A Randomised Controlled Trial Assessing the Effectiveness, Safety and Cost-effectiveness of Methotrexate versus Ciclosporin in the Treatment of Severe Atopic Eczema in Children: The **TRE**atment of Severe **A**topic Eczema **T**rial (TREAT)

Version 3.0 23rd October 2015

Study Co-Sponsor(s):
King's College London and Guy's and St. Thomas' NHS Foundation Trust

EudraCT number: 2015-002013-29

ISRCTN number:

Other:

Protocol Approval

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General Information

This document describes the TREAT trial and provides information about procedures for entering patients into it. The protocol should not be used as an aide-memoir or guide for the treatment of other patients; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but centres entering patients for the first time are advised to contact the coordinating centre (Medicines for Children Clinical Trials Unit) to confirm they have the most up to date version. Clinical problems relating to this trial should be referred to the relevant Chief Investigator via the CTRC.

This protocol defines the participant characteristics required for study entry and the schedule of treatment and follow-up. Participant recruitment will be undertaken in compliance with this document and applicable regulatory and governance requirements and waivers to authorise non-compliance are not permitted.

Incidence of protocol non-compliance, whether reported prospectively (e.g. where a treatment cannot be administered on a scheduled date as a result of public holidays) or retrospectively noted (e.g. as a result of central monitoring) are recorded as protocol deviations, the incidence of which are monitored and reported to trial oversight committees.

Statement of Compliance

This study will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and the Tokyo (1975), Venice (1983), Hong Kong (1989) and South Africa (1996) amendments and will be conducted in compliance with the protocol, CTRC and KHP CTO Standard Operating Procedures and EU Directive 2001/20/EC, transposed into UK law as the UK Statutory Instrument 2004 No 1031: Medicines for Human Use (Clinical Trials) Regulations 2004 as amended.

Relationship Statements

The UK Clinical Research Collaboration (UKCRC; www.ukcrc.org) is a partnership organisation working to establish the UK as a world leader in clinical research. Following a review by an international panel, the Clinical Trials Research Centre (CTRC) at the University of Liverpool has been assessed as reaching the highest quality standard required by the UKCRC and achieved full UKCRC registration.

The CTRC encompasses clinical trials activity in areas including medicines for children (The Medicines for Children Clinical Trials Unit; MC CTU), cancer (The Liverpool Cancer Trials Unit; LCTU), epilepsy, oral health and obstetrics and gynecology (http://www.ctrc.org.uk/). All CTRC activities are underpinned by methodological rigour, a modern data management system, similar technical requirements and a common set of standard operating procedures.

The NIHR Clinical Research Network: Children is part of the National Institute for Health Research Clinical Research Network.

The KHP CTO Quality Team was established in 2008 to manage the Sponsor responsibilities for Clinical Trials of Medicinal Products (CTIMPs), as defined in the Regulations, for trials sponsored or co-sponsored by King's Health Partner Organisations. Also to facilitate Chief Investigators with the set up and initiation of their trial and to ensure

that these trials are conducted according to GCP and the Regulations, throughout the life of the trial.

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CONTENTS

Glossary

AE	Adverse Event
AR	Adverse Reaction
AZA	Azathioprine
CDLQI	Children's Dermatology Life Quality Index
CI	Chief Investigator
CRF	Case Report Form
CS	Corticosteroids
CTRC	Clinical Trials Research Centre
CYA	Ciclosporin A
DFI	Dermatology Family Index
DQOL	Dermatology Quality of Life questionnaire
EASI	Eczema Area Severity Index
FLG	Filaggrin
GP	General Practitioner
IB	Investigator's Brochure
IDSMC	Independent Data and Safety and Monitoring Committee
IEC	Independent Ethical Committee
IGA	Investigator Global Assessment
IMP	Investigational Medicinal Product
KHP CTO	King's Health Partners Clinical Trials Office
MC CTU	Medicines for Children Clinical Trials Unit
MTX	Methotrexate
MREC	Multi-centre Research Ethics Committee
NIHR CRN	National Institute for Health Research Clinical Research Network
PI	Principal Investigator
PML	Progressive Multifocal Leukoencephalopathy
QOL	Quality of Life
R&D	Research & Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RN	Research Nurse. When RN is referred to in this protocol it means either the RN or someone who has been delegated that duty.
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SCORAD	SCORing Atopic Dermatitis severity index
SDV	Source Data Verification
SPC	Summary of product characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TMF	Trial Master File
TMG	Trial Management Group
TPMT	Thiopurine Methyltransferase
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction

1 PROTOCOL SUMMARY

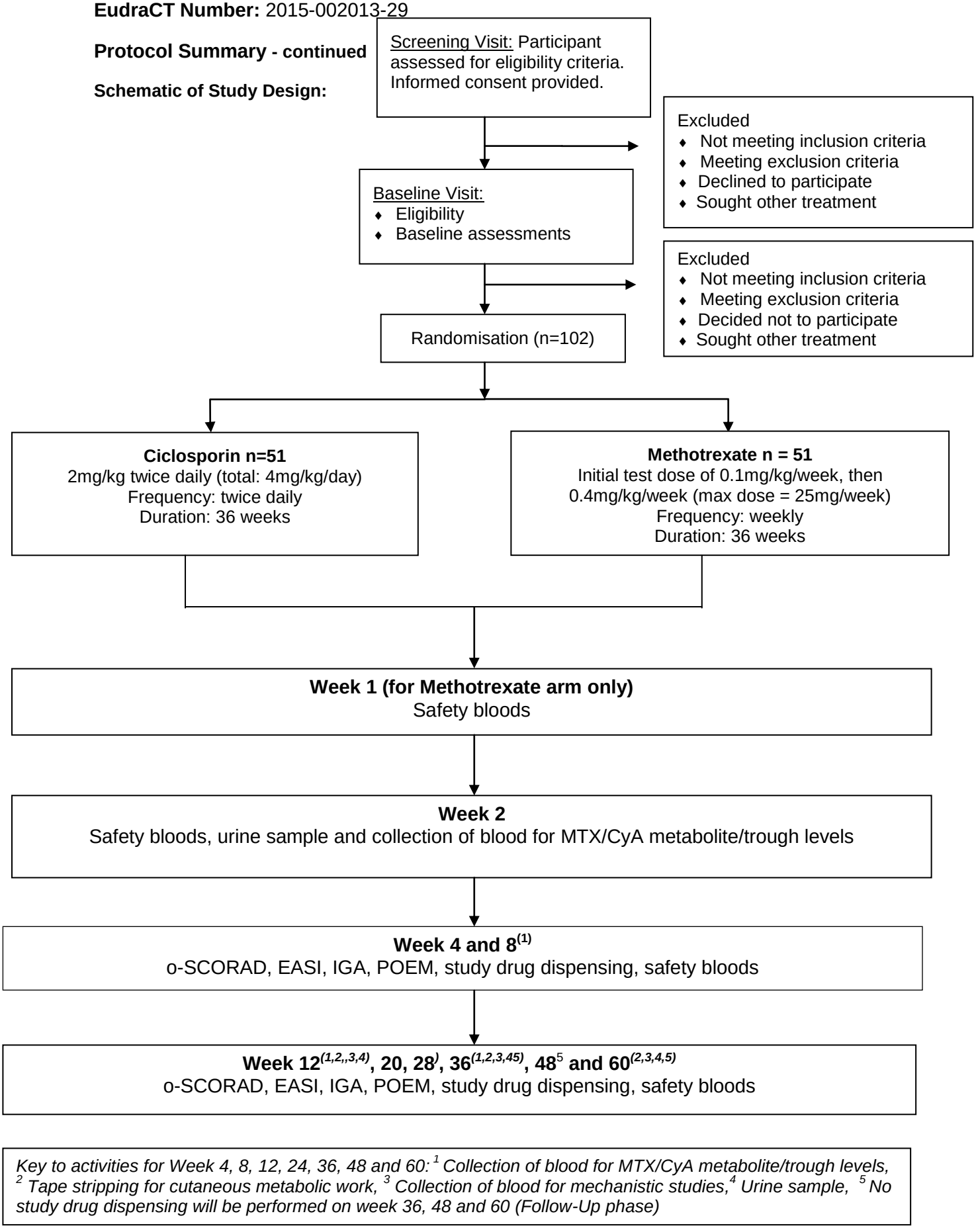
Study title:	Randomised controlled trial assessing the effectiveness, safety and cost-effectiveness of methotrexate (MTX) versus ciclosporin (CyA) in the treatment of severe atopic eczema in Children: The **TRE**atment of Severe **A**topic Eczema **T**rial (TREAT)
Protocol Short Title/Acronym:	TREAT Trial
Phase:	III
Co-Sponsor names:	King's College London and Guy's & St Thomas' NHS Foundation Trust
Chief Investigator:	Dr Carsten Flohr
Eudract number:	2015-002013-29
REC number:	To be confirmed
Study design:	Randomised multicentre trial comparing methotrexate (MTX) and ciclosporin (CyA) in patients with severe paediatric atopic eczema. 102 participants will be randomised applying a ratio of 1:1.
Population:	Children age 2-16 years with severe atopic eczema (o-SCORAD≥30) and inadequately responding to potent topical treatment. Children should not have received UV light therapy within the past 6 months & should never have received any systemic immuno-suppressive therapy, except for oral corticosteroids for acute flares.
Centres and Distribution:	Secondary and tertiary paediatric dermatology centres.
Study Duration:	All participants will be treated for 36 weeks on either therapy, with another 24 weeks follow up post treatment cessation (total duration 60 weeks per participant).
Intervention:	1. CyA: 4mg/kg/day (in divided doses); OR 2. MTX: started at 0.1mg/kg/week (test dose) and then continued on 0.4mg/kg/week (Max dose = 25mg/week)). Tablet as standard, but MTX can be given subcutaneously if gastrointestinal side effects warrant this.
Primary Objective:	The study has two co-primary objectives. 1. To assess the change in atopic eczema severity between baseline & 12 weeks of treatment in the two treatment arms, and 2. To examine disease remission during the 24 weeks after treatment cessation in the MTX vs CyA groups.
Secondary Objective/s:	-To examine atopic eczema severity using the EASI, IGA, o-SCORAD & POEM scores between 0 and 12, 36, 48, 60 weeks and using the o-SCORAD at 36, 48 and 60 weeks -To compare the number of flares in each study arm as

	well as the proportion of children who re-flared during the 24 weeks after treatment cessation. -To study the impact on quality of life: change in CDLQI/IDQOL & DFI scores between 0, 12, 36, 48 and 60 weeks -To determine the proportion of participants achieving 50% improvement in the o-SCORAD index at 12, 36, 48, and 60 weeks. -To capture the proportion of participants who withdraw from treatment because of AEs. -To assess the cost-effectiveness of CyA vs MTX. -To study the immuno-metabolic 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. -To compare the drug side effects/toxicity profiles of both MTX and CyA, - To examine the association between MTX polyglutamate and CyA trough levels and reduction in atopic eczema severity as well as drug-related side effects, and -To study the impact of FLG carriage (yes/no) on reduction in atopic eczema severity.
Endpoints:	<u>Co-Primary Endpoints:</u> 1. Change in atopic eczema severity between baseline and 12 weeks of treatment, using the o-SCORAD index. 2. Time to first flare during the 24 weeks after treatment cessation in the MTX vs CyA groups. <u>Secondary Endpoints:</u> 1. Change in atopic eczema severity using the EASI, IGA, o-SCORAD and POEM between baseline and 12, 36, 48, and 60 weeks. 2. Number of flares in each study arm as well as the proportion of children who re-flared during the 24 weeks after treatment cessation. 3. Proportion of participants achieving 50% improvement in the o-SCORAD and EASI index at 12, 36, 48, and 60 weeks. 4. Proportion of participants who withdraw from treatment because of AEs. 5. Disease-specific patient and parental quality of life (QoL) measured with the CDLQI/IDQOL and DFI scores between baseline and 12, 36, 48 & 60 weeks. 6. Assess the cost/QALY of CyA vs MTX. 7. Immuno-metabolic 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 6 months after completion of treatment. 8. Drug-related side effects of both MTX and CyA and their association with MTX polyglutamate and CyA trough levels. 9. The association between MTX polyglutamate and CyA

	trough levels and treatment response (reduction in disease severity). 10. The association between FLG carriage (yes/no) and treatment response.
Sample Size:	102
Summary of eligibility criteria:	1. Aged 2-16 years at the time of the screening and randomisation visit 2. Diagnosis of severe recalcitrant atopic eczema 3. History of inadequate clinical response (in the opinion of the treating clinician) to mild to potent topical corticosteroids. 4. An objective (o)-SCORAD severity score of at least 30
Version and date of protocol amendments:	V1.0 28/07/15 V2.0 08/10/2015

Protocol Summary - continued

Schematic of Study Design:



Key to activities for Week 4, 8, 12, 24, 36, 48 and 60: [1] Collection of blood for MTX/CyA metabolite/trough levels, [2] Tape stripping for cutaneous metabolic work, [3] Collection of blood for mechanistic studies, [4] Urine sample, [5] No study drug dispensing will be performed on week 36, 48 and 60 (Follow-Up phase)

2 BACKGROUND INFORMATION

2.1 Introduction

Background

Atopic eczema is a chronic, pruritic inflammatory skin disease and affects around 20% of UK children, 16% of whom have moderate-severe disease(1). It comes at a high cost, both for the individual patient and their family as well as society at large (~£500mio per year in the UK alone, 21st cause of non-fatal burden of all diseases) (2, 3). Patients with severe atopic eczema suffer significant sleep disturbance, show poor school attendance and are often socially withdrawn and are significantly more likely to suffer of attention-deficit hyperactivity disorder. There is also a clear link with anxiety and depression. Skin infections, in particular with Staphylococcus aureus but also herpes simplex, leading to hospital admissions are another typical feature of poorly controlled eczema(4). Although most cases of atopic eczema are adequately controlled with emollients and topical treatments and/or UV therapy, around 2% of children require oral immuno-suppressive treatment to induce and maintain disease control (5).The European TREAT Survey

The currently available treatment options for severe atopic eczema in children are very limited, and there is concern about their potential short and long-term side effects (5). We consequently conducted the TREatment of severe Atopic eczema in children Taskforce (TREAT) survey among 765 consultant dermatologists and paediatricians from 8 European countries. This showed that 43% of European physicians who look after children with severe atopic eczema use CyA as their first choice systemic immuno-suppressive agent (6). 31% use oral corticosteroids (CS) and 22% azathioprine (AZA) as 1st choice. However, the situation in the UK is a little different, where 39% use AZA first line compared to 35% for CyA and 19% for CS. Although MTX was only the 3rd most commonly used systemic treatment for severe atopic eczema in the TREAT survey, there has been a lot of interest in its use since two recent randomised controlled trials (RCTs) suggested no significant difference in efficacy between MTX and AZA (adults with severe atopic eczema, n=42) and MTX and CyA (children, n=40) (7, 8). However, both studies were statistically underpowered (9). In addition, the paediatric trial lacked an intention-to-treat analysis and lower than conventional drug doses were used (CyA 2mg/kg/d; MTX 7.5mg/week, not adjusted by weight).

