

The TREATment of Severe Atopic Eczema Trial (TREAT)

A Randomised Controlled Trial Assessing the Effectiveness, Safety and Cost-effectiveness of Methotrexate versus Ciclosporin in the Treatment of Severe Atopic Eczema in Children

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Participant Information Sheet and Consent Form—16 Year Old

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How to contact us

If you would like more information or have any questions about the TREAT study please talk to
 <name/names> at:
 <telephone number>

Or visit the TREAT website: www.treat-trial.org.uk

If you wish to discuss the study with someone independent of the research team you can contact the local NHS Patient Advice and Liaison Service (PALS) on: <telephone number>

Your are invited to take part in the TREAT research study

- ⇒ The TREAT study is a national study organised by King’s College London and Guy’s and St Thomas’ NHS Foundation Trust. It is funded by the Department of Health (Efficacy and Mechanism Evaluation programme).
- ⇒ We are inviting you to consider giving consent to take part in a research study (also called a clinical trial) comparing two treatments for severe eczema.
- ⇒ Before you decide if you would like to take part, it is important for you to understand why this research is being done and what taking part would mean for you.
- ⇒ Please take your time to read this information very carefully, before deciding whether you would like to take part.
- ⇒ It is entirely up to you whether you take part in this study.
- ⇒ Thank you for taking the time to read this information sheet. We hope you will find this information helpful.



Important things you need to know

One way of treating severe eczema is to use medicines that help to dampen down the body's immune system. Two medicines used in this way as part of established NHS care are:

- Methotrexate and
- Ciclosporin

However, we currently don't know which of the two medicines is the best to use in children and young people. We want to carry out a study to find this out. Being part of the study means you will have to attend only one more clinic visit than would usually take place.

You will still be able use moisturisers (that help to prevent skin dryness) and creams that settle down skin redness and itching (either steroid creams or so-called calcineurin inhibitors), whilst taking part in the study.

Why are we doing the TREAT study?

Eczema treatment aims to reduce skin inflammation, relieve itching and skin irritation and stop flare ups to improve a child or young person's quality of life. Usually, using moisturisers and steroid creams can do this. Although most children grow out of their eczema over time, in a small group of patients the disease is so severe that specialist medicines are needed.

One way of treating severe eczema is to use medicines that help to dampen down the body's immune system (the part of our body that fights infections and in eczema shows increased activity). Two medicines that are used in this way are Methotrexate and Ciclosporin. Both are already used for severe eczema in standard care, and we know that they work well. In this study, we want to find out which is the best to use.

There has already been a study among 40 children with severe eczema comparing ciclosporin and methotrexate, the medicines we are also testing in this study. Although there were side effects reported during this, none of the children stopped the medication due to the side effects and all side effects reported disappeared once the study ended. They found that the medicines worked equally well but this was only a small study, and the medicines were only taken for three months.

We are hoping that taking the study medicines for longer will mean that the severity of the eczema will reduce further and if it returns then it is easier to treat. In this study, once the study medicine has stopped, we will still ask you to attend study visits for another 6 months to see whether the eczema returns. If so, we can prescribe other medicines to help improve your symptoms.

In the study, we will compare the two treatments in terms of:

- How well they reduce eczema severity
- How they affect flare ups
- How the treatment affects quality of life
- Whether the medicines have side effects

Why have I been asked to take part in the TREAT study?

You are invited to take part in this study because you have been diagnosed with severe, difficult to manage eczema.

The study aims to recruit a total of 102 children and young people aged between 2 and 16 years.

What will I have to do if I take part?

Visit 1

At your first visit, we will talk to you about the TREAT study. You will be able to talk to a member of the research team and ask any questions that you may have. If you have had all of your questions answered and are happy to take part then you will be asked to sign a consent form. You will be given a copy of the consent form and the study information to keep. At this visit, you will be asked some questions about your medical history and any medicines that you take. We will also do an assessment of your eczema and ask you if we can take a saliva (spit) sample. You will have a blood test (numbing cream would be used before we take the blood) to make sure you are completely healthy and able to start one of the study medicines. If you are female and of a childbearing potential, we will ask if we can carry out a pregnancy test.

Before you start any treatment your study doctor may ask you to have a chest X-ray if you have recently travelled to a country where tuberculosis (TB) is common or someone in your family has TB. This is to check if your chest is healthy.



What will I have to do if I take part? (continued)

Visit 2

Once we know that the blood tests from the first visit are normal, we will use a computer programme to allocate you to one of the two treatment groups (medicines) in the study. This visit will usually be a week after the first visit.

