs known to interact with CyA or MTX may be prescribed when considered necessary for the patient's safety and well-being. If concomitant drugs are given, careful monitoring for drug-related adverse effects is recommended, as would be the case in clinical practice. As CyA is metabolized by cytochrome p450 (CYP3A) isoenzymes, in particular CYP3A4, drugs known to alter plasma or whole blood concentrations of CyA significantly through this route are prohibited during the study.

Concomitant medication

Participants will continue on their standard eczema care in line with National Institute for Health and Care Excellence (NICE) guidance, including regular emollients, (antiseptic) bath additives and mild-to-potent topical corticosteroids, topical calcineurin inhibitors and oral antihistamines of the patient's/local investigator's choice. Rescue oral antibiotics and oral corticosteroids are also permitted. Any medication required for any ongoing illness and any rescue medications are recorded both during the treatment and follow-up period. Use of wet wraps or other occlusive dressings are prohibited throughout the study period.

Results

Primary outcomes

There are two primary outcomes:

(i) the change in atopic eczema severity between baseline and 12 weeks of treatment in the two treatment arms using the o-SCORAD; and
(ii) time to first flare (defined as time to return to baseline or worse o-SCORAD score) during the 24 weeks after treatment cessation in the MTX vs. CyA groups.

Secondary outcomes

There are the following secondary outcomes:
(i) to examine atopic eczema severity using validated severity scores: Eczema Area and Severity Index (EASI), Investigator's Global Assessment (IGA), o-SCORAD and Patient Orientated Eczema Measure (POEM) scores between 0 and 12, 36, 48, 60 weeks;

(ii) to compare the number of flares in each study arm in addition to the proportion of children who re-flared during the 24 weeks after treatment cessation;
(iii) to study the impact on quality of life through change in Children's Dermatology Life Quality Index (CDLQI, children age ≥ 4 years), Infant's Dermatology Quality of Life Index (IDQOL, children < 4 years of age), Dermatitis Family Index (DFI) and Child Health Utility 9D (CHU-9D) scores between 0, 12, 36, 48 and 60 weeks;

(iv) to determine the proportion of participants achieving 50% improvement in the o-SCORAD and EASI index at 12, 36, 48, and 60 weeks;

(v) the difference in the proportion of participants withdrawing from treatment because of adverse events;

(vi) to assess the cost-effectiveness of CyA vs. MTX;

(vii) to study the immunometabolic effects of MTX and CyA, especially in relation to markers of glycolytic activation and T-cell cytokine signature, at baseline, during treatment and up to 24 weeks after completion of treatment;

(viii) to compare the drug side-effects/toxicity profiles of both MTX and CyA;
(ix) to examine the association between MTX polyglutamate and CyA trough levels and reduction in atopic eczema severity in addition to drug-related side-effects; and
(x) to study the impact of the *FLG* genotype (yes/no) on reduction in atopic eczema severity.

Sample size

Randomizing a total of 102 participants, 51 into each of the study arms, satisfies both of the following sample size calculations. For the first primary outcome (o-SCORAD), the change from baseline to 12 weeks will be calculated for each participant. The study aims to detect a minimum clinically important difference of eight o-SCORAD points between the two treatment groups, assuming a SD of 10 [based on the only other paediatric RCT with systemic immunosuppressive medication in children which saw a SD of 6.3 (MTX arm) vs. 8.9 (CyA arm) at 12 weeks][7] a sample size of 41 per group, increasing to 49 per group to allow for an estimated 18% loss to follow-up, will be required to provide 90% power using a *t*-test with a 0.025 two-sided significance level.

The co-primary outcome of this trial is whether or not a patient re-flares following treatment, as this may be an important factor influencing potential change in prescribing behaviour. The number of patients on CyA burst treatment who went into remission after 3 months of treatment in the study by Harper *et al.* was three out of 21, indicating that 86% of patients re-flared.[23] Assuming a similar flare risk in our CyA group, a sample size of 43 in each group (51 in each group with estimated loss to follow-up of 18%) will have 80% power to detect a reduction in re-flare of 30% (from 86% to 56%), using a two-sided test with a 0.025 significance level.

Recruitment

Participants will be identified by the clinical team at each centre via a search of the patient database/s or clinic list review. At the routine clinic visit, the patient will be provided with verbal and written information about the study and instructions on how to proceed if they are interested in taking part. All patients will be provided with a full explanation of the trial, before informed written consent/assent is taken.