Cyclosporine A

Cyclosporine is a potent inhibitor of T-lymphocyte-dependent immune responses. A systematic review of 11 clinical trials suggested that it is an efficacious treatment but that relapse is often seen, certainly when it is used only for short bursts(10). The effectiveness of cyclosporine A was similar in children and adults, with good tolerability seen in younger patients with co-morbidities, even at the 5mg/kg/day dose(11). The open label RCT by Harper et al. suggested that more long-term treatment with CyA might result in disease remission, compared to short-term burst treatment (11), but none of the clinical trials included an observation period, after treatment was stopped to assess the effect on natural history. The main potential side effects with more long-term use of CyA are increases in blood pressure due to nephrotoxicity, and regular blood pressure and renal function measurements are therefore important.

Azathioprine

Azathioprine inhibits purine synthesis and thus proliferation of leucocytes. The target cells and mechanism of action in atopic eczema are not fully elucidated(12). Azathioprine has a complex metabolism with several immunosuppressant metabolites. The balance between thiopurine metabolites is governed by thiopurine methyltransferase (TPMT) activity, and the pre-treatment determination of TPMT genotype or activity level allows informed drug dosing to minimise myelotoxicity. Other side effects include headache and gastrointestinal upset,

hepatotoxicity and drug hypersensitivity. There is concern about the potential long-term risk of lymphoma based on observations in inflammatory bowel disease, but the risk increase seen may be related to inflammatory bowel disease itself rather than be drug-related(13). More recently, the emergence of progressive multifocal leukoencephalopathy (PML) in patients treated with azathioprine, either in combination with other immunomodulators, or as a single agent, has given further pause regarding this agent. A large scale ecological study of reported cases of PML in patients on immune suppression suggests that azathioprine appears to confer a significantly higher risk of PML compared to Cyclosporine (lower risk) or Methotrexate (minimal risk). These risks may be most relevant in the context of autoimmune disease and have not been reported in atopic dermatitis(14). Azathioprine has a slow onset of action, with clinical improvement sometimes only seen 8 weeks into therapy. Two double-blind, placebo controlled trials in adults with severe atopic eczema reported significant improvement in disease severity and quality of life. More recently, a RCT comparing azathioprine and methotrexate in adults with severe atopic eczema suggested comparable efficacy, but this trial (n=42) was not adequately powered to demonstrate equivalence in efficacy between the two drugs(8).

Methotrexate

As with azathioprine, the mechanism of action of methotrexate in atopic ezcema is not fully understood, but it is known to have anti-inflammatory properties and to also reduce allergen-specific T cell activity(1). Gastrointestinal disturbance, in particular nausea, liver function abnormalities and bone-marrow suppression are potential side effects, but the medication is generally well tolerated in children and considered safe in the long-term, partly based on rheumatology experience in children and adults. Onset of action is equally slow as seen with azathioprine. Subcutaneous administration may improve bioavailability and tolerability in patients who have either failed to respond to treatment or who suffer significant gastrointestinal intolerance. In addition to the RCT that compared methotrexate with azathioprine in adults, there has been one recent RCT in children (n=40), comparing methotrexate with cyclosporine, also suggesting equal treatment responses(7).

The case for choosing CyA and MTX for the TREAT trial

Ciclosporin (CyA) is currently the only systemic immuno-suppressive medication licensed for the treatment of severe atopic eczema, and this only in patients ≥18 years of age and for a maximum of 8 weeks and is by far the most commonly used systemic agent in paediatric patients with recalcitrant atopic eczema. MTX is increasingly being used in the same patient group, partly because of the two small, underpowered RCTs mentioned above. There is therefore a clear need to compare methotrexate (MTX) with the most established immuno-suppressive medication, CyA. This has also been highlighted in a recent systematic review of oral immuno-modulatory medication in severe atopic eczema (15). Further support for research into the use of immuno-suppressive medication in severe atopic eczema in children was provided by a national research priority setting exercise run by the James Lind alliance in conjunction with the National Eczema Society in 2012, which involved patients, nurses and dermatologists, and listed the use of immune-suppressants in severe recalcitrant atopic eczema as one of the top five priority areas. This also specifically mentioned the need to compare MTX with more established immuno-suppressive therapies.

2.2 **(5)(6)(7, 8)(9)Rationale**

It is in particular the reported risk of rebound flares that warrants robust evaluation of CyA as a first line treatment approach against a comparator drug that is not only efficacious and safe but potentially also has the ability to alter the natural history of the disease. We propose that MTX fulfils all three requirements. As the anti-inflammatory action of MTX is poorly understood, this trial will include laboratory research that aims to shed further light on how

MTX achieves its anti-inflammatory effect with the potential to explain re-programming of the disease process.

2.3 Objectives

The main aim of this RCT is to assess the safety and efficacy (during therapy and also reduction in the number of flares up to 24 weeks after treatment has been stopped) of MTX versus CyA in severe recalcitrant atopic eczema in children.

In addition, we will examine the effect of both drugs on novel systemic and cutaneous markers of inflammation during and up to 24 weeks after treatment. Drug metabolites of MTX and trough levels of CyA will be measured throughout treatment to see whether they are able to predict treatment response and tolerability. Furthermore, filaggrin (FLG) genotype and T cell cytokine signatures will be determined in all trial participants to see whether these impact on treatment efficacy. We will also perform a health economic evaluation, comparing the cost effectiveness of both trial interventions.

Primary objectives:
1. To assess the change in atopic eczema severity between baseline & 12 weeks of treatment in the two treatment arms, and
2. To examine disease remission (time to first flare) during the 24 weeks after treatment cessation in the MTX vs CyA groups.

Secondary objectives:
1. To examine atopic eczema severity using the EASI, IGA, o-SCORAD & POEM scores between 0 and 12, 36, 48, 60 weeks,
2. To compare the number of flares in each study arm as well as the proportion of children who re-flared during the 24 weeks after treatment cessation,
3. To study the impact on quality of life: change in CDLQI/IDQOL & DFI scores between 0, 12, 36, 48 and 60 weeks,
4. To determine the proportion of participants achieving 50% improvement in the o-SCORAD and EASI index at 12, 36, 48, and 60 weeks,
5. To capture the proportion of participants who withdraw from treatment because of AEs,
6. To assess the cost-effectiveness of CyA vs MTX,
7. To study the immuno-metabolic 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,
8. To compare the drug side effects/toxicity profiles of both MTX and CyA, and
9. To examine the association between MTX polyglutamate and CyA trough levels and reduction in atopic eczema severity as well as drug-related side effects.
10. To study the impact of FLG carriage (yes/no) on reduction in atopic eczema severity.

2.4 Potential Risks and Benefits

Patients with severe atopic eczema suffer significant sleep loss because of intractable generalised itching, commonly show poor school attendance and are often socially withdrawn. Attention-deficit hyperactivity disorder has recently been linked to severe atopic eczema, and these patients often go on to develop anxiety and depression(16, 17). Skin infections, in particular with *Staphylococcus aureus* but also herpes simplex, leading to hospital admissions are another typical feature (4, 5). The National Institute for Clinical Excellence guidelines for the treatment of children with severe eczema recommends systemic immuno-suppressive therapy with CyA or MTX(18). Indeed, both CyA and MTX have been used in severe inflammatory skin diseases for many years, including children with uncontrolled psoriasis and atopic eczema and are part of established NHS care and clinical practice internationally(6). There are also American Academy of Dermatologists treatment

guidelines for systemic immuno-suppressive therapies in children with severe atopic eczema, which we adhere to in terms of treatment dose and safety monitoring. However, both treatments are used off label in this paediatric patient population, and patient safety is a key secondary outcome measure of the trial.

2.4.1 Potential Risksisks:

The use of CyA and MTX in children is seen in clinical practice for a large number of diseases and conditions. While malignant diseases, such as lymphoblastic leukaemia and lymphoblastic lymphoma are often treated at high doses, chronic inflammatory conditions, such as juvenile idiopathic arthritis, juvenile dermatomyositis, systemic lupus erythematosus, and scleroderma are treated at lower doses. For severe uncontrolled inflammatory skin diseases, such as psoriasis, typically a therapeutic dose of 0.4mg/kg/week MTX (max 25mg per week) is used(19), as indicated in the Children's British National Formulary, the dose we are using in the TREAT trial. The Children's British National Formulary indicates a therapeutic dose of 5mg/kg/day for CyA severe atopic eczema, while our trial protocol stipulates 4mg/kg/day, although treating TREAT trial physicians can go up to 5mg/kg/day, depending on treatment response.
The main potential side effects with the use of CyA are increases in blood pressure due to nephrotoxicity. Follow up of 42 paediatric patients with severe atopic eczema in a randomised controlled trial using continuous (n=21) vs repeated burst treatment (n=21) with 5mg/kg/day of CyA found no clinically significant change in mean serum creatinine or blood pressure over a 12 months period and tolerability was considered either 'good' or 'very good' in 80% of patients (11). The main reported side effects were: nausea (n=8), paraesthesia (7), hypertrichosis (5), swollen gums (4), headache (4), rhinitis (3), upper respiratory tract infection (3), abdominal pain (3), and hyperuricaemia(11). The only RCT that used CyA (vs MTX) in children with severe atopic eczema found the following side effects over a 12 weeks treatment period: nausea/vomiting (2/20), glossitis/oral ulceration (1/20), diarrhoea (3/20), pancytopenia (3/20), anaemia (4/20), leukopenia (7/20), thrombocytopenia (2/20), abnormal liver profile (2/20), abnormal renal function (3/20), and hypertension (1/20). Regular blood pressure and renal function measurements are the main safety investigations in the CyA arm of the study. To provide an assessment of renal function above and beyond standard NHS care, we are not only determining plasma creatinine but also cystatin C levels (baseline, 2 weeks, 8 weeks, 12 weeks, 36 weeks and 60 weeks) as well as urinary tubular N-acetyl-beta-D-glucosaminidase (at baseline, 2 weeks, 12 weeks, 36 weeks and 60 weeks).
(11).

As for MTX, gastrointestinal disturbance, in particular nausea, liver function abnormalities and bone-marrow suppression are the main potential side effects, but the medication is well tolerated in the majority of cases and considered safe in the long-term, partly based on the extensive rheumatology and gastroenterology experience in children, using similar if not higher doses for longer periods of time and often in combination with biologics(4, 5, 20-23) . In addition, the only RCT using MTX in children with severe atopic eczema over a 12 week period, the following adverse events were recorded: nausea/vomiting (4/20), abdominal pain (1/20), glossitis/oral ulceration (4/20), diarrhoea (5/20), pancytopenia (1/20), anaemia (6/20), leukopenia (2/20), abnormal liver function (5/20), abnormal renal function (1/20), fatigue (6/20), headache (3/20), and flu-like symptoms (1/20). This overall favourable side effect profile has been confirmed by three observational studies, involving a total of 102 paediatric patients with treatment durations of up to 38 months(24-26). We are performing safety bloods after the initial test dose for MTX to capture rare idiosyncratic reactions early and review participants in both study arms with safety bloods and enquiry about adverse events fortnightly for the first month, then monthly until week 12 and then eight-weekly, while on treatment, in keeping with the American Academy of Dermatology guidelines for the use of these systemic agents in children with severe atopic eczema(27). Patients are also encouraged to contact the study team in case of any concerns about drug adverse reactions between study visits. In addition, all potential

participants and their parents will be informed about common and rare serious side effects in the Patient Information Leaflets and also instructed to contact the study team/seek medical advice straight away if any of the following occur:

Methotrexate::

- Infections, including fever (temperature above 38^{o}C), chills, sore throat or chicken pox
- Skin rash, changes in nail or skin colour, or skin ulcers
- Jaundice
- Bleeding gums, unexpected bruising or bleeding that doesn't stop as quickly as normal
- Melaena
- Chest pain, difficulty breathing or chronic dry cough
- Severe and continuing diarrhoea, vomiting or stomach pains

- Ciclosporin:Infections, including fever (temperature above 38^{o}C), chills, sore throat or chicken pox
- Unusual bleeding that is difficult to stop
- Severe bruising
- Headaches and associated visual disturbance

2.4.2 Known Potential Benefits

Both drugs have been demonstrated to reduce atopic eczema severity and improve quality of life(4, 5) However, there is equipoise with regard to which of the treatments is superior in terms of short-term efficacy (first primary outcome looks at the effectiveness of CyA vs MTX at 12 weeks) and more long-term disease control (secondary outcome is disease control during the six months follow up period).

Ciclosporin:

A systematic review of 11 clinical trials suggested that CyA is an efficacious treatment but that relapse is often seen, certainly when it is used only for short bursts of 2-3 months.[i] The effectiveness of CyA was similar in children and adults, with good tolerability seen in younger patients with co-morbidities, even at the 5mg/kg/day dose(11). The open label RCT by Harper et al. suggested that more long-term treatment with CyA might result in disease remission, compared to short-term burst treatment(4), but none of the clinical trials included an observation period, after treatment was stopped to assess the effect on natural history.

Methotrexate:

Although the evidence base for MTX is smaller than for CyA in severe atopic eczema, the RCT that compared methotrexate with azathioprine in adults (n=42, MTX vs AZA)(8), and the RCT in children (n=40, MTX vs CyA)(7) clearly demonstrated its positive effect on disease severity and quality of life, also underpinned by the three observational studies already discussed above.

3 SELECTION OF CENTRES/CLINICIANS

Study centres will be initiated once all global (e.g. local R&D approval) and study-specific conditions (e.g. training requirements) have been met, and all necessary documents have been returned to CTRC. Initiation meetings will cover the requirements outlined in CTRC and KHP CTO SOPs.