If you are in the group that receives Methotrexate, you will receive the study medicine once a week (either as a tablet or an injection). You will also receive a vitamin tablet called folic acid on all days except the methotrexate day. If you are in the group that receives Ciclosporin then you will receive the study medicine twice a day as a tablet, every day of the week. You will be asked to take the study medicine for 36 weeks (approximately 9 months).

Further Visits

After visit 2, we would like you to attend every two weeks for the first month, then every 4 weeks for the two months after this. After this, you will need to come every 8 weeks, until your study treatment stops. You will take the study treatment for a total of 36 weeks (approximately 9 months). We will then ask you to attend every 12 weeks for the rest of the study. The whole study will last for 61 weeks (approximately 15 months). Please see the timeline on page 4 for the schedule of the study visits.

If you are in the group that receives methotrexate, then you will need to attend one more visit for the study at week 2 for a blood test. This is to check how you are getting on with the medicine and whether it is OK to increase to the full treatment dose.

You will be asked to complete a diary whilst you are taking part in the study. The diary will ask you to record how your eczema has been in the last week, whether you needed to use any additional treatments or needed to see any healthcare professionals for your eczema. You will also be asked to record when you have taken the study medicine and if you have experienced any side effects. You will be asked whether you needed any time off due to your eczema and whether you have had any skin infections.

After the initial assessments as part of the study, the frequency of study visits is similar to what would happen if you weren't taking part in the study.

At each of the visits (apart from Visit 1) the following will occur:

- The research team will ask how you are doing
- You will be given the study medicine (for 36 weeks (week 1—week 37))
- The research team will assess your eczema severity
- You will be asked to complete a short questionnaire about any flare ups, side effects of the medicines and your quality of life
- Your blood pressure will be taken (to check that the study medicines do not affect this)
- Your study doctor will carry out a physical examination
- Your height and weight will be measured (at some visits)

If you were receiving one of the study medicines as part of standard care, blood would be taken at the same times as in the study. The additional samples that we would like to take for the study are as follows:

- additional blood when routine samples are taken (no extra needles required).
- urine sample (at some visits)
- saliva sample (one of the things we would like to look at are the genes in your saliva to see if they affect how you respond to the study medication). If you aren't able to provide a saliva sample then we can do this by looking at a sample of your blood. This will be a one-off sample at Visit 1.

Whilst you are receiving the study treatment, the research team will use blood samples collected to check that the study medicine hasn't affected your liver, kidneys or blood count. If the dose of the study medicine needs reducing, then the study team will be able to do this for you.

Once the study is complete, all samples will be destroyed.

At visits 2, 6, 9 and 11 we will ask you if we can use a special tape to remove a few skin cells. This does not hurt and is the same as if you were to use sticky tape on your skin, lifting it up gently after applying it.



How will I know which treatment I am going to have?

In research studies we often split patients up into groups to look at how different treatments work. Patients in one group get a different treatment to patients in another group. In the TREAT study there are two treatment groups:

Group A - Methotrexate

Group B - Ciclosporin

It is really important that the two groups for the TREAT study have a similar mix of patients in them. Having a similar mix means that we know that if one group of patients does better than the other, it is very likely to be because of the treatment and not because there are differences in the types of patients in each group.

We use a computer programme that puts patients 'at random' into one of the groups – you might hear this described as 'randomisation' or 'random allocation', but they all mean the same thing. Neither you nor your doctor choose which group you are in.

In the TREAT study you are equally likely to be in Group A as you are to be in Group B. Your healthcare team will let you know which group you are in.

What are the possible benefits of taking part?