Consent

Age-appropriate participant information sheets are provided for parents/guardians and children (available from the authors on request). The process of obtaining patient assent and parent/guardian informed consent is in accordance with the Research Ethics Committee guidance, and Good Clinical Practice. The investigator, or their nominee (medically qualified physician), and the participant and/or parent/guardian sign and date the consent form, before the participant can participate in the study. No trial-specific procedures are conducted before informed consent has been obtained, and participants

are reminded that they may withdraw from the trial at any time without it affecting the quality of their care in the future. Information on the collection, storage and use of the trial samples is provided in the participant information sheets and consent form.

Confidentiality

Data that contain names or other participant identifiers, such as informed consent forms, will be stored separately from the case report forms (CRFs), questionnaires and patient diaries identified by screening/randomization numbers. The database will be secured with password-protected access systems. Individual participant medical information obtained as a result of this study is considered confidential. Participants' study information will not be released outside of the study without the written permission of the participant, except as necessary for monitoring by authorized individuals [i.e. Clinical Trials Research Centre (CTRC), sponsor, regulatory authorities and NHS trust], which is clearly stated in the consent form. The CTRC will preserve the confidentiality of participants taking part in the study and The University of Liverpool is registered as a data controller with the Information Commissioners Office.

Screening visit

Informed consent can be taken at or prior to the screening visit, just prior to assessments. Patients are assigned a screening number for use on study documentation until randomization takes place. At screening, a full medical history is taken, with review of concomitant medication and full assessment against the eligibility criteria in addition to a pregnancy test, where indicated. An o-SCORAD is completed together with safety bloods. As a safety measure, some patients may require a chest X-ray at the screening visit if there is a risk of tuberculosis exposure, with a radiology report of clear/normal chest X-ray needed before randomization occurs. Patients who fail screening, based on the inclusion/exclusion criteria (see Tables 1 and 2), can be invited for re-screening after 14 days, if appropriate.

Baseline visit

The baseline visit will occur within a maximum of 14 days of the screening visit. However, the screening and baseline visit can be carried out on the same day. At this visit, informed consent status is checked, as is eligibility and a review of concomitant medication. As per Table 3, the clinician conducts a physical examination and the masked assessor completes an o-SCORAD, EASI and IGA. An additional pregnancy

test will be performed where indicated. The parent and child complete quality of life questionnaires, POEM, health-related quality of life during the visit and are given a patient diary (including POEM) to complete at home. Blood and urine samples are collected for safety screening and *FLG* genotyping and skin tape strips for mechanistic work. (Tape strips and mechanistic bloods are not collected at all sites.) All participants who provide consent and fulfil the eligibility criteria (confirmed by a medically qualified physician) will be randomized by the local investigator or their nominee and either CyA or MTX are dispensed.

Randomization method

Participants will be randomized to receive MTX or CyA in a 1 : 1 ratio at the baseline visit. Randomization lists will be generated by an independent statistician using a computer-generated randomization schedule stratified by site, using a secure (24 h) web-based randomization program controlled centrally by the CTRC. The block sizes will not be disclosed in order to ensure allocation concealment.

Participant timeline

Once the participant is randomized to their allocated treatment during the baseline visit (week 0), each participant will be enrolled for 60 weeks (36 weeks treatment, followed by a 24-week observational period). Details of the timeline for participants are summarized in Figure 1.

Masking

Masking of the local investigator, research nurse and the participant will not be possible, as CyA is given in two divided doses daily and MTX only once a week, but the severity assessors (o-SCORAD, EASI and IGA), are masked to treatment allocation. At each visit, data are collected as to whether or not the assessment is made masked. These data are monitored centrally and reviewed on a regular basis.

Visit schedule

The schedule for assessments during the treatment and the follow-up phase are shown in Table 3.

Participant retention

Participants may withdraw from treatment if the parent/legal representative (or the participant where applicable) withdraws consent, develops an unacceptable toxicity based on the local investigator's judgement, development of illness preventing further treatment or any change to the participant's condition that justifies the discontinuation of treatment. If a participant withdraws from trial treatment then centres will explain the importance of remaining on the trial follow-up to allow complete data capture.

Safety reporting

The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) definitions of an adverse event, adverse reaction, serious adverse event, serious adverse reaction and suspected unexpected serious adverse reaction (SUSARs) will be used during the course of the trial. All adverse evvents will be reported from randomization until 4 weeks after treatment cessation. Nonserious adverse reactions and adverse events should be reported to the CTRC within 7 days of the site being made aware of the event.

Serious adverse reactions/serious adverse events/SUSARs should be reported to the CTRC within 24 h of the site being made aware of the event. SUSARs will be reported to the Medicines and Healthcare products Regulatory Agency by the King's Health Partners Clinical Trials Office and the CTRC will notify main research ethics committee of all SUSARs. All investigator will be informed of all SUSARS occurring throughout the course of the study.