3.1 Centre/Clinician inclusion criteria

Each participating centre (and Principal Investigator; PI) has been identified on the basis of:

- Having at least one consultant dermatologist with a specific interest in, and responsibility for supervision and management of patients with severe atopic eczema
- Showing enthusiasm to participate in the study
- Ensuring that sufficient time, staff and adequate facilities are available for the trial
- Providing information to all supporting staff members involved with the trial or with other elements of patient management
- Identifying that they will be able to recruit the required number of patients
- Acknowledging and agreeing to conform to the administrative and ethical requirements and responsibility of the study including adhering to GCP and other regulatory documentation
- Other important criteria are:
  a. Local R&D approval
  b. Completion and return of 'Signature and Delegation Log' to CTRC
  c. Signed contract between site and sponsor
  d. CTRC and KHP CTO green light process criteria are met

3.2 Centre/Clinician Exclusion Criteria

a. Not meeting the inclusion criteria listed above

4 TRIAL DESIGN

This study is a phase III, multi-centre randomised trial comparing methotrexate and ciclosporin. Treatment duration is for 36 weeks and participants will be followed up for 24 weeks following treatment cessation.

Participants will be randomised applying a ratio of 1:1.

5 STUDY POPULATION

5.1 Inclusion Criteria

1. Written informed consent for study participation obtained from the patient or parents / legal guardian, with assent as appropriate by the patient, depending on the level of understanding.
2. Aged 2-16 years at the time of the screening and randomisation visit
3. Diagnosis of severe recalcitrant atopic eczema
4. History of inadequate clinical response (in the opinion of the treating clinician) to mild to potent topical corticosteroids.
5. An objective (o)-SCORAD severity score of at least 30
6. Participants must live within travelling distance of the recruiting centre
7. Females of childbearing potential and males, who are sexually active, must commit to consistent and correct use of an acceptable method of contraception for the duration of the trial and for 6 months after the last dose of study drug.
    a. Females of childbearing potential for this study are: Females, regardless of their age, with functioning ovaries and no documented impairment of oviductal or uterine function that would cause sterility. This category includes young females who have begun to menstruate, or females with oligomenorrhea.
8. Willingness to comply with study requirements
9. Ability to swallow tablets/capsules
10. Baseline visit within 2 weeks of the screening visit

5.2 Exclusion Criteria

1. Serious underlying medical condition which in the opinion of the Investigator would compromise the safety of the patient.
2. Pregnant or nursing (lactating) females, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
3. Any active and/or chronic infection at screening or baseline (randomisation) visit that, based on the investigator's clinical assessment, makes the subject an unsuitable candidate for the study.
4. Presence of moderate to severe impaired renal function as indicated by clinically significantly abnormal creatinine (≥ 1.5 x upper normal limit (ULN) for age and sex) or eGFR <60ml/min/1.73m^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 AST, ALT, GGT, alkaline phosphatase, or serum bilirubin (must not exceed 1.5 x the upper limit value of the normal range for age and sex).
6. Total WBC count <3x10^9/L, or platelets <150x10^9/L or neutrophils <1.5x10^9/L or haemoglobin <8.5 g/dL at screening visit.
7. Blood pressure values > 95th percentile for age and sex at screening *and* baseline visit.
8. Received systemic cortico-steroids 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 biologic agents or systemic immuno-suppressive therapy, except for oral corticosteroids (CS) 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 PI - see section 7.1 for further details)
14. Receiving treatment with medicines that are substrates for the multidrug efflux transporter P-glycoprotein or the organic anion transporter proteins (OATP) 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
17. Receiving oral treatment with everolimus and sirolimus
18. Receiving oral treatment with lercanidipine
19. Currently participating in a conflicting study or participation in a clinical study involving a medicinal product in the last 28 days or less than 5 half-lives of the medicinal product prior to the screening visit.
20. Known hypersensitivity to methotrexate or ciclosporin products.
21. Insufficient understanding of the trial.

*Formula for measuring eGFR = height (cm) x 40/plasma creatinine (micromol/l)

6 ENROLMENT, RANDOMISATION AND WITHDRAWAL

6.1 Recruitment and Screening

Participants will be identified by the clinical team at each centre via a search of the patient database/s either electronically or manually or clinic list review to find potentially eligible patients. At the routine clinic visit, the patient will be asked whether they would be willing to participate in the study. A Patient Information Sheet and instructions on how to proceed if they are interested in taking part or finding out more about the study will be given to the patient. They will be provided with a telephone number to contact the research nurse if they need to discuss or need further information. All patients will be provided with a full explanation of the trial before obtaining informed written consent (see Section 11.3 for the consent procedure) at the screening visit.

The time taken from initial contact and provision of information to obtaining written consent should be sufficient to enable appropriate discussions with the patient / family about the trial, explanation of the protocol and procedures, and seeking formal consent. Generally this will be a minimum period of 24 hours.

A 'Screening Log' will be maintained of all the patients who undergo screening regardless of whether they decide to participate in the study or are found ineligible to participate. Reasons for not being eligible will be recorded. Reasons for declining to participate will be asked routinely but it will be made clear that they do not have to provide a reason unless happy to do so.

6.2 Screening Visit

The screening visit of potentially eligible participants will take place following informed consent to participate. Informed consent can also be taken at the screening visit, just prior to assessments. If taken prior to the screening visit, then the screening visit should occur within 14 days of informed consent. Patients will be assigned a screening number for use on study documentation until randomisation takes place.

The visit will include:

a. Written informed consent will be obtained from parent/legal guardian or patient (or verification of this if obtained previous to the visit)
b. full medical history
c. assessment of eligibility criteria
d. review of concomitant medication
e. pregnancy test where indicated
f. collection of saliva/blood for FLG phenotyping
g. safety bloods
h. collection of demographic data
i. completion of o-SCORAD
j. consent/assent forms to be submitted to CTRC within 7 days of screening visit

Please note patients who fail screening can be invited for re-screening after 14 days, if it is appropriate to do so.

6.3 Baseline

Baseline visit should be within 2 weeks of the screening visit.

Baseline visit procedure:

a. confirm Informed Consent status
b. assess eligibility
c. review of concomitant medication
d. clinician to conduct physical exam
e. RN to conduct o-SCORAD, EASI and IGA
f. patient to complete POEM
g. parent and child to complete QoL questionnaires
h. height, weight, BP, urine sample collection
i. collection of blood samples and skin tape strips for mechanistic work

6.4 Randomisation and blinding

6.4.1 Randomisation

Participants will be randomised to receive MTX or CyA in a 1:1 ratio at the Baseline Visit once:

1. Eligibility criteria have been fulfilled;
2. Fully informed written consent has been obtained;
3. Baseline assessments have been completed

Participants will be randomised using a secure (24-hour) web based randomisation programme controlled centrally by CTRC.

Randomisation web access: https://ctrc.liv.ac.uk/Randomisation/Treat

If there are problems with web randomisation, please contact the trial coordinator

(Note that the CTRC is open from 0900 – 1700, Monday – Friday, excluding public holidays)

Randomisation backup envelopes will be used in case of failure of the randomisation systems outside CTRC working hours.

Research staff will be trained to use the randomisation system and will be added to the trial delegation log and authorised to carry out this role. Following this (and the green light for their site), they will be issued with usernames and passwords to access the system.

In the event of a randomisation system failure, the centre should contact the trial coordinator at CTRC (Monday to Friday between 9:00 to 17:00 excluding bank holidays) to try to resolve the problem.

Centres will be provided with emergency back-up randomisation envelopes to be used in the event of a system failure that occurs outside CTRC office hours or when a system failure cannot be resolved in a reasonable timeframe. In the event that emergency back-up

envelopes are required, the randomising person will select the next sequentially numbered, opaque, pressure-sealed envelope that will give the randomisation allocation. The envelope will be similar to those used for pay slips, which cannot be viewed without fully opening and their construction is resistant to accidental damage or tampering. Page 1 of the randomisation envelope containing information on the allocation should be returned to the coordinating centre in a pre-paid envelope, and pages 2 & 3 of the randomisation envelope should be inserted into the patient's medical records.

The research staff will check to ensure that the correct number of randomisation envelopes is present, that they are intact and that the sequential numbering system is maintained. Any discrepancies should be immediately reported to the CTRC.

6.4.2 Blinding

As the trial interventions are at different frequencies (daily vs once weekly), have rather different side effect profiles and since no placebo is used as part of the study, blinding of the local investigator and research nurse will not be possible. However, the research nurses who will perform the severity assessments will be blinded to the trial allocation. The following steps are in place to ensure blinding is maintained:

-All severity assessments will be conducted by an independent research nurse, who has no other contact with the trial participants
- Participants will be reminded in their study visits not to mention the treatment they are on to the independent research nurses
- The research nurses will wear a badge at the severity assessment, reminding participants not to mention what treatment they are on
- All questions relating to the acceptability and use of the trial drugs will be completed in a patient diary that will be returned to the study research nurse
- Dispensing of study drugs will be completely independent from the assessing research nurses

Following each severity assessment, the independent research nurse will be asked whether they had become unblinded to the allocation and this information will be recorded in the Case Report Form. If the research nurse does become unblinded, this will be used to inform a sensitivity analysis.

Whilst it will not be possible to blind participants to their treatment allocation either, efforts will be made to minimise expectation bias by emphasising in the trial literature that there is currently no strong evidence favouring either drug choice in severe atopic eczema in children.

6.5 Patient Transfer and Withdrawal

Follow-up of patients who transfer or withdraw will be continued through the trial Research Nurses, the lead investigator at each centre and, where these are unsuccessful, through the child's GP, unless the participant explicitly also withdraws consent for follow-up.

6.5.1 Patient Transfers

For patients moving from the area, every effort should be made for the patient to be followed-up at another participating trial centre and for this trial centre to take over responsibility for the patient or for follow-up via GP.

A copy of the patient CRFs should be provided to the new site. The patient (or parent/legal representative) will have to sign a new consent form at the new site, and until this occurs, the patient remains the responsibility of the original centre. The CTRC should be notified in writing of patient transfers.

6.5.2 Withdrawal from Trial Intervention

Patients will be withdrawn from treatment for any of the following reasons:

a. Parent/ legal representative (or, where applicable, the patient) withdraws consent.
b. Unacceptable toxicity based on investigator's judgement
c. Development of illness preventing further treatment.
d. Any change in the patient's condition that justifies the discontinuation of treatment in the clinician's opinion.

If a patient wishes to withdraw from trial treatment, centres should nevertheless explain the importance of remaining on trial follow-up, or failing this, of allowing routine follow-up data to be used for trial purposes. Generally, follow-up will continue unless the patient explicitly also withdraws consent for follow-up (see section 6.5.3).

6.5.3 Withdrawal from Trial Completely

Patients are free to withdraw consent at any time without providing a reason. In consenting to the trial, patients are consented to trial treatment, trial procedures, follow-up phase after treatment cessation and data collection. If voluntary withdrawal occurs, the patient (or parent/legal representative, where applicable) should be asked to allow continuation of scheduled evaluations, complete an end-of-study evaluation and be given appropriate care under medical supervision until the symptoms of any adverse event resolve or the subject's condition becomes stable. If consent is withdrawn completely then the reasons for withdrawal of consent will be collected (if possible) and reported for both groups. Participants who wish to withdraw consent for the trial will have anonymised data collected up to the point of that withdrawal of consent included in the analyses unless the patient explicitly states that this is not their wish. The patient will not contribute further data to the study, and the CTRC should be informed in writing by the responsible physician and a withdrawal CRF should be completed.

7 TRIAL TREATMENTS

7.1 Introduction

Table 1:Investigational Medicinal Products (IMPS) and Approved Formulations

Arm	IMPs	Formulations
CyA	Ciclosporin	Brand: Neoral® Capsules: 10mg, 25mg, 50mg, 100mg
MTX	Methotrexate	Brand: any brand with marketing authorisation within EEA Tablets: 2.5mg
	Methotrexate	Brand: any brand with marketing authorisation within EEA Injection: 50mg/ml prefilled pen

Please note that folic acid (for those randomised to methotrexate) is classed as non-investigational medicinal product (NIMP) in this trial. The product should be dispensed by pharmacies in accordance to standard clinical practice.

Oral liquid preparations of ciclosporin and methotrexate that offer an important option for children who are unable to swallow the oral solid formulations are planned for evaluation. Currently, only ciclosporin is available as a licensed product, with a licensed preparation of methotrexate oral solution becoming available in the UK in the next few months. These oral liquid preparations will be reflected in a protocol amendment which will be submitted for approval prior to recruiting children who are unable to swallow tablets/capsules.

The provision of both IMPs and NIMPs is the responsibility of each individual participating site in accordance with standard purchasing arrangement (see pharmacy guideline for the ordering of methotrexate oral solution). Both IMPs and NIMPs used in this trial are not provided free of charge from the sponsor, as they are considered an NHS treatment cost.

The drug dosing for MTX and CyA as well as the frequency of the study visits and safety assessments, including safety bloods, are in keeping with SmPC guidance and the American Academy of Dermatology guidelines for the use of systemic immuno-suppressive therapy in children and young people with severe atopic eczema (27) (see Section 80, page 39).

Also in keeping with the SmPC guidance, as a safety measure some patients may require a chest x-ray at the screening visit at the discretion of the Principal Investigator. Such patients are those who are at high risk of tuberculosis (TB) (recent travel to a country where TB is common or have been in contact with someone who has active TB). The patient will need to have a radiology report of clear/normal chest X-ray, before randomisation occurs. If the patient has an abnormal radiology report they will not be eligible to be randomised.
Countries where TB is common can be found at the following link: https://www.gov.uk/tb-test-visa/countries-where-you-need-a-tb-test-to-enter-the-uk

7.2 Arm A - Ciclosporin

7.2.1 Ciclosporin - Formulation, Packaging, Labelling, Storage and Stability

Table 2: Ciclosporin approved formulation

Arm	IMP	Formulation
CyA	Ciclosporin	Brand: Neoral® Capsules: 10mg, 25mg, 50mg, 100mg

The Sponsor will provide MHRA approved regulatory compliant IMP labels for the trial; these should be kept in the Pharmacy File until the point of dispensing. Please contact the CTRC for further supplies of trial labels or request a pdf file of the label for local printing in an appropriate label format. The subject randomisation number and name of investigator should be recorded on the trial label at dispensing.

Refer to the relevant SmPC for information on storage requirements.

Temperature monitoring should be in line with local requirements for general medicine supplies held in Pharmacy.

7.2.2 Preparation, Dosage and Administration of Study Treatment/s

Table 3: Ciclosporin capsules

	Ciclosporin capsules - Neoral® brand only
Dose	2mg/kg (total: 4mg/kg/day) (rounded to the nearest whole capsule where applicable)
Frequency	Twice daily
Duration	36 weeks
Route	Oral
Notes	Advise participants to avoid grapefruit juice

7.2.3 Ciclosporin - Dose Modifications

Patients should remain on the full treatment dose (4mg/kg/day for CyA) for the 8 weeks. After that, dose increases to a maximum of 5mg/kg/day or dose decreases are allowed, according to the treatment response. For decisions on treatment continuation, PIs should refer to the table below. For situations not included in the below table, this is down to the individual study centre PI and any dose changes will be recorded in the CRF.

Table 4: Dose modification schedule

Monitoring parameters	Values	Action
eGFR	Fall of >=20%	Discuss with trial nephrologist
Blood pressure	>95th centile for age and sex on two consecutive visits	CyA dose adjustment, reduction by 20% initially and patient review with repeat BP after a fortnight
Liver function test	AST, ALT or alkaline	CyA dose adjustment

	phosphatase more than 2× upper limit of reference range	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	CyA 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	CyA 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 CyA

Treatments may be suspended for clinical reasons. However, this can only be for up to a maximum cumulative period of 4 weeks throughout the duration of the protocol treatment phase. Patients requiring intermittent or continuous suspension of treatment for a cumulative period longer than 4 weeks will be considered a treatment failure and should discontinue trial treatment. Patients who discontinue trial treatment should be asked to continue with study assessments.

Occasional monitoring of ciclosporin blood levels is recommended eg. when Neoral is co-administered with medicines that are known to interact with ciclosporin or where the patient is not responding to the therapy. This will be assessed by the local investigator on a per patient basis and put in place where deemed clinically appropriate.

7.3 Arm B - Methotrexate

7.3.1 Methotrexate - Formulation, Packaging, Labelling, Storage and Stability

Table 5: Methotrexate approved formulations

Arm	IMPs	Formulations
MTX	Methotrexate	Brand: any brand with marketing authorisation within EEA Tablets: 2.5mg
	Methotrexate	Brand: any brand with marketing authorisation within EEA Injection: 50mg/ml prefilled pen

The Sponsor will provide MHRA approved regulatory compliant IMP labels for the trial; these should be kept in the Pharmacy File until the point of dispensing. Please contact the CTRC for further supplies of trial labels or request a pdf file of the label for local printing in an appropriate label format. The subject trial number and name of investigator should be recorded on the trial label at dispensing.

Refer to the relevant SmPC for information on storage requirements for methotrexate tablets.

Temperature monitoring should be in line with local requirements for general medicine supplies held in Pharmacy.

7.3.2 Methotrexate - Preparation, Dosage and Administration of Study Treatment/s

Table 6: Methotrexate tablets/ subcutaneous injection

<table>
<tr><th></th><th>Methotrexate tablets / subcutaneous injection</th></tr>
<tr><td>Dose</td><td>Initial dose of 0.1mg/kg/week, then 0.4mg/kg/week (maximum 25mg/week)
Where applicable, doses should be rounded to the nearest whole tablet as follows:
<table>
<tr><th>Weight band</th><th>0.1mg/kg test dose</th><th>0.4mg/kg dose</th></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>
<tr><td></td><td></td><td></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>
<tr><td>Note</td><td>The methotrexate dosing regimen reflects current clinical practice across European paediatric dermatology departments (based on TREAT survey among >300 paediatric dermatologists from 8 European countries)(6). It is also</td></tr>
</table>

	in keeping with the British National Formulary guidance for the treatment of severe cutaneous inflammatory disease in children (19), and that of the American Academy of Dermatology for severe paediatric eczema (27). It is acknowledged that extra precaution is necessary when prescribing and dispensing methotrexate and the following additional measures as listed below should be implemented for this trial in line with standard clinical care: - The child and their parents/carers must be carefully advised of the dose and frequency and the reason for taking methotrexate and folic acid at each visit. - Only the 2.5mg strength of methotrexate tablet will be prescribed and dispensed. - The prescription and the dispensing label will clearly show the dose and frequency of methotrexate administration. - The child and their parents/carers will be provided with a methotrexate drug monitoring booklet which will provide additional supporting information on dose, frequency and adverse effects monitoring.

7.3.3 Methotrexate - Dose Modifications

Patients should remain on the full treatment dose (0.4mg/kg/week for MTX – maximum dose of 25mg/week) for the 8 weeks. After that, dose modifications are allowed, according to the treatment response (maximum dose of 25mg/week). For decisions on treatment continuation, PIs should refer to the table below. For situations not included in the below table, this is down to the individual study centre PI and any dose changes will be recorded in the CRF.

Table 7: Methotrexate dose modification schedule

Monitoring parameters	Values	Action
eGFR	Fall of >=20%	Discuss with trial nephrologist
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

The MTX dose/route should remain within the trial parameters (0.4mg/kg/week, maximum dose of 25mg/week/patient) for the first two months on the therapeutic dose. A dose increase is acceptable for growth (at same dose/kg as at trial entry).

Methotrexate treatment may be suspended for clinical reasons. However, this can only be for up to a maximum cumulative period of 4 weeks throughout the duration of the protocol treatment phase. Patients requiring intermittent or continuous suspension of methotrexate treatment for a cumulative period longer than 4 weeks will be considered a treatment failure and should discontinue trial treatment. Patients who discontinue trial treatment should be asked to continue with study assessments.

7.4 Unblinding

Unblinding is not applicable as PIs, RNs and pharmacists will be aware of treatment allocation. Subjects will not be blinded to the treatment allocation either, as there is no placebo and both treatments are given at different frequencies (daily vs weekly).

The research nurse who carries out the severity assessment will be blinded to the trial allocation.

7.5 Accountability Procedures for Study Treatments

All IMP is to be sourced via usual NHS procurement arrangements. The research team will liaise with the local pharmacy department to ensure that the site has enough of the IMP in stock with appropriate shelf life to be used in the study.

Responsible site personnel must maintain accurate accountability records of the IMP dispensed, including details of the manufacturer, name, form, strength, batch number, expiry date and quantity, to whom dispensed and date of transaction. Local procedures should be used if the manufacturer issues a recall.

7.6 Assessment of Compliance with Study Treatment/s

Patients should be instructed to return any unused IMPs.

Accountability Log provides space to record IMP supplies returned by trial patients before destruction. Returned or unused IMP doses should be disposed/destroyed on an ongoing basis according to local policy.

7.7 Concomitant Medications/Treatments

A concomitant medication/treatment is any drug or substance administered between the screening visit and the visit at week 60. All such medications should be reported to the investigator and recorded on the Concomitant Medications CRF.

7.7.1 Medications Permitted

It is expected that all trial participants will be on concomitant topical therapy for their atopic eczema, in particular regular emollients but also (antiseptic) bath additives and mild-to-potent topical corticosteroids (TCS) of the patient's/local investigator's choice. Topical calcineurin inhibitors and oral antihistamines and antibiotics as well as rescue oral corticosteroids are also permitted.

Any medication required for any ongoing illness (illnesses not listed in the exclusion criteria in section 5.2), birth contraception and any rescue medications will also be permitted and recorded both during the treatment and follow up period.

The following are also permitted medications:

- Oral contraceptives or hormone-replacement therapy
- Maintenance therapy for other medical conditions listed in the patients' medical history at the time of screening
- Medications for the treatment of asthma which may include but are not limited to inhaled therapies, such as corticosteroids, short acting bronchodilators, combination corticosteroids/long acting bronchodilators, and oral therapies (eg montelukast, theophylline)
- Intranasal corticosteroids used for the treatment of allergic rhinitis
- Medications such as paracetamol and non-steroidal anti-inflammatory drugs (eg ibuprofen) and routinely-taken dietary supplements, including vitamins, are allowed at the discretion of the local PI and provided that the medication in question has no discernible impact on the study
- Fixed regimen of psychiatric medications, including but not limited to tricyclic antidepressants, serotonin reuptake inhibitors, or benzodiazepines
- Antiviral medications to treat non-systemic *Herpes simplex* virus (eg acyclovir for cold sores or herpes zoster).
- Inactivated vaccine
- Antibiotics for treatment of atopic eczema-related skin infections, unless specified in the protocol

Female patients who have attained menarche will undergo a pregnancy test at the screening visit. They will be counselled against pregnancy during the course of treatment, and will be advised to use contraceptive measures if appropriate.

7.7.2 Medications Not Permitted/ Precautions Required

The local investigator should instruct the patients and their parents/caregivers to notify the study site about any new medications he/she takes after the start of the study drug.

The following therapies are prohibited during the study **for all patients**:

- Use of wet wraps or other occlusive dressings

- Concomitant systemic anti-inflammatory or immunosuppressant medication, including but not limited to azathioprine and mycophenolate mofetil
- Phototherapy or tanning booth/parlour
- Allergen immunotherapy
- Biologic agents
- Live vaccines 4 weeks prior to baseline, while in the study, and for 12 weeks following the last dose of study drug.

Patients who discontinue the study drug due to the use of one of the above should be asked to continue with study assessments.

Patients who use any of the following therapies during the study should not be discontinued from study drug and should not be withdrawn from the study. The investigator must enter the therapies into the concomitant medications CRF. The investigator should contact the trial coordinator (who will contact the Chief Investigator) if questions arise regarding the safety risks associated with continuing study drug.

- Antibiotics for treatment of atopic eczema-related skin infections, unless specified in the protocol
- Other/alternative therapies which may include, but is not limited, to acupuncture, phytotherapy, and herbal substances used for the treatment of atopic eczema. The investigator should ask the patient to stop these therapies for the remainder of the study if in their opinion it is safe to do so.
- Patients are advised to avoid self-medication with over the counter ibuprofen if on the methotrexate arm of the study due to the potential interaction between the two medicines. Patients are instead advised to take paracetamol. If accidental use of over the counter ibuprofen occurs, this will not lead to the withdrawal of the patient from the study drug or trial, and clinicians are advised to monitor closely in line with current practice.

7.7.2.1 Those randomised to ciclosporin

Ciclosporin is extensively metabolised by CYP 3A isoenzymes, in particular CYP3A4, and is a substrate of the multidrug efflux transporter P-glycoprotein. Various drugs are known to either increase or decrease plasma or whole blood concentrations of ciclosporin.

Treatment with the following concomitant medications is prohibited during the study:
- Bosentan
- Dabigatran etexilate
- Aliskiren
- Hypericum perforatum (St. John's wort)
- Tacrolimus (except for topical treatment – see section 7.7.1)
- Everolimus and sirolimus
- Lercanidipine
- Treatment with a live (attenuated) vaccine

Other drugs known to interact with ciclosporin may be prescribed at the discretion of the local Investigator when considered necessary for the patient's safety and well being. If drugs are given concomitantly, careful monitoring for drug-related adverse effects is recommended

in line with clinical practice. Investigators should refer to the SmPC for further information, and the following points should be considered:

Drugs that decrease ciclosporin concentration include:

- Barbiturates (e.g. Phenobarbital), carbamazepine, oxcarbazepine, phenytoin; nafcillin, intravenous sulfadimidine, probucol, orlistat, ticlopidine, sulfinpyrazone, terbinafine, rifampicin, octerotide.

Drugs that increase ciclosporin concentration include:

- Nicardipine, metoclopramide, oral contraceptives, methylprednisolone (high dose), allopurinol, cholic acid and derivatives, protease inhibitors, imatinib, colchicine, nefazodone.
- Macrolide antibiotics: azithromycin, clarithromycin,
- Erythromycin (Note: Erythromycin may be used as rescue medicine but it should not be used for longer than two weeks in the trial).
- Azole antibiotics: Ketoconazole, fluconazole, itraconazole and voriconazole
- Verapamil
- Telaprevir
- Amiodarone
- Danazol
- Diliazem
- Imatinib

Care should also be taken when using ciclosporin together with other active substances that exhibit nephrotoxic synergy such as: aminoglycosides (including gentamycin, tobramycin), amphotericin B, ciprofloxacin, vancomycin, trimethoprim (+ sulfamethoxazole); fibric acid derivatives (e.g. bezafibrate, fenofibrate); NSAIDs (including diclofenac, naproxen, sulindac); melphalan histamine H_2-receptor antagonists (e.g. cimetidine, ranitidine); methotrexate.

Ciclosporin is also an inhibitor of CYP3A4, the multidrug efflux transporter P-glycoprotein and organic anion transporter proteins (OATP) and may increase plasma levels of co-medications that are substrates of this enzyme and/or transporters. Ciclosporin may reduce the clearance of digoxin, *colchicine, statins, etoposide* prednisolone, non-steroidal anti-inflammatory drugs (NSAIDs), and others.

7.7.2.2 Those randomised to methotrexate

Drugs known to interact with methotrexate may be prescribed at the discretion of the local Investigator when considered necessary for the patient's safety and well being. If drugs are given concomitantly, careful monitoring for drug-related adverse effects is recommended in line with clinical practice. Investigators should refer to the SmPC for further information, and the following points should be considered:

- Concomitant use of hepatotoxic medicinal products
- Concomitant use of haemataotic medicinal products
- Oral antibiotics like tetracyclines, chloramphenicol, and non-absorbable broad-spectrum antibiotics can interfere with the enterohepatic circulation, by inhibition of the intestinal flora or suppression of the bacterial metabolism
- Antibiotics, like penicillines, glycopeptides, sulfonamides, ciprofloxacin and cefalotin can, in individual cases, reduce the renal clearance of methotrexate
- Methotrexate is plasma protein bound and may be displaced by other protein bound drugs such as salicylates, hypoglycaemics, diuretics, sulphonamides, diphenylhydantoins, tetracyclines, chloramphenicol and p-aminobenzoic acid, and the

acidic anti-inflammatory agents, which can lead to increased toxicity when used concurrently.