Mechanistic studies

Immunological parameters will be studied to see if there are significant changes in the percentages of regulatory T cells, pro/anti-inflammatory cytokine-expressing $CD4^+$ T cells, or in the corresponding levels of these cytokines in serum following treatment. Comparison will be made between MTX- vs. CyA-treated patients, and investigation as to whether there is a correlation between cytokine levels and treatment response at 12 and 36 weeks and the risk of re-flares at 60 weeks.

Systemic metabolic and local skin inflammatory parameters will be studied to see if the initial treatment response at 12 weeks to MTX (vs. CyA) is already associated at that stage with differences in the systemic metabolic profiles (shift from proinflammatory glycolytic activation to an anti-inflammatory metabolic profile), and whether this is also seen at 36 and 60 weeks, explaining a more sustained disease remission following MTX

(vs. CyA) therapy. Assessment will include whether observed systemic metabolic changes are associated with corresponding inflammatory profiles in the skin.

Mechanistic blood samples will only be collected from sites that can transport (via courier) samples to the King's College London biobank facility by 16.00 h on the same day (within maximum of 6 h postvenesection).

Data management

Each centre will undertake training in study requirements before being allowed to open to recruitment. This will include training on taking informed consent, completion of CRFs, randomization and safety reporting. Specific training will also be given on the severity assessment measures and quality of life questionnaires.

The CRFs are the primary data collection instrument and are sent to the CTRC with copies retained at site. A full description of the data management procedures are provided in the 'data management plan' and the 'data entry and cleaning manual', which can be made available from the authors upon request. All identifiable patient data is pseudonymized and source data are collected in the patients' medical records.

Templates of the data collection tools completed by the study site and/or participant, including CRFs and questionnaires, are available from the authors on request.

Statistical analysis

A separate statistical analysis plan is available from the authors on request, which details all analyses to be conducted for both the primary and secondary outcomes and also the methods that will be used to handle missing data and sensitivity analyses. Below is a brief summary of these analyses.

The primary analysis will be by intention-to-treat, based on all randomized participants, as far as is practically possible. The analysis of change in o-SCORAD from baseline to 12 weeks will be examined using analysis of covariance with treatment group and baseline measurements as covariates. Analysis of time to first flare after treatment cessation will be summarized by Kaplan–Meier curves for each treatment group and compared overall, using the log-rank test and survival regression methods.

For the secondary outcomes, continuous data will be reported as the difference in means and will be analysed using ANCOVA where appropriate and binary data will be reported

in terms of relative risk with appropriate 95% confidence intervals. Missing data will be monitored and strategies developed to minimize its occurrence. The robustness of the complete case analysis will be assessed using various imputation assumptions; however, these will be informed by data collected on the reasons for missing data.

This trial will contain an internal pilot study, to check the assumptions made in the sample size calculation. After the primary outcome data are available from 25 patients (o-SCORAD index at 12 weeks) the SD of the 25 scores, and the 95% confidence limits for this estimate, will be calculated without unmasking allocation. If the 95% confidence limits of the estimate of the SD of the o-SCORAD index at 12 weeks overlap 10 the trial will continue unchanged. If the upper 95% confidence limit of the estimate of the SD of the o-SCORAD index at 12 weeks is less than 10 the trial will continue unchanged but the trial steering committee will be informed that the trial power is greater than planned. If the lower 95% confidence limit of the estimate of the SD is greater than 10 the study is underpowered. The funder will then decide whether to invite an extension or close the study.

Cost-effectiveness analyses

A within-trial cost-effectiveness analysis will be conducted to assess whether CyA offers value for money compared with MTX for children with moderate-to-severe adverse events using standard methodology[24–26] and in accordance with the NICE reference case.[27] It will seek to: estimate resource use and costs in severe paediatric atopic eczema in the MTX compared with the CyA arm; estimate the quality-adjusted life years (QALYs) in severe paediatric atopic eczema in both arms; undertake cost-effectiveness and cost-utility analyses to assess which treatment represents best value for money for NHS provision; and estimate uncertainty levels surrounding the decision on which treatment to provide.

We will monitor levels of resource use associated with both interventions including drug costs, monitoring costs and adverse event costs over the 36-week treatment period. In addition, other potentially atopic eczema-related NHS resource items, including primary care visits, prescriptions and other healthcare contacts will be recorded in participant diaries at baseline and weeks 4, 8, 12, 20, 28, 36, 48 and 60. We will attach appropriate unit costs to resource-use data using published sources for a common price year[28–30] to estimate the mean overall cost per participant per study arm. Separately, we

will record the time-off work parents take because of their child's atopic eczema and cost this using the human capital approach using published average wages.[31] Children's time away from school will be recorded in units of time but not monetarized.