- Probenecid, weak organic acids such as loop diuretics, and pyrazoles (phenylbutazone) can reduce the elimination of methotrexate
- The concomitant administration of products which cause folate deficiency (e.g. sulphonamides, trimethoprim-sulphamethoxazole) can lead to increased methotrexate toxicity.
- Vitamin preparations or other products containing folic acid, folinic acid or their derivatives may decrease the effectiveness of methotrexate.
- Concomitant use of mercaptopurine
- Concomitant administration of proton-pump inhibitors like omeprazole or pantoprazole may delay clearance of methotrexate.
- Methotrexate may decrease the clearance of theophylline
- Combined treatment with methotrexate and retinoids like acitretin or etretinate increases the risk of hepatotoxicity

For any other medication in question, the local investigator should consult the prescribing information (Summary of product characteristics: www.medicines.org.uk/emc/).The trial coordinator should be contacted (who will contact the study CI) to ensure that there are no safety risks associated with continuing study drug.

7.7.3 Data on Concomitant Medication

All concomitant medication must be recorded on the subject's CRF, according to instructions for CRF completion.

7.8 Co-enrolment Guidelines

To avoid potentially confounding issues, ideally patients should not be recruited into other trials. Individuals who have participated in a trial testing a medicinal product within 28 days or less than 5 half lives of the IMP preceding screening will be ineligible for the TREAT trial. Where recruitment into another trial is considered to be appropriate and without having any detrimental effect on the TREAT trial, this must first be discussed with the CTRC who will contact the Chief Investigator Dr Carsten Flohr.

8 ASSESSMENTS AND PROCEDURES

8.1 Schedule for assessments during the treatment and the follow-up phase

The total duration of the study is for 60 weeks. Patients will receive IMP for 36 weeks and then will be followed-up for 24 weeks. The below interventions will take place according to the study visit schedule table at the stated time points. However, the following visit windows are allowed: 2 days +/- at week 1 and 2, 1 week +/- at week 4, and then 2 weeks +/- thereafter. Deviations from this schedule need to be discussed with the CI.

Table 8: Schedule of study procedures

Procedures	Screen	Week 0 Baseline/ Randomisation	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
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
Demographics	x											
Physical exam (including mouth/throat examination and chest auscultation)		x	X	X	X	X	X	X	X	X	X	X
o-SCORAD (nurse-assessed)	x	x			x	x	x	X	X	x	x	x
EASI, IGA (nurse-assessed)		x			x	x	x	X	X	x	x	x
POEM (patient assessed)		x			x	x	x	X	X	x	x	x
Parent and child QoL		x					x			x	x	x
Height & weight		x		x			x			x		x
Blood pressure		x		x	x	x	x	X	X	x		x
Adverse events (AE & SAE)**			x	x	x	x	x	X	X	x		
Safety bloods***	X****		x	x	X****	x	x	X	X	x		x
Chest X-Ray*****	x											
Pregnancy test (beta-HCG)	x											
Urine sample collection (NAG)		x		x			x			x		x
Randomisation		x										
Study drug dispensing (4 weeks supply at week 0, then further supply as needed at each subsequent visit)		x			x	x	x	X	X			
MTX metabolite level (blood)				x		x	x			x		
CyA trough level (blood)******				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		x					x			x		x
Collection of blood for mechanistic studies		x					x			x		x
Collection of /saliva blood for FLG genotyping	x											

*Week 1 visit only for Methotrexate arm

** Collect until 4 weeks after treatment stopped (ie. until week 40)

Safety bloods includes assessment of liver function, renal function and full blood count*Lipids to also be assessed at these time points as part of safety bloods

*****Screening chest X-Ray on discretion of the local PI in those at risk of TB

******Collection of blood for ciclosporin levels should be measured in the morning, 12 hours (+/-30 minutes) 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. 0730 and 1930), 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.

8.1.1 Assessments:

a. Children will be assessed by trained research nurses at 0, 4, 8, 12, 20,28, 36, 48 and 60 weeks (o-SCORAD, EASI, & IGA). POEM will be completed by the patient/parent.
b. The number of flares, side effects and adverse events during treatment will be captured through questionnaires administered by the research nurses and through a diary collected by the patient or parent/guardian.
c. Child and parental QoL will be assessed at baseline, 12, 36, 48 and 60 weeks.
d. Blood for drug metabolite/trough levels will be taken at 2, 8, 12, 36 weeks.
e. Blood and tape strips for mechanistic work will be taken at baseline, 12, 36, and 60 weeks.
f. A saliva sample will be collected at the week 1 visit for filaggrin analysis. If a saliva sample cannot be collected a blood sample will be used for this analysis.
g. AE and SAE data will be collected up to week 40.

8.1.2 Visit Summary

The following provides the activities to be completed at each visit:

Screening visit

- Informed consent
- Inclusion/exclusion criteria
- Medical history
- Concomitant drugs
- Demographics
- o-SCORAD (nurse assessed)
- Safety bloods*
- Pregnancy test for females of child bearing potential
- Collection of saliva/blood for FLG genotyping
- Chest X-Ray in those at risk of TB (discretion of local PI)

*Lipid assessment will occur as part of safety bloods at this time point.

Baseline/randomisation visit – Week 0

- Inclusion/exclusion criteria
- Concomitant drugs
- Physical exam
- o-SCORAD (nurse assessed)
- EASI, IGA (nurse assessed)
- POEM (patient assessed)
- Parent & child QoL
- Height & weight
- Blood pressure
- Urine sample collection (NAG)

- Randomisation
- Study drug dispensing- 4 weeks supply
- Blood sample for cystatin C level and creatinine level
- Tape stripping for cutaneous metabolic work
- Collection of blood for mechanistic studies

Visit 1 – Week 1 (only for methotrexate arm)

- Safety bloods
- Adverse events
- Concomitant medications
- Physical examination

Visit 2 – Week 2

- Concomitant drugs
- Height & weight
- Blood pressure
- Adverse events (AE & SAE)
- Safety bloods
- Urine sample collection (NAG)
- Collection of blood for MTX/CyA metabolite/trough levels, cystatin C level and creatinine level

Visit 3 – Week 4

- Concomitant drugs
- o-SCORAD (nurse assessed)
- EASI, IGA (nurse assessed)
- POEM (patient assessed)
- Blood pressure
- Adverse events (AE & SAE)
- Safety bloods
- Study drug dispensing

*Lipid assessment will occur as part of safety bloods at this time point.

Visit 4 – Week 8

- Concomitant drugs
- o-SCORAD (nurse assessed)

- EASI, IGA (nurse assessed)
- POEM (patient assessed)
- Blood pressure
- Adverse events (AE & SAE)
- Safety bloods*
- Study drug dispensing
- Collection of blood for MTX/CyA metabolite/trough levels, cystatin C level and creatinine level

Visit 5 – Week 12

- Concomitant drugs
- o-SCORAD (nurse assessed)
- EASI, IGA (nurse assessed)
- POEM (patient assessed)
- Parent & child QoL
- Height & weight
- Blood pressure
- Adverse events (AE & SAE)
- Safety bloods
- Urine sample collection (NAG)
- Study drug dispensing
- Collection of blood for MTX/CyA metabolite/trough levels, cystatin C level and creatinine level
- Tape stripping for cutaneous metabolic work
- Collection of blood for mechanistic studies

Visit 6 – Week 20

- Concomitant drugs
- o-SCORAD (nurse assessed)
- EASI, IGA (nurse assessed)
- POEM (patient assessed)
- Blood pressure
- Adverse events (AE & SAE)
- Safety bloods
- Study drug dispensing

Visit 7 – Week 28

- Concomitant drugs
- o-SCORAD (nurse assessed)
- EASI, IGA (nurse assessed)
- POEM (patient assessed)
- Blood pressure
- Adverse events (AE & SAE)
- Safety bloods
- Study drug dispensing

Visit 8 – Week 36

- Concomitant drugs
- o-SCORAD (nurse assessed)
- EASI, IGA (nurse assessed)
- POEM (patient assessed)
- Parent & child QoL
- Height & weight
- Blood pressure
- Adverse events (AE & SAE)
- Safety bloods
- Urine sample collection (NAG)
- Collection of blood for MTX/CyA metabolite/trough levels, Cystatin C level and Creatinine level
- Tape stripping for cutaneous metabolic work
- Collection of blood for mechanistic studies

Visit 9 – Week 48

- Concomitant drugs
- o-SCORAD (nurse assessed)
- EASI, IGA (nurse assessed)
- POEM (patient assessed)
- Parent & child QoL

Visit 10 – Week 60

- Concomitant drugs
- o-SCORAD (nurse assessed)
- EASI, IGA (nurse assessed)

- POEM (patient assessed)
- Parent & child QoL
- Height & weight
- Blood pressure
- Safety bloods
- Urine sample collection (NAG)
- Collection of blood for Cystatin C level and Creatinine level
- Tape stripping for cutaneous metabolic work
- Collection of blood for mechanistic studies

Patient Diary

All participants will be asked to complete a diary during treatment. The diary will ask participants to record how often they have taken the study medication and if they have experienced any side effects. The diary will also include POEM, questions on flares and use of medications for eczema. On a monthly basis, there will be questions to find out if it has been necessary to see a health care professional, whether antibiotic creams or tablets were prescribed for a skin infection and whether any time off nursery or school was required.

8.2 Procedures for Assessing Efficacy

Efficacy of trial treatments will be assessed throughout the period of the study using objective measures.

The first co-primary outcome measure for the trial is change in atopic eczema severity between baseline and 12 weeks of treatment, using the objective SCORing Atopic Dermatitis (o-SCORAD) severity index, conducted by the research nurse at baseline and at 12 weeks.

The second co-primary outcome is the time to first flare during the 24 weeks after treatment cessation in the MTX vs CyA groups. The number of flares will be recorded in questionnaires.

The secondary outcome of change in atopic eczema severity using the o-SCORAD, EASI, IGA and Patient Oriented Eczema Measure (POEM) scores will be assessed between baseline and 12, 36, 48, 60 weeks.

8.3 Procedures for Assessing Safety

The following safety bloods and investigations will be performed:

a. Safety blood profiles (full blood count, renal function and liver function) will be taken at screening, 2, 4, 8, 12, 20, 28, 36 and 60 weeks. Lipids will also be assessed at baseline and week 4 as part of the safety blood profile. Safety bloods will also be taken at week 1 for the methotrexate arm.
b. BP will be taken at baseline, 2, 4, 8, 12, 20, 28, 36 and 60 weeks
c. Markers of renal function and tubular damage, including plasma creatinine and cystatin C (baseline, 2, 8, 12, 36 and 60)
d. Urinary tubular N-acetyl-beta-D-glucosaminidase (at baseline, 2, 12, 36 and 60)
e. Chest X-Ray in those at risk of TB (discretion of local PI) at screening visit
f. Physical examination will be carried out at each visit.

An Independent Data and Safety Monitoring Committee (IDSMC) will be constituted and will monitor adverse events and patient safety during the trial. Data on adverse events, including severity, seriousness, and expectedness as part of pharmacovigilance will be recorded at each follow-up visit and communicated to the CTRC. Requirements for pharmacovigilance reporting is detailed fully in Section 10 (Pharmacovigilance).

8.4 Other Assessments

8.4.1 Quality of Life and Health Economics

Quality of life assessments of the patient and family will be conducted via paper-based questionnaires and quality of life sheets to the patients and carers. If necessary the RN/member of the research team will provide guidance on how to complete the questionnaires and will collect them from the patients and carers at the end of the study visits. Similarly, information relating to the health economic evaluation, such as GP visits and attendance at other healthcare professionals due to their eczema, will also be gathered via a paper based participant completed diary. The diary will also record whether medications were required to treat a skin infection and whether the participant has required time off school or nursery due to their eczema.

We will assess the cost effectiveness of both medications (methotrexate vs ciclosporin) over the 9 months treatment and 6 months follow up periods, comparing the severity outcomes (objective SCORAD and POEM) and costs in the MTX vs CyA group. This will include the drug treatment costs, the cost of GP consultations & hospital admissions. We are also collecting data on GP prescriptions for topical eczema treatments.

Costs will be estimated using national unit costs. Incremental cost-effectiveness will be assessed by estimating the cost per unit change in SCORAD and patient-orientated eczema measure. These can be compared with estimates from other interventions which have been evaluated using these outcomes.

However, there is no straightforward means of assessing what cost/unit change represents a good use of NHS resources. A cost-utility study which provided a cost/QALY gained would be more interpretable. Two approaches to estimating QALYs will be explored, one using a condition-specific preference-based measure and another using a generic paediatric preference-based measure.

8.4.2 Special Assays or Procedures

Blood sample collection

The following blood samples will be collected for mechanistic work at weeks 0 (baseline), 12, 36 and 60 using standard phlebotomy techniques:

a). 1x 5 ml Z serumSep Clot Activator vacuette tube (gold top) for blood serum

b). 1x remaining blood allowed for immunology (fresh PBMCs) and metabolic work (frozen PBMCs)

Sample transport, processing and storage for mechanistic work:

We aim to collect 15 participant samples per trial arm at each of the four time points (0, 12, 36, and 60 weeks) for the immunology and metabolic work, and we will make use of our own fully established biobanking facilities at Guy's Hospital to process and store samples.

Samples will be transported by courier, ensuring that they are fully processed within 6 hours. The lab work will commence at the end of the third year of the trial and will be performed over a 10-month period by full-time lab technicians in London and Dublin.

Cutaneous tape strip collection:

Round adhesive tape discs (3.8 cm2, D-Squame; CuDerm, Dallas, Tex) will be attached to the skin of the forearm. Each tape will be pressed onto the volar aspect of the forearm for 10 seconds with standardized force by using a disc pressure applicator (CuDerm). The tape strip will be gently removed with tweezers and stored in a closed vial at -80^{o}C until analysis. The first strip will be discarded because it might contain dirt and remnants of cosmetic products; the second, third, and fourth tape strips will be applied on the same skin spot.

Mechanistic studies:

- *Immunological parameters:*

We will study whether significant changes are observed in the percentages of Tregs, in the percentages of pro/anti-inflammatory cytokine-expressing CD4+ T cells, or in the corresponding levels of these cytokines in serum following treatment, whether this is different in MTX vs CyA treated patients, and whether this correlates to response to treatment at 12 and 36 weeks and the risk of re-flares at 60 weeks.

- *Systemic and local metabolic parameters:*

We will examine whether the initial treatment response at 12 weeks to MTX (vs CyA) is already associated with differences in the systemic metabolic profiles (shift from pro-inflammatory 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. We will also study whether the observed systemic metabolic changes are associated with corresponding metabolic profiles and gene expression in the skin.

8.5 Loss to Follow-up

If any of the trial participants are lost to follow up contact will initially be attempted through the PI or designated research staff at each centre. If the lead investigator at the trial centre is not the participant's usual clinician responsible for their specialist care then follow up will also be attempted through this latter clinician. Where these attempts are unsuccessful, the participants GP will be asked to contact the patient or the participants' family to provide follow up information to the recruiting centre.

Where possible, information on the reason for loss to follow up will be recorded.

8.6 Trial Closure

The end of the trial is defined to be the date on which data for all participants is frozen and data entry privileges are withdrawn from the trial database. However, the trial may be closed prematurely by the Trial Steering Committee (TSC), on the recommendation of the Independent Data and Safety Monitoring Committee (IDSMC). Should the trial be closed prematurely, all active participants (receiving treatment or in follow up) will be called in for a final follow up visit and assessments will be undertaken. Ongoing care will be at the discretion of the treating clinician.

9 STATISTICAL CONSIDERATIONS

9.1 Introduction

A separate and full statistical analysis plan (SAP) will be developed prior to the final analysis of the trial. The main features of these planned statistical analyses are included here in the main protocol.

9.2 Method of Randomisation

Participants will be randomised using a secure (24-hour) web-based randomisation programme controlled centrally by the CTRC. Randomisation lists will be generated in a 1:1 ratio using simple block randomisation with random variable block length (see section 6.4 for back-up randomisation method).

9.3 Outcome Measures

9.4 Co-Primary Endpoints

1. Change in atopic eczema severity between baseline and 12 weeks of treatment, using the o-SCORAD index.

2. Time to first flare during the 24 weeks after treatment cessation in the MTX vs CyA groups.

9.5 Secondary Endpoint(s)

1. Change in atopic eczema severity using the EASI, IGA, o-SCORAD and POEM between baseline and 12, 36, 48, and 60 weeks.

2. Number of flares in each study arm as well as the proportion of children who re-flared during the 24 weeks after treatment cessation.

3. Proportion of participants achieving 50% improvement in the o-SCORAD index at 12, 36, 48, and 60 weeks.

4. Proportion of participants who withdraw from treatment because of AEs.

5. Disease-specific patient and parental quality of life (QoL) measured with the CDLQI/IDQOL and DFI scores between baseline and 12, 36, 48 & 60 weeks.

6. Assess the cost-effectiveness of CyA vs MTX, using a cost/QALY analysis.

7. Immuno-metabolic 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.

8. Drug-related side effects of both MTX and CyA and their association with MTX polyglutamate and CyA trough levels.

9. The association between MTX polyglutamate and CyA trough levels and treatment response (reduction in disease severity).

10. The association between FLG carriage (yes/no) and treatment response.

9.6 Sample Size

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 difference of 8 o-SCORAD points, assuming a standard deviation (SD) of 10 (based on the only other paediatric RCT with systemic immunosuppressive medication in children (7), which saw a SD of 6.3 (MTX arm) vs 8.9 (CyA arm) at 12 weeks) 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. Our assumption of 8 Units in the o-SCORAD index representing the minimal clinically important difference between treatments is based on calculations from three other RCTs with immuno-suppressive medication in children and adults with severe atopic eczema (28).

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 the first three months of treatment in the study by Harper et al was three out of 21, indicating that 86% of patients re-flared. 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.

Randomising a total of 102 participants, 51 into each of the study arms, satisfies both sample size calculations.

9.7 Interim Monitoring and Analyses

Formal interim analyses of the accumulating data will be performed at regular intervals (at least annually) for review by an Independent Data Monitoring and Safety Committee (IDSMC). These analyses will be performed at the Clinical Trials Research Centre. The IDSMC will be asked to give advice on whether the accumulated data from the trial, together with results from other relevant trials, justifies continuing recruitment of further patients or further follow-up. A decision to discontinue recruitment, in all patients or in selected subgroups will be made only if the result is likely to convince a broad range of clinicians including participants in the trial and the general clinical community. If a decision is made to continue, the IDSMC will advise on the frequency of future reviews of the data on the basis of accrual and event rates. The IDSMC will make recommendations to the Trial Steering Committee (TSC, see section 16) as to the continuation of the trial.

After the primary outcome data are available from 25 patients (o-SCORAD index at 12 weeks) the standard deviation of the 25 scores, and the 95% confidence limits for this estimate, will be calculated without unblinding 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 TSC 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. EME will decide whether to invite an extension or close the study.

A comprehensive statistical analysis plan will be developed before any formal statistical analyses are carried out.

The primary analysis will use the principle of intention to treat based on all the randomised participants, as far as is practically possible. If consent for treatment is withdrawn but the

participant is happy to remain in the study for follow-up, they will be followed up until completion. However if they decide to withdraw consent completely then the reasons for withdrawal of consent will be collected (if possible) and reported for both groups.

The analysis of change in o-SCORAD from baseline to 12 weeks will use the method of analysis of covariance and the covariates that will be used in the model will be treatment group and the baseline measurement

Analysis of time to first flare will be summarised 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 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 minimise its occurrence. Missing data will be handled by considering the robustness of the complete case analysis to sensitivity analyses using various imputation assumptions; however these will be informed by data collected on the reasons for missing data.

10 PHARMACOVIGILANCE

10.1 Terms and Definitions

The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) definitions:

Adverse Event (AE)
Any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

Adverse Reaction (AR)
Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.

Unexpected Adverse Reaction (UAR)
An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in:
In the case of a product with a marketing authorization, in the summary of product characteristics for that product
In the case of any other investigational medicinal product, in the investigator's brochure relating to the trial in question.

Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)
Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that:

- results in death
- is life-threatening* (subject at immediate risk of death)
- requires in-patient hospitalisation or prolongation of existing hospitalisation**
- results in persistent or significant disability or incapacity, or
- consists of a congenital anomaly or birth defect
- Other important medical events***

*'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.
***Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event/experience when, based upon appropriate medical judgment, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

10.2 Notes on Adverse Event Inclusions and Exclusions

10.2.1 Include

- An exacerbation of a pre-existing illness
- An increase in frequency or intensity of a pre-existing episodic event/condition
- A condition (even though it may have been present prior to the start of the trial) detected after trial drug administration

- Continuous persistent disease or symptoms present at baseline that worsens following the administration of the study/trial treatment
- Laboratory abnormalities that require clinical intervention or further investigation (unless they are associated with an already reported clinical event).
- Abnormalities in physiological testing or physical examination that require further investigation or clinical intervention
- Injury or accidents

10.2.2 Do Not Include

- Medical or surgical procedures- the condition which leads to the procedure is the adverse event
- Pre-existing disease or conditions present before treatment that do not worsen
- Situations where an untoward medical occurrence has occurred e.g. cosmetic elective surgery
- Overdose of medication without signs or symptoms
- The disease being treated or associated symptoms/signs unless more severe than expected for the patient's condition

10.2.3 Reporting of Pregnancy

Females of childbearing potential will be tested for pregnancy as part of the trial screening visit. Any pregnancy that occurs during the study should be reported as a SAE to the CTRC within 24 hours of the site becoming aware of its occurrence and the participant should be instructed immediately to stop taking the study drug. All pregnancies that occur during treatment need to be followed up until after the outcome using the SAE form. Consent to report information regarding these pregnancy outcomes should be obtained from the mother prior to completion and faxing of the SAE form. Any SAE experienced during pregnancy must be reported on the SAE form.

The investigator should contact the participant to discuss the risks of continuing with the pregnancy and the possible effect to the foetus. Appropriate Obstetric care should be arranged.

The CTRC will report all pregnancies to the trial Sponsor, MHRA and MREC.

10.3 Notes Severity / Grading of Adverse Events

The assignment of the severity/grading should be made by the investigator responsible for the care of the participant using the definitions below.
Regardless of the classification of an AE as serious or not, its severity must be assessed according to medical criteria alone using the following categories:

Mild: does not interfere with routine activities
Moderate: interferes with routine activities
Severe: impossible to perform routine activities

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity (see above) whereas seriousness is defined using the criteria in section 10.1, hence, a severe AE need not necessarily be a Serious Adverse Event.

10.4 Relationship to Trial Treatment

The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in table 9.
If any doubt about the causality exists the local investigator should inform the study coordination centre who will notify the Chief Investigator. In the case of discrepant views on causality between the investigator and others, the MHRA will be informed of both points of view.

Table 9: Definitions of Causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship. N.B. An alternative cause for the AE should be given
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possibly	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probably	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Almost certainly	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

10.5 Expectedness

An AE whose causal relationship to the study drug is assessed by the investigator as "possibly", "probably", or "almost certainly" is an Adverse Drug Reaction.

All events judged by the investigator to be possibly, probably, or almost certainly related to the IMP, graded as serious and **unexpected** (see SPC for list of Expected Adverse Events) should be reported as a SUSAR.

10.6 Follow-up After Adverse Events

All adverse events should be followed until satisfactory resolution or until the investigator responsible for the care of the participant deems the event to be chronic or the patient to be stable.
When reporting SAEs and SUSARs the investigator responsible for the care of the participant should apply the following criteria to provide information relating to event outcomes: resolved; resolved with sequelae (specifying with additional narrative); not resolved/ongoing; ongoing at final follow-up; fatal or unknown.

10.7 Reporting Procedures

All adverse events should be reported from randomisation until week 40. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the CTRC in the first instance. A flowchart is given below to aid in determining reporting requirements.

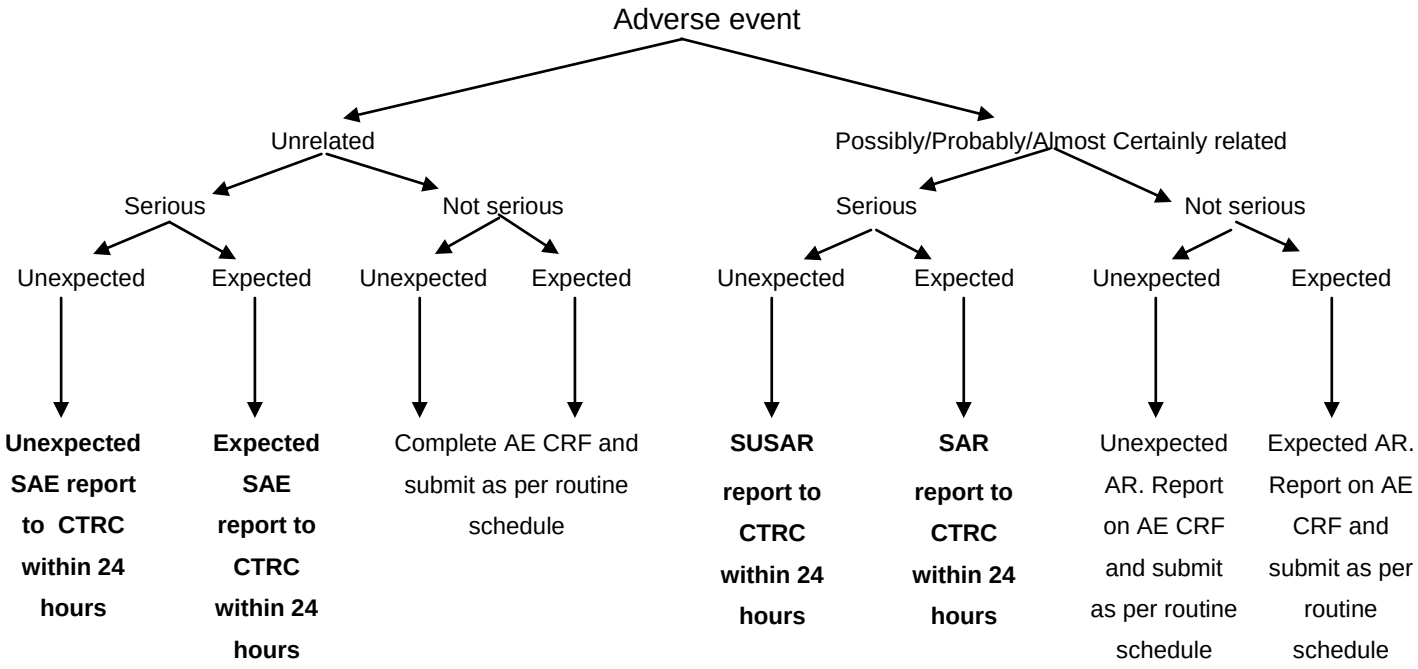
10.7.1 Non serious ARs/AEs

All such events, whether expected or not, should be recorded on an Adverse Event Form, which should be transmitted to the CTRC within seven days of the form being due.

10.7.2 Serious ARs/AEs/SUSARs

SARs, SAEs and SUSARs should be reported to the CTRC within 24 hours of the local site becoming aware of the event. The SAE form asks for the nature of event, date of onset, severity, corrective therapies given, outcome and causality. The responsible investigator should sign the causality of the event. Additional information should be sent within 5 days of the reaction has not resolved at the time of reporting.

The CTRC will pass on any SUSARs to Kings Health Partners Clinical Trials Office (KHP CTO) who will notify the MHRA of all SUSARs occurring during the study.The CTRC will notify the main REC of all SUSARs occurring during the study. The MHRA and main REC will be notified according to the following timelines; fatal and life-threatening within 7 days of notification and non-life threatening within 15 days. All investigators will be informed of all SUSARs occurring throughout the study. Local investigators should report any SUSARs and /or SAEs as required locally.



10.8 Responsibilities – Investigator

The Investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study product.

All SAEs must be reported immediately (but no later than 24 hours) by the investigator to the CTRC on an SAE form unless the SAE is specified in the protocol as not requiring immediate reporting. All other adverse events should be reported on the regular progress/follow-up reports.