The economic evaluation will estimate the mean incremental cost and mean incremental effect of MTX compared with CyA [separate mean incremental effects will be estimated for: CHU-9D (QALY gain); change in o-SCORAD; and flare number]. The base case analysis will be the cost-utility analysis where QALY for the trial period (based upon the CHU-9D[32] instrument) is captured at baseline and weeks 12, 36, 48 and 60, using the proxy version for those aged under 7 years (with additional guidance notes for parents of those aged under 5 years provided by the instrument developer), using linear interpolation and area under the curve with baseline adjustment.[33]

Costs and outcomes will be discounted at recommended rates[19] in weeks 53–60 to reflect the time frame greater than 12 months. A regression-based approach (for instance seemingly unrelated regression equations if assumptions are met)[34] will be used to estimate the mean incremental cost and effects. Bootstrapping will explore uncertainty levels associated with the decision to adopt either treatment through the estimation of cost-effectiveness acceptability curves.[35] A specific health economics analysis plan will be written and finalized in advance of the trial database being locked.

Monitoring

Study data is centrally monitored by the CTRC. A number of monitoring features are in place at the CTRC to ensure reliability and validity of the trial data, these are detailed in the 'trial monitoring plan', available from the authors on request. Onsite monitoring visits can be triggered if necessary and will be carried out by either representatives of the CTRC or sponsor.

Ethics and dissemination

Initial review and approval of the trial protocol along with the participant facing documents were submitted to the East of England – Cambridge East Ethics Committee, which gave a favourable opinion (16 January 2016). Any subsequent amendments to the protocol and/or participant facing documents will require ethical approval.

Protocol amendments

Protocol amendments are assessed by the trial management group and approved by the sponsor, research ethics committees and by the regulatory authorities in the U.K. and Ireland.

Discussion

TREAT addresses key clinical questions for the management of children with severe atopic eczema using systemic medication, in particular whether there is a difference in speed of onset, effectiveness, side-effect profile and reduction in flares post-treatment between CyA and MTX, and, if so, the cost-effectiveness of the drugs. Furthermore, TREAT examines mechanistically how both drugs exert their anti-inflammatory profile systemically and in the skin.

The results from different centres will be analysed together and published as soon as possible. Individual clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the trial management group. Access to fully anonymized participant-level datasets and statistical codes can be made by requests to the trial management group, once the final results of the trial have been published.

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Appendix

Trial steering committee

Independent members: Alison Layton (Chair, consultant dermatologist and associate medical director for research); Tim Burton (patient and public representative); Michael Grainge (statistician); Michael Arden-Jones (dermatologist); Saskia King (patient and public representative); Michael Perkin (consultant paediatric allergist); Alain Taieb (paediatric dermatologist). Nonindependent member: Carsten Flohr (chief investigator).

Independent data and safety monitoring committee

Anthony Ormerod (Chair, Emeritus Professor in dermatology, University of Aberdeen and honorary consultant dermatologist NHS Grampian); Robert Chalmers (honorary

consultant dermatologist, co-chair and managing editor, Dermatology Topic Advisory Group, World Health Organization International Statistical Classification of Diseases and Related Health Problems Revision Project); Xinxue Liu (honorary research fellow).

Trial management group

Amina Ahmed (patient and public representative); Farhiya Ashoor (trial manager); Carsten Flohr (chief investigator, chair); Anna Rosala-Hallas (trial statistician); Amy Holton (sponsor representative); Alan Irvine (principal investigator); Ashley Jones (lead statistician), Tracey Sach (health economist); Catherine Spowart (supervising trial manager); Mandy Wan (lead pharmacist); Charlotte Walker (lead research nurse), Paula Williamson (director of the clinical trials research centre).

Principal investigators

Suzannah August (Poole Hospital); Paula Beattie (Royal Hospital for Children, Glasgow); Sara Brown (Ninewells Hospital, Dundee); Mike Cork (Sheffield Children's Hospital); Ben Esdaile (Whittington); Carsten Flohr (Guy's & St Thomas' Hospital); Joanna Gach (University Hospitals Coventry & Warwickshire); Emma Howard (Birmingham Children's Hospital); Alan Irvine (Our Lady's Children's Hospital, Dublin); Tess McPherson (Oxford University Hospitals); Donal O'Kane (Royal Victoria Hospital, Belfast); Jane Ravenscroft (Nottingham University Hospitals); Lindsay Shaw (Bristol Royal Hospital for Children).