Minimum information required for reporting:

- Study identifier
- Study centre
- Patient number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

i. The SAE form should be completed by a designated investigator, a physician named on the 'signature list and delegation of responsibilities log' as responsible for reporting SAEs and making trial related medical decisions. The investigator should assess the SAE for the likelihood that it is a response to the investigational medicinal product. In the absence of the designated investigator the form should be completed and signed by an alternative member of the research site trial team and submitted to the CTRC. As soon as possible thereafter the responsible investigator should check the SAE form, make amendments as appropriate, sign and re-send to the CTRC. The initial report shall be followed by detailed reports as appropriate.

ii. When submitting an SAE to the CTRC research sites should also telephone the appropriate trial co-ordinator/data manager to advise that an SAE report has been submitted.

iii. Send the SAE form by fax (within 24 hours or next working day) to the CTRC

iv. The responsible investigator must **notify** their R&D department of the event (as per standard local governance procedures).

v. In the case of an SAE the subject must be followed-up until clinical recovery is complete and laboratory results have returned to normal, or until the event has stabilised. Follow-up may continue after completion of protocol treatment if necessary.

vi. Follow-up information is noted on another SAE form by ticking the box marked 'follow-up' and faxing to the CTRC as information becomes available. Extra, annotated information and/or copies of test results may be provided separately.

vii. The patient **must** be identified by trial number, date of birth and initials only. The patient's name **should not** be used on any correspondence.

10.8.1 Maintenance of Blinding

Investigators at sites will be aware of participants allocation as are the dermatology research nurses who look at the trial patients on a day-to-day basis. However, the research nurses who will perform the severity assessments will be blinded to the trial allocation.

10.9 Responsibilities – CTRC and KHP CTO

The CTRC is undertaking duties delegated by the trial co-sponsor/s, Guys and St Thomas' Foundation Trust and King's College London and will forward completed SAE reports of SUSARs to KHP CTO. KHP CTO is responsible for the reporting of SUSARs and other SARs to the regulatory authorities (MHRA, competent authorities of other European member states in which the trial is taking place) and, the CTRC is responsible for the reporting to the research ethics committees as follows:

- SUSARs which are fatal or life-threatening must be reported not later than 7 days after the CTRC is first aware of the reaction. Any additional relevant information must be reported within a further 8 days.
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the CTRC first becoming aware of the reaction.
- A list of all SARs (expected and unexpected) must be reported annually.

It is recommended that the following safety issues should also be reported in an expedited fashion:

- An increase in the rate of occurrence or a qualitative change of an expected serious adverse reaction, which is judged to be clinically important;
- Post-study SUSARs that occur after the patient has completed a clinical trial and are notified by the investigator to the sponsor;
- New events related to the conduct of the trial or the development of the IMPs and likely to affect the safety of the subjects, such as:
    a. A SAE which could be associated with the trial procedures and which could modify the conduct of the trial;
    b. A significant hazard to the subject population, such as lack of efficacy of an IMP used for the treatment of a life-threatening disease;
    c. A major safety finding from a newly completed animal study (such as carcinogenicity).
    d. Any anticipated end or temporary halt of a trial for safety reasons and conducted with the same IMP in another country by the same sponsor;
- Recommendations of the Independent Data and Safety Monitoring Committee, if any, where relevant for the safety of the subjects.

Staff at the CTRC will liaise with the Chief Investigator (or designated other specified in the protocol) who will evaluate all SAEs received for seriousness, expectedness and causality. Investigator reports of suspected SARs will be reviewed immediately and those that are SUSARs identified and forwarded to Kings Health Partners Clinical Trials Office for onward reporting to the regulatory authority. The CTRC will be responsible for onward reporting to the MREC of any SUSARs. The causality assessment given by the Local Investigator at the hospital cannot be overruled and in the case of disagreement, both opinions will be provided with the report.

The PIs at all institutions participating in the trial will be notified of any SUSARs.
Patient safety incidents that take place in the course of research should be reported to the National Patient Safety Agency (NPSA) by each participating NHS Trust in accordance with local reporting procedures.

10.9.1 Safety reports

Safety reports will be generated during the course of the trial which allows for monitoring of SAE and ADR reporting rates across sites. The CTRC/KHP CTO will send developmental safety update reports containing a list of all SARs to regulatory authorities and MREC. Any concerns raised by the IDSMC or inconsistencies noted at a given site may prompt

additional training at sites, with the potential for the CTRC/KHP CTO to carry out site visits if there is suspicion of unreported AEs in patient case notes. Additional training will also be provided if unacceptable delay in safety reporting timelines. If any safety reports identify issues that have implications for the safety of trial participants, the PIs at all institutions participating in the trial will be notified.

10.10 Contact Details and Out-of-hours Medical Cover

The patient diary will direct patients to contact the research team at their site should medical advice be required during office hours. If medical advice is required outside of office hours then the participant will be advised to seek usual medical advice. The reviewing physician will be able to make the decision to cease the trial medication if the participant is receiving it at the time.

11 ETHICAL CONSIDERATIONS

11.1 Ethical Considerations

The study will abide by the principles of the World Medical Association Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements, including but not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments.

This protocol and related documents will be submitted for review to the REC, and to the MHRA for Clinical Trial Authorisation.

The Chief Investigator will submit a final report at conclusion of the trial to the KHP-CTO (on behalf of the Sponsor), the REC and the MHRA within the timelines defined in the Regulations.

There are no major ethical issues however the following points have been considered:

- **Study interventions:** Whilst both CyA and MTX have potential side effects, both medications are used in standard NHS practice. Full information about possible risks and benefits of both medications will be provided to parents and participants and data on adverse events will be collected and monitored throughout the trial. In addition, the treatment of severe atopic eczema in participants will not be compromised by participation in the trial. The precise risks and benefits of participating in the study will be outlined in patient information sheets, to be formulated with service user involvement.

- **Blood and other tests:** The risks of taking blood include temporary discomfort from the needle in the arm, bleeding, bruising, swelling at the needle site and, in rare instances, infection. None of the other investigations and procedures, including BP measurement, urine testing, and tape stripping are uncomfortable or harmful.

- **Ongoing treatment after the study has been completed:** All participants will be able to receive further systemic immuno-suppressive therapy via the NHS if required, after the study has been completed.

- **Consent in paediatric population:** Children up to the age of 16 will be eligible for enrolment in the trial and so age-appropriate Participant Information Sheets (PISs) will be prepared in line with current guidelines. Please see section 11.2 for further details.

11.2 Ethical Approval

The trial protocol will not be initiated until it has received the favourable opinion of a Multi-centre Research Ethics Committee (MREC). Subsequent to this, it must also undergo independent review at R&D offices at the R&D offices at participating sites. The local R&D office should be sent the appropriate site specific information form complete with the necessary authorisation signatures, plus any other documentation requested for review. A copy of local Research & Development (R&D) approval should be forwarded to CTRC before the site is initiated and patients recruited.

Children from the age of 2 to 16 will be eligible for enrolment in the trial. Proxy consent from the parent or legally acceptable representative should be obtained prior to each patient participating in the trial, after a full explanation has been given of the treatment options, including the conventional and generally accepted methods of treatment. Age and stage-of development specific Patient Information and Consent Forms (PISC) should also be implemented and patient assent obtained where appropriate. The right of the parent/ legal representative to refuse consent for the minor to participate in the trial without giving reasons must be respected. After the patient has entered the trial, the clinician must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the patient. However, the reason for doing so should be recorded and the patient will remain within the trial for the purpose of follow-up and data analysis. Similarly, the parent/legal representative of the patient remains free to withdraw the patient at any time from the protocol treatment and trial follow-up without giving reasons and without prejudicing the further treatment of the minor.

For children of school age, efforts will be made to arrange appointments outside of school hours whenever possible.

11.3 Informed Consent Process

Informed consent is a process initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. Informed consent is required for all patients participating in CTRC coordinated trials. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki.

Discussion of objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted are to be provided to patients by medically qualified physicians with experience in obtaining informed consent. Where appropriate, age-and-stage-of-development appropriate Patient Information and Consent forms, describing in detail the trial interventions/products, trial procedures and risks will be approved by an independent ethical committee (IEC) and the patient (parent/legal representative in the case of minors) will be asked to read and review the document. Upon reviewing the document, the investigator/medically qualified physician will explain the research study to the patient (parent/legal representative in the case of minors). This information will emphasise that participation in the trial is voluntary and that the participant may withdraw from the trial at any time and for any reason. All participants will be given opportunity to ask any questions that may arise, should have the opportunity to discuss the study with their surrogates and time to consider the information prior to agreeing to participate. A contact point where further information about the trial may be obtained will be provided.

The patient (parent or legal representative in the case of minors) will then sign and date the informed consent document. Both the person taking consent (medically qualified physician on the delegation log) and the participant must personally sign and date the form. A copy of the informed consent document will be given to the patient/their legally acceptable representative for their records. The original copy will be filed in the Investigator Site File,

and a further copy will go in the participants medical notes. One final copy of the consent form should be sent to the CTRC.

Adequate time to consider trial entry (at least 24 hours) will be allowed before written consent of the participants/parent/legal representative will be obtained by the responsible clinician.

The patient may, without being subject to any resulting detriment, withdraw from the trial at any time by revoking the informed consent (Similarly, the parent or legal representative may withdraw a minor under the same conditions). The rights and welfare of the patients will be protected by emphasising to them that the quality of medical care will not be adversely affected if they decline to participate in this study.

11.3.1 Assent in minors

If capable, and under appropriate circumstances, minors should be approached to provide assent by a delegated clinician with experience with minors. Age-and-state-of-development IEC-approved Patient Information Sheet and Assent forms, describing (in simplified terms) the details of the trial intervention/product, trial procedures and risks should be used. The minor should personally write their name and date the assent form, which is then signed by the parent/legal representative and the researcher.

Assent forms do not substitute for the consent form signed by the patient's legally acceptable representative. Assent should be taken where appropriate and documented in the patient notes, however the absence of assent does not exclude the patient provided consent has been obtained from the parent/legal representative.

11.4 Study Discontinuation

In the event that the study is discontinued, it would be possible for patients to continue on the medication prescribed at their site under the NHS, but this would be at the discretion of the clinician responsible for their care.

12 REGULATORY APPROVAL

This trial falls within the remit of the EU Directive 2001/20/EC, transposed into UK law as the UK Statutory Instrument 2004 No 1031: Medicines for Human Use (Clinical Trials) Regulations 2004 as amended. This trial has been registered with the MHRA and has been granted a Clinical Trial Authorisation (CTA).

13 TRIAL MONITORING

Trial monitoring is carried out to ensure that the rights and well-being of human participants are protected during the course of a clinical trial. A risk assessment is performed for each trial coordinated by the CTRC and KHP CTO to determine the level and type of monitoring required for specific hazards. The nature and extent of monitoring will be specific to the individual trial.

Trial Oversight Committees related to the monitoring of the trial are detailed in section 16.

13.1 Risk Assessment

In accordance with the CTRC SOP TM005 this trial is undergoing a risk assessment, to be completed in partnership between:

- Representative/s of the Trial Sponsor
- Chief Investigator
- Trial Coordinator and supervising Trial Manager
- Trial Statistician and supervising Statistician
- Information Systems team
- CTRC Director

Guidance issued by the MRC, Department of Health and the MHRA on risk-adapted approaches to the management of CTIMPs (Ref) propose a three level categorisation for the potential risk associated with the IMP, assigned according to the following categories:

Type A *'no higher than that of standard medical care';*
Type B *'somewhat higher than that of standard medical care';*
Type C *'markedly higher than that of standard medical care'.*

The TREAT trial falls into the second category (Type B). This level of risk informs the risk assessment, regulatory requirements, nature and extent of the monitoring, and the management processes used in the trial.

13.2 Source Documents

Source data*: All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH E6, 1.51).*
Source documents*: Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial). (ICH E6, 1.52).*

In order to resolve possible discrepancies between information appearing in the CRF and any other patient related documents, it is important to know what constitutes the source document and therefore the source data for all information in the CRF. The data that is to be recorded in the CRF should be consistent and verifiable with source data in source documents *other* than the CRF (e.g. medical record, laboratory reports and nurses' notes). For the data where no prior record exists and which is recorded directly in the CRF, the CRF will be considered the **source document**, unless otherwise indicated by the investigator.

In addition to the above, date(s) of conducting informed consent (plus assent where appropriate and if taken) process including date of provision of patient information, registration number, randomisation number and the fact that the patient is participating in a clinical trial (including possible treatment arms) should be added to the patient's medical record chronologically, i.e. when treatment is allocated to the patient.
Investigators and the institutions will permit trial-related monitoring, audits, REC review, and regulatory inspections (where appropriate) by providing direct access to source data and other documents (i.e. patients' case sheets, blood test reports, X-ray reports, histology reports etc).

13.3 Data Capture Methods

13.3.1 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. CTRC will provide participating sites with CRFs and guidance on how the CRF should be completed. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". Or if the data item is un-known, write "NK". If a data item has not been recorded on source data then write 'NR'. All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialled and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

13.4 Central Monitoring

Data stored at CTRC will be checked for missing or unusual values (range checks) and checked for consistency within participants over time. Any suspect data will be returned to the site in the form of data queries. Data query forms will be produced at the CTRC from the trial database and sent either electronically or through the post to a named individual (as listed on the site delegation log). Sites will respond to the queries providing an explanation/resolution to the discrepancies and return the data query forms to CTRC. The forms will then be filed along with the appropriate CRFs and the appropriate corrections made on the database. There are a number of monitoring features in place at the CTRC to ensure reliability and validity of the trial data, to be detailed in the trial monitoring plan.

13.5 Clinical Site Monitoring

In order to perform their role effectively, Kings Health Partners Clinical Trials Office, the trial coordinator (or monitor) and persons involved in Quality Assurance and Inspection may need direct access to primary data, e.g. patient records, laboratory reports, appointment books, etc. Since this affects the patient's confidentiality, this fact is included on the Parent Information Sheet and Informed Consent Form.

13.5.1 Confidentiality

Individual participant medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted below.
Case report forms will be labelled with the patient's initials and unique trial screening and/or randomisation number. Medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

The CTRC will be undertaking activities requiring the transfer of identifiable data:
Verification that appropriate informed consent is obtained will be enabled by the provision of copies of participant's signed informed consent/assent forms being supplied to the CTRC by recruiting centres, which requires that name data will be transferred to the CTRC. This transfer of identifiable data is disclosed in the PISC.

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.