Co-investigators

Caroline Allen (Oxford University Hospitals); Susannah Baron (Guy's & St Thomas' Hospital); Danielle Greenblatt (Guy's & St Thomas' Hospital); Robert Hearn (Ninewells Hospital, Dundee); Susannah Hoey (Royal Victoria Hospital, Belfast); Rachael Jarret (Oxford University Hospitals); Catherine Jury (Royal Hospital for Children, Glasgow); Charlie Mitchell (Poole Hospital); Ruth Murphy (Sheffield Children's Hospital); Graham Ogg (Oxford University Hospitals); Alice Plant (Poole Hospital); Louise Newell (Bristol Royal Hospital for Children); Jothsana Srinivasan (Nottingham University Hospitals), Emma Wedgeworth (Guy's & St Thomas' Hospital)

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.

Supporting Information

Additional Supporting Information may be found in the online version of the article at the publisher's website:

Table S1 Sites participating in the TREatment of severe Atopic eczema Trial.

Table S2 Investigational medicinal products and approved formulations.

Table S3 Ciclosporin dose modification schedule.

Table S4 Methotrexate tablets/subcutaneous injection/oral solution used in the TREatment of severe Atopic eczema Trial.

Table S5 Methotrexate dose modification schedule in the TREatment of severe Atopic eczema Trial.

Fig 1. Patient journey through the TREatment of severe Atopic eczema Trial. MTX, methotrexate; CyA, ciclosporin; o-SCORAD, Objective Severity Scoring of Atopic Dermatitis; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; POEM, Patient Orientated Eczema Measure.

Table 1 TREatment of severe Atopic eczema Trial inclusion criteria

1	Written informed consent for study participation obtained from the patient or parents/legal guardian, with assent as appropriate by the age/understanding of the patient
2	Aged 2–16 years at the time of the screening and randomization visit
3	Diagnosis of severe, recalcitrant atopic eczema
4	History of inadequate clinical response (in the opinion of the treating clinician) to potent topical corticosteroids on the body and moderate strength topical corticosteroids on the face
5	An Objective Severity Scoring of Atopic Dermatitis severity score of ≥ 30
6	Participants must live within travelling distance of the recruiting centre
7	Female patients of childbearing potential and male patients, who are sexually active, must commit to consistent and correct use of a highly effective method of contraception (e.g. combined hormonal contraception, intrauterine device, physical barrier or abstinence) for the duration of the trial and for 6 months after the last dose of study drug
8	Willingness to comply with study requirements
9	Baseline visit within maximum of 2 weeks of the screening visit

Table 2 TREatment of severe Atopic eczema Trial exclusion criteria

1	Serious underlying medical condition
2	Pregnant or nursing (lactating) female patients
3	Any active and/or chronic infection at screening or baseline (randomization) visit that, based on the investigator's clinical assessment, makes the individual an unsuitable candidate for the study
4	Presence of moderate-to-severe impaired renal function as indicated by clinically significantly abnormal creatinine ($\geq 1.5 \times$ upper normal limit for age and sex) AND estimated glomerular filtration rate < 60 mL min^{-2} per 1.73 m^2 at screening visit
5	Clinical evidence of liver disease or liver injury at screening visit as indicated by abnormal liver function tests such as aspartate aminotransferase, alanine aminotransferase, gamma glutamyltransferase, alkaline phosphatase or serum bilirubin (must not exceed $1.5 \times$ the upper limit value of the normal range for age and sex)
6	Total white blood cell count $< 3 \times 10^9$ L^{-1}, or platelets $< 150\times 10^9$ L^{-1} or neutrophils $< 1.5 \times 10^9$ L^{-1} or haemoglobin < 8.5 g $\times$ L^{-1} at screening visit
7	Blood pressure values > 95th percentile for age and sex at screening and baseline visit
8	Received systemic corticosteroids within 14 days prior to screening visit and 28 days of baseline visit
9	Received phototherapy within 4 weeks prior to screening visit and 6 weeks of the baseline visit
10	Previous exposure to any biological agents or systemic immunosuppressive therapy, except for oral corticosteroids for acute flare management
11	Concomitant use of disease-modifying and/or immunosuppressive drugs
12	Received live vaccines within 4 weeks prior to baseline visit
13	Radiology report of abnormal chest X-ray at the screening visit (at the discretion of the principal investigator/medically qualified physician)
14	Receiving treatment with medicines that are substrates for the multidrug efflux transporter P-glycoprotein or the organic anion transporter proteins for which elevated plasma concentrations are associated with serious and/or life-threatening events; this includes bosentan, dabigatran, etexilate and aliskiren
15	Receiving treatment with products containing *Hypericum perforatum* (St. John's

	wort)
16	Receiving oral treatment with tacrolimus, everolimus, sirolimus or lercanidipine
17	Currently participating in a conflicting study or participation in a clinical study involving a medicinal product in the last 28 days or less than five half-lives of the medicinal product prior to the screening visit
18	Known hypersensitivity to methotrexate or ciclosporin products
19	Insufficient understanding of the trial by the patient and/or parent/guardian

Table 3 Schedule for assessments during the treatment and follow-up phase

Procedures	Screening visit	Week 0, baseline/ randomization	Week 1 (MTX arm only), visit 1	Week 2, visit 2	Week 4, visit 3	Week 8, visit 4	Week 12, visit 5	Week 20, visit 6	Week 28, visit 7	Week 36, visit 8	Week 48, visit 9	Week 60, visit 10	Unscheduled visit
Informed consent	X												
Inclusion/exclusion criteria	X	X											
Medical history	X												
Concomitant drugs	X	X	X	X	X	X	X	X	X	X	X	X	X
Demographics	X												
Physical exam (including mouth/throat examination and chest auscultation)		X	X	X	X	X	X	X	X	X	X	X	
e-SCORAD	X	X			X	X	X	X	X	X	X	X	X[h]
EASI, IGA		X			X	X	X	X	X	X	X	X	X[h]
POEM (patient assessed)		X			X	X	X	X	X	X	X		
Parent and child quality of life (CDLQI/IDQOL and DFI)		X					X			X	X	X	
Child health-related quality of life (CHU-9D)		X					X			X	X	X	
Resource use (patient diary)		X			X	X	X	X	X	X	X	X	
Height and weight		X	X	X	X	X	X	X	X	X		X	
Height	X												
Blood pressure		X		X	X	X	X	X	X	X		X	X (only if required)

Adverse events (AE and SAE)[a]			X	X	X	X	X	X	X	X			X
Safety bloods[b]	X[c]		X	X	X[c]	X	X	X	X	X		X	X (only if required)
Chest X-ray[d]	X												
Pregnancy test (beta-HCG)	X	X											
Confirmation of appropriate contraception use, where applicable	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine sample collection (NAG)		X		X			X			X		X	
Randomization		X											
Study drug dispensing (as needed at each visit)		X			X	X	X	X	X				
MTX metabolite level (blood)				X		X	X			X			
CyA trough level (blood)[e]				X		X	X			X			
Cystatin C level (blood)		X		X		X	X			X		X	
Creatinine level (blood)		X		X		X	X			X		X	
Tape stripping for cutaneous metabolic work[f]		X					X			X		X	
Collection of blood for mechanistic studies[g]		X					X			X		X	
Collection of blood/saliva for *FLG* genotyping		X											

MTX, Methotrexate; o-SCORAD, Objective Severity Scoring of Atopic Dermatitis; EASI, Eczema Area and Severity Index, IGA, Investigator's Global Assessment; POEM, Patient Orientated Eczema Measure; CDLQI, Children's Dermatology Life Quality Index; IDQOL, Infant's Dermatology Quality of Life Index; DFI, Dermatitis Family Index; CHU-9D, Child Health Utility 9D (CHU-9D); AE, adverse event; SAE, serious adverse event; HCG, human chorionic gonadotropin; NAG, N-acetyl-beta-D-glucosaminidase; CyA, ciclosporin. [a]Collect until 4 weeks after treatment stopped; [b]safety bloods include

assessment of liver function, renal function and full blood count; [c]lipids to also be assessed at these time points as part of safety bloods; [d]screening chest X-ray on discretion of the local principal investigator/medically qualified physician in those at risk of tuberculosis; [e]collection of blood for ciclosporin levels should be measured in the morning, 12 hours (+/– 30 min) after the previous evening's dose, immediately prior to the administration of the morning dose. In younger children, where regular ciclosporin dosing occurs prior to school and in the early evening prior to bedtime (e.g. 07.30 h and 19.30 h), on the evenings prior to study visits where the ciclosporin level is to be measured, the evening dose should be given later in accordance with the time of the visit appointment; [f]not collected by all participating sites; [g]sites that can transport samples to King's College London by 16.00 h on the same day and within a maximum of 6 h postvenesection only; [h]severity assessments only to be collected if an unscheduled visit occurs between week 36 and week 60.