13.5.2 Quality Assurance and Control

QA includes all the planned and systematic actions established to ensure the trial is performed and data generated, documented/recorded and reported in compliance with applicable regulatory requirements. QC includes the operational techniques and activities done within the QA system to verify that the requirements for quality of the trial-related activities are fulfilled. The level and nature of monitoring will be described in the trial monitoring plans, which will be finalised upon completion of the trial risk assessment. To ensure the integrity of the data the following policies will be observed:

- Data will be evaluated for compliance with protocol and accuracy in relation to source documents
- The study will be conducted in accordance with procedures identified in the protocol.
- The Principal Investigator and RN for each site will attend the training visit, which will incorporate elements of trial specific training necessary to fulfil the requirements of the protocol.
- A greenlight checklist will be completed by the trial coordinator/KHP CTO to verify appropriate approvals and documentation are in place prior to initiation of a site and the relevant personnel have received trial specific training
- The CTRC will monitor screening, recruitment and withdrawal rates between sites and report to the TMG
- Regular QC checks will be performed on data already inputted to ensure data entered is of a high standard
- Independent oversight of the study will be provided by the Independent Data and Safety Monitoring Committee and the Trial Steering Committee

13.6 Records Retention

The investigator at each investigational site must make arrangements to store the essential trial documents, (as defined in Essential Documents for the Conduct of a Clinical Trial (ICH E6, Guideline for Good Clinical Practice)) including the Investigator Site File and Pharmacy

Site File, until the Clinical Trials Unit informs the investigator that the documents are no longer to be retained, or for a maximum period of 15 years (whichever is soonest).
In addition, the investigator is responsible for archiving of all relevant source documents so that the trial data can be compared against source data after completion of the trial (e.g. in case of inspection from authorities).

The investigator is required to ensure the continued storage of the documents, even if the investigator, for example, leaves the clinic/practice or retires before the end of required storage period. Delegation must be documented in writing.

The CTRC undertakes to store originally completed CRFs for the same period, except for source documents pertaining to the individual investigational site, which are kept by the investigator only. The CTRC will archive the documents in compliance with ICH GCP utilising the Records Management Service of the University of Liverpool. All electronic CRFs and trial data will be archived onto an appropriate media for long term accessible storage. Hard copies of data will be boxed and transferred to specially renovated, secure, premises where unique reference numbers are applied to enable confidentiality, tracking and retrieval.

14 INDEMNITY

The TREAT trial is sponsored by Guys and St Thomas' NHS Foundation Trust and Kings College London and co-ordinated by the CTRC in the University of Liverpool.

Kings College London has clinical trial insurance and professional indemnities in place to cover its liabilities in regards to any work undertaken by its staff in the course of their employment at the University. As this is an investigator-initiated study, the Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation by the pharmaceutical industry do not apply.

The Guys and St Thomas' NHS Foundation Trust does not hold insurance against claims for compensation for injury caused by participation in a clinical trial and they cannot offer any indemnity. As this is an investigator-initiated study, The Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation by the pharmaceutical industry do not apply. However, in terms of liability, NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and they are legally liable for the negligent acts and omission of their employees. Compensation is therefore available in the event of clinical negligence being proven.

Clinical negligence is defined as:
"A breach of duty of care by members of the health care professions employed by NHS bodies or by others consequent on decisions or judgments made by members of those professions acting in their professional capacity in the course of their employment, and which are admitted as negligent by the employer or are determined as such through the legal process".

15 FINANCIAL ARRANGEMENTS

This trial is funded by the MRC-NIHR Efficacy and Mechanism Evaluation (EME) Board of the Department of Health. Contractual agreements will be in place between the sponsor and collaborating sites that will incorporate financial agreements.

15.1 Collaborating Centre Payments

Collaborating/recruiting centres will receive a per patient payment.

15.2 Research Team

As the study is funded by the MRC-NIHR EME, it will be automatically adopted onto the NIHR portfolio, which will allow trusts to apply to their comprehensive local research network for service support costs as required.

16 TRIAL COMMITTEES

16.1 Trial Management Group (TMG)

A Trial Management Group (TMG) will be formed comprising the Chief Investigator, other lead investigators (clinical and non-clinical) and members of the Clinical Trials Unit. The TMG will be responsible for the day-to-day running and management of the trial and will meet approximately 3 times a year. Refer to the TMG terms of reference and trial oversight committee membership document for further details.

16.2 Trial Steering Committee (TSC)

The Trial Steering Committee will consist of an independent chairperson, an independent expert in the field of dermatology and a medical statistician and appropriate members of the TMG. The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chairman. The ultimate decision for the continuation of the trial lies with the TSC. Refer to the TSC terms of reference and trial oversight committee membership document for further details.

16.3 Independent Data and Safety Monitoring Committee (IDSMC)

The independent Data and Safety Monitoring Committee (IDSMC) consists of an independent chairperson, plus 2 independent members: one who is an expert in the field of dermatology and one who is an expert in medical statistics.

The IDSMC will be responsible for reviewing and assessing recruitment, interim monitoring of safety and effectiveness, trial conduct and external data. The IDSMC will first convene prior to the start of recruitment and will then define frequency of subsequent meetings (at least annually). Details of monitoring are provided in section 9.
The IDSMC will provide a recommendation to the Trial Steering Committee concerning the continuation of the study. Refer to the IDSMC charter and trial oversight committee membership document for further details.

17 PUBLICATION

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.

The Trial Management Group will form the basis of the Writing Committee and advise on the nature of publications. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) will be respected. All publications shall include a list of participants, and if there are named authors, these should include the trial's Chief Investigator(s), Statistician(s) and Trial Manager(s) involved at least. If there are no named authors (i.e. group authorship) then a writing committee will be identified that would usually include these people, at least. The ISRCTN allocated to this trial should be attached to any publications resulting from this trial.

The members of the TSC and IDSMC should be listed with their affiliations in the Acknowledgements/Appendix of the main publication.

18 PROTOCOL AMENDMENTS

18.1 Version 2 (08/10/2015)

page 2 & 7 – change from Senior Lecturer to Reader for Dr Carsten Flohr
page 22 – change to exclusion criteria 7 to include males and to say that an acceptable method of contraception must be used for 6 months after the last dose of study drug
page 23 – addition of the following to the exclusion criteria:

- Receiving treatment with medicines that are substrates for the multidrug efflux transporter P-glycoprotein or the organic anion transporter proteins (OATP) for which elevated plasma concentrations are associated with serious and/or life-threatening events; this includes bosentan, dabigatran etexilate and aliskiren.
- Receiving treatment with products containing *Hypericum perforatum* (St. John's wort)
- Receiving oral treatment with tacrolimus
- Receiving oral treatment with everolimus and sirolimus
- Receiving oral treatment with lercanidipine

page 26 – section 6.5.2 has been amended to say that patients who develop an unacceptable toxicity based on the investigator's judgement will be withdrawn.
page 31 – text added to explain the dosing regimen for methotrexate
page 34-36 – Details have been added to section 7.7.2 to describe any medications that are not permitted and any precautions that are required to be taken with regards to administration of concomitant medications.

18.2 Version 3.0 09/10/2015

Page 2 – addition of qualifications for Carsten Flohr and Ashley Jones.
Page 5 – title altered to 'Professor' for Leonie Taams
Page 11 – Progressive Multifocal Leukoencephalopathy (PML), Tuberculosis (TB) and Thiopurine Methyltransferase (TPMT) added to Glossary
Page 15 – schematic of study design altered to reflect new schedule and figures for recruitment corrected
Page 16-17 – Further details added on why we are comparing ciclopsorin with methotrexate.
Page 18-20 – Further detail on risk:benefit ratio of trial interventions added
Page 24 – Exclusion to reflect abnormal chest x-ray added to the exclusion criteria
Page 27 – Details on steps in place to ensure blinding is maintained added
Page 29 – Details added on the drug dosing for the trial Investigational Medicinal Products and information regarding chest x-rays required for patients with a risk of TB
Page 31 – Information on when occasional monitoring of ciclopsorin is recommended added
Page 32-33 – Further details on precautions to be taken when prescribing and dispensing methotrexate added
Page 34 – 'New or worsening unexplained dyspnoea or cough' added to the monitoring parameters for Methotrexate
Page 36 – Information added with regards to avoiding ibuprofen whilst taking methotrexate and management of this if it occurs.
Page 39 – window added for week 1 and 2.
Page 40 – Table of study procedures altered to reflect new schedule.
Page 41-45 – Visit summary altered to reflect new schedule
Page 45 – Details on what is recorded in patient diary added
Page 45 – Procedures for assessing safety updated to reflect new schedule
Page 46 – Details on what is recorded in patient diary added
Page 46 – 'intervention vs control' changed to 'MTX vs CyA'
Page 59 – Patient information leaflets changed to patient information sheets

19 REFERENCES

1. Emerson RM, Williams HC, Allen BR. Severity distribution of atopic dermatitis in the community and its relationship to secondary referral. Br J Dermatol. 1998;139(1):73-6.
2. Ben-Gashir MA, Seed PT, Hay RJ. Are quality of family life and disease severity related in childhood atopic dermatitis? Journal of the European Academy of Dermatology and Venereology : JEADV. 2002;16(5):455-62.
3. Kemp AS. Cost of illness of atopic dermatitis in children: a societal perspective. PharmacoEconomics. 2003;21(2):105-13.
4. McAleer MA, Flohr C, Irvine AD. Management of difficult and severe eczema in childhood. Bmj. 2012;345:e4770.
5. Flohr C, Irvine AD. Systemic therapies for severe atopic dermatitis in children and adults. The Journal of allergy and clinical immunology. 2013;132(3):774- e6.
6. Proudfoot LE, Powell AM, Ayis S, Barbarot S, Baselga Torres E, Deleuran M, et al. The European TREatment of severe Atopic eczema in children Taskforce (TREAT) survey. Br J Dermatol. 2013;169(4):901-9.
7. El-Khalawany MA, Hassan H, Shaaban D, Ghonaim N, Eassa B. Methotrexate versus cyclosporine in the treatment of severe atopic dermatitis in children: a multicenter experience from Egypt. European journal of pediatrics. 2013;172(3):351-6.
8. Schram ME, Roekevisch E, Leeflang MM, Bos JD, Schmitt J, Spuls PI. A randomized trial of methotrexate versus azathioprine for severe atopic eczema. The Journal of allergy and clinical immunology. 2011;128(2):353-9.
9. Williams HC. Commentary: are methotrexate and azathioprine really equivalent for treating severe atopic eczema? Brit J Dermatol. 2012;166:705-6.
10. Schmitt J, Schmitt N, Meurer M. Cyclosporin in the treatment of patients with atopic eczema - a systematic review and meta-analysis. Journal of the European Academy of Dermatology and Venereology : JEADV. 2007;21(5):606-19.
11. Harper JI, Ahmed I, Barclay G, Lacour M, Hoeger P, Cork MJ, et al. Cyclosporin for severe childhood atopic dermatitis: short course versus continuous therapy. Br J Dermatol. 2000;142(1):52-8.
12. Meggit SJ GJ, Reynolds NJ. Azathioprine dosed by thiopurine methyltransferase activity for moderate-to-severe atopic eczema: a double-blind, randomised controlled trial. . Lancet. 2006;367:839-46.
13. Masunaga Y, Ohno K, Ogawa R, Hashiguchi M, Echizen H, Ogata H. Meta-analysis of risk of malignancy with immunosuppressive drugs in inflammatory bowel disease. The Annals of pharmacotherapy. 2007;41(1):21-8.
14. Schmedt N, Andersohn F, Garbe E. Signals of progressive multifocal leukoencephalopathy for immunosuppressants: a disproportionality analysis of spontaneous reports within the US Adverse Event Reporting System (AERS). Pharmacoepidemiology and drug safety. 2012;21(11):1216-20.
15. Roekevisch E, Spuls PI, Kuester D, Limpens J, Schmitt J. Efficacy and safety of systemic treatments for moderate-to-severe atopic dermatitis: a systematic review. The Journal of allergy and clinical immunology. 2014;133(2):429-38.
16. Schmitt J RM, Pfennig A, Leopold K, Meurer M. Psychiatric comorbidity in adult eczema. British Journal of Dermatology. 2009;161(4):878-83.
17. Schmitt J BA, Meurer M. Atopic exzema in adulthood. Hautarzt. 2008;59(10):841-50.
18. Guidelines N. Atopic eczema in children from birth up to the age of 12 years. 2007.
19. Press JFCBNFoLBGaP.
20. Sunseri W HJ, Lerer T et. al. Retrospective cohort study of methotrexate use in the treatment of pedaitric Crohn's disease. Inflammatory Bowel Diseases. 2014;20(8):1341-5.
21. Klein A KI, Foeldvari I et al. Efficacy and safety of oral and parenteral methotrexate therapy in children with juvenile idiopathic arthritis: an observational study with patients from the German Methotrexate Registry. Arthritis Care & Research. 2012;64(9):1349-56.

22. Willot S NA, Deslandres C. Methotrexate in the treatment of inflammatory bowel disease: an 8-year retrospective study in a Canadian pediatric IBD center. Inflammatory Bowel Diseases. 2011;17(12):2521-6.
23. Uhlen S BR, Narebski K, Goulet O, Schmitz J, Cezard JP, Turck D, Ruemmele FM. Efficacy of methotrexate in pediatric Crohn's disease: a French multicenter study. Inflammatory Bowel Diseases. 2006;12(11):1053-7.
24. Deo M YA, Hill S et al. Methotrexate for treatment of atopic dermatitis in children and adolescents. International journal of dermatology. 2014;53:1037-41.
25. Rahman SI SE, Flanagan KH et al. The methotrexate polyglutamate assay supports the efficacy of methotrexate for severe inflammatory skin disease in children. J Am Acad Dermatology. 2014;70:252-6.
26. Roberts H OD. Methotrexate is a safe and effective treatment for paediatric discoid (nummular) eczema: a case series of 25 children. Australas J Dermatol. 2010;51:128-30.
27. Sidbury R DD, Cohen DE et al. American Academy of Dermatology. Guidelines of care for the management of atopic dermatitis Section 3. Management and treatment with phototherapy and systemic agents. Journal of the American Academy of Dermatology. 2014;71(2):327-49.
28. Schram ME, Spuls PI, Leeflang MM, Lindeboom R, Bos JD, Schmitt J. EASI, (objective) SCORAD and POEM for atopic eczema: responsiveness and minimal clinically important difference. Allergy. 2012;67(1):99-106.