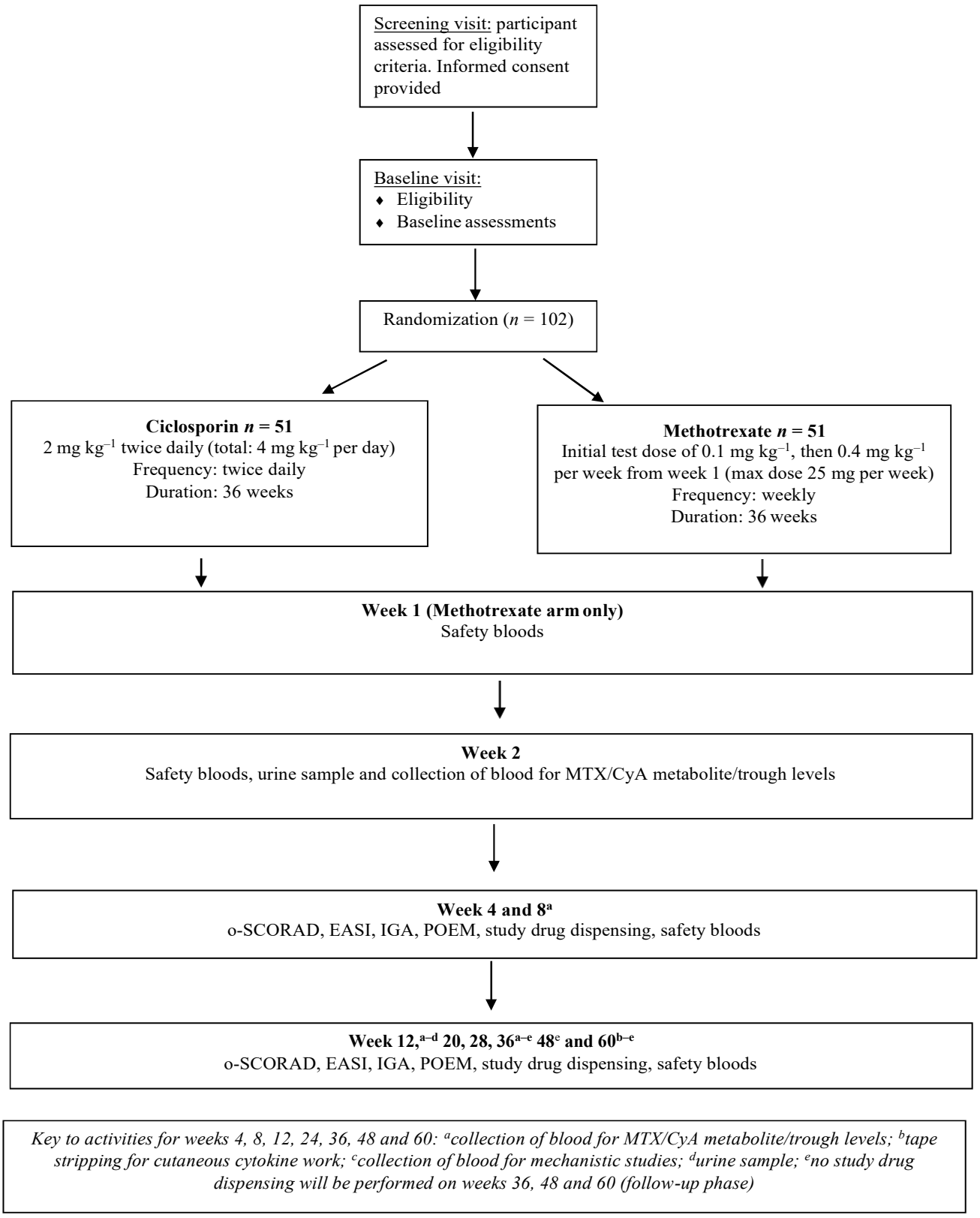
Screening visit: participant assessed for eligibility criteria. Informed consent provided
Baseline visit:
♦ Eligibility
♦ Baseline assessments
Randomization (n = 102)
Ciclosporin n = 51
2 mg kg–1 twice daily (total: 4 mg kg–1 per day)
Frequency: twice daily
Duration: 36 weeks
Methotrexate n = 51
Initial test dose of 0.1 mg kg–1, then 0.4 mg kg–1 per week from week 1 (max dose 25 mg per week)
Frequency: weekly
Duration: 36 weeks
Week 1 (Methotrexate arm only)
Safety bloods
Week 2
Safety bloods, urine sample and collection of blood for MTX/CyA metabolite/trough levels
Week 4 and 8a
o-SCORAD, EASI, IGA, POEM, study drug dispensing, safety bloods
Week 12,a–d 20, 28, 36a–e 48e and 60b–e
o-SCORAD, EASI, IGA, POEM, study drug dispensing, safety bloods
Key to activities for weeks 4, 8, 12, 24, 36, 48 and 60: acollection of blood for MTX/CyA metabolite/trough levels; btape stripping for cutaneous cytokine work; ccollection of blood for mechanistic studies; durine sample; eno study drug dispensing will be performed on weeks 36, 48 and 60 (follow-up phase)

Table S1: Sites participating in the TREAT trial

Guy's & St Thomas' NHS Foundation Trust, London (lead site)	Royal Hospital for Children, Glasgow
John Radcliffe Hospital and Churchill Hospital, Oxford	Whittington Hospital, London
Royal Victoria Hospital, Belfast	Birmingham Children's Hospital
Bristol Royal Hospital for Children	Poole Hospital
University Hospital Coventry and Warwickshire NHS Trust	Nottingham University NHS Trust – Queen's Medical Centre
Our Lady's Children's Hospital, Crumlin, Dublin	Sheffield Children's Hospital
Ninewells Hospital, Dundee	

Table S2: Investigational medicinal products (IMPs) and approved formulations

Arm	IMPs	Formulations
CyA	Ciclosporin	Brand: Neoral® Capsules: 10mg, 25mg, 50mg, 100mg
	Ciclosporin	Brand: Neoral® Oral solution: 100mg/ml
MTX	Methotrexate	Brand: any brand with marketing authorisation within European Economic Area (EEA) Tablets: 2.5mg
	Methotrexate	Brand: any brand with marketing authorisation within EEA Injection: 50mg/ml or 25mg/ml prefilled pen
	Methotrexate	Brand: any brand with marketing authorisation within EEA Oral solution: 2mg/ml

Table S4: Methotrexate tablets/ subcutaneous injection/ oral solution used in TREAT

<table>
<tr><th></th><th>Methotrexate tablets / subcutaneous injection/ oral solution</th></tr>
<tr><td>Dos</td><td>Initial dose of 0.1mg/kg/week, then 0.4mg/kg/week from week 1 (maximum 25mg/week).

For patients ≥ 22kg, doses should be rounded as per table below irrespective of formulation.

<table>
<tr><th>Weight band</th><th>0.1mg/kg test dose</th><th>0.4mg/kg dose</th></tr>
<tr><td><22kg</td><td colspan="2">no rounding required</td></tr>
<tr><td>22 to <29 kg</td><td>2.5mg</td><td>10mg</td></tr>
<tr><td>29 to <36 kg</td><td>2.5mg</td><td>12.5mg</td></tr>
<tr><td>36 to <43 kg</td><td>5mg</td><td>15mg</td></tr>
<tr><td>43 to <50 kg</td><td>5mg</td><td>17.5mg</td></tr>
<tr><td>50 to <57 kg</td><td>5mg</td><td>20mg</td></tr>
<tr><td>57 to <63kg</td><td>5mg</td><td>22.5mg</td></tr>
<tr><td>63kg +</td><td>7.5mg</td><td>25mg</td></tr>
</table>
</td></tr>
<tr><td>Frequency</td><td>Weekly</td></tr>
<tr><td>Duration</td><td>36 weeks</td></tr>
<tr><td>Route</td><td>Oral or subcutaneous</td></tr>
<tr><td>Formulation</td><td>Decision about formulation used to be made by local clinician, taking into account patient’s preference</td></tr>
</table>

Table S5: Methotrexate dose modification schedule TREAT trial

Monitoring parameters	Values	Action
eGFR	Fall of >=20% (compared with eGFR value that was used to confirm eligibility)	Repeat renal profile should be done within 2 weeks of the last visit. If eGFR falls again >=20 % following repeat bloods, the trial nephrologist must be contacted to discuss potential dose reduction. If repeat bloods cannot be obtained within 2 weeks of the last visit, the trial nephrologist must be contacted within 48 hours of the site becoming aware that a repeat renal profile cannot be obtained within the timeframe (2 weeks), to discuss potential dose reduction.
Blood pressure	>95th centile for age and sex on two consecutive visits	MTX dose adjustment, reduction by 20% initially and patient review with repeat BP after a fortnight.
Liver function test	AST, ALT or alkaline phosphatase more than 2× upper limit of reference range	MTX dose adjustment reduction by 20% initially. Repeat LFT weekly. Further reductions in dose or stopping medication may be required but should be discussed with the Chief Investigator.
Platelet count	<100x10^9/L	MTX dose adjustment reduction by 20% initially. Repeat platelets weekly. Further reductions in dose or stopping medication may be required but should be discussed with the Chief Investigator.
Neutrophil count	<1.5x10^9/L	MTX dose adjustment reduction by 20% initially. Repeat neutrophils weekly. Further reductions in dose or stopping medication may be required but should be discussed with the Chief Investigator.
Unexplained bruising, chicken pox contact or rash suspected to be chicken pox infection	Not applicable	Review by the PI prior to continuing with MTX.

New or worsening unexplained dyspnoea or cough	Not applicable	Review by the PI prior to continuing with MTX