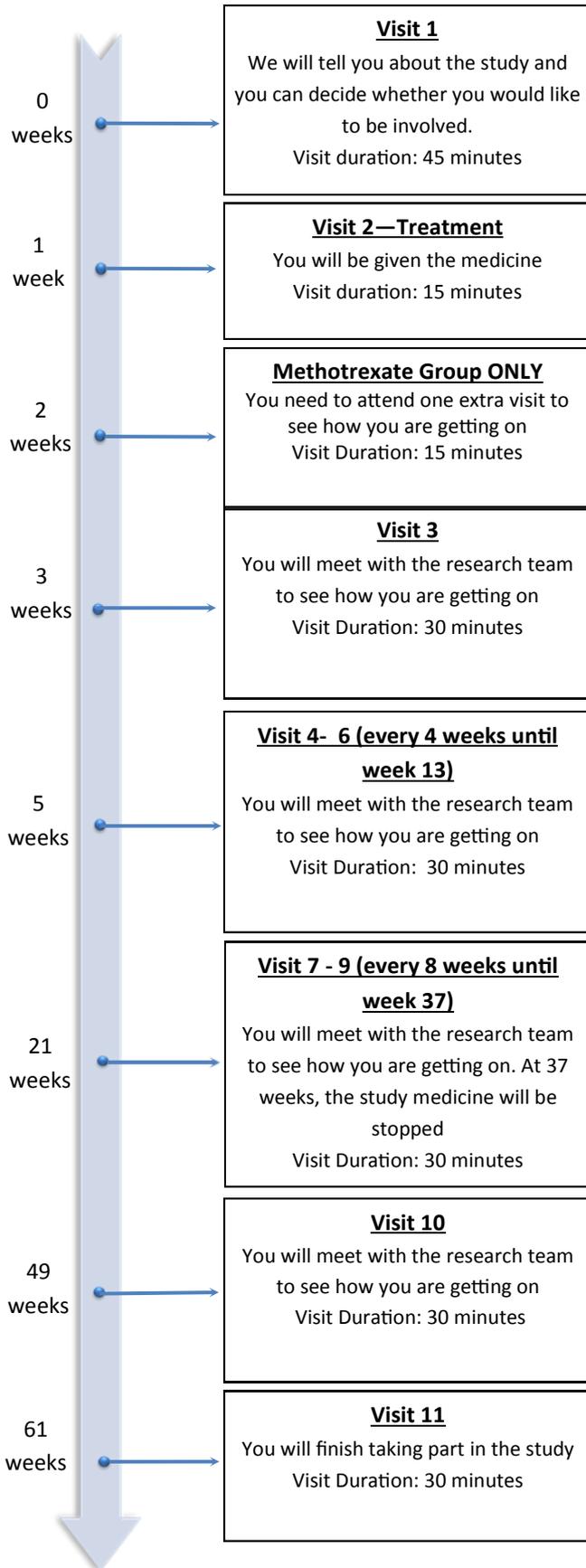
There is no direct benefit to you participating in this study, since both treatments are already available on the NHS. We hope that the study treatment will improve your eczema, however this cannot be guaranteed. The information you provide will help doctors and patients to choose the most suitable treatment for severe eczema in the future.

What are the possible risks of taking part?

There are no additional risks involved in participating in the study compared to if you were to choose to receive one of the study treatments as part of standard care. The only additional assessments that will take place in the study are collection of urine samples, tape strips, a saliva sample and additional blood (when you are having blood taken anyway as required by standard care) and these do not carry any additional risks. You can choose not to receive either medication as part of standard care as you can freely choose not to participate in the trial.

Both medicines have been used for many years in patients with severe eczema and other conditions, such as rheumatoid arthritis. As with all medicines, there are a number of side effects that have been reported.

Timeline of Visits





What are the possible risks of taking part? (continued)

Methotrexate

Methotrexate is used to treat many conditions, including arthritis and certain types of cancer. For these conditions it is usually used at a higher dose and more often than when it is used for skin conditions. Many of the side-effects of methotrexate that you may read about are more likely when it is used for these illnesses. Side effects are much less likely when methotrexate is given once a week for psoriasis or severe eczema (as it is given in the study). If side effects do occur they are usually reversible when treatment is stopped.

Side effects with methotrexate		
Very common (in at least 1 in 10 people)	Common (in at least 1 in 100 people)	Other possible side effects (unknown frequency in children)
Nausea (feeling sickly) This is usually mild and significantly helped by taking folic acid and taking the tablets in the evening	Tiredness	Difficulty in sleeping
Indigestion	Headache	Sensitivity to sunlight
Loss of appetite	Inflammation of the lung	Loss of hair
	Diarrhoea	
	Mouth ulcers	
	Inflammation of the liver	
	Change in blood count -fewer white blood cells and platelets (the part that clots the blood) being made. This can mean that you may get tired more easily, that you may be at a higher risk of infection, and that your blood may not clot as quickly.	

What are the possible risks of taking part? (continued)

There are certain side effects that we would like you to tell the research team about straight away (if it is out of office hours then please get in touch with your usual local NHS out of hours services). These are as follows:

- Infections, including fever (temperature above 38^oC), chills, sore throat or chicken pox
- Skin rash, changes in nail or skin colour, or skin ulcers
- Yellowing of the skin or whites of the eyes
- Bleeding gums, unexpected bruising or bleeding that doesn't stop as quickly as normal
- Black 'tarry' stools
- Chest pain, difficulty breathing or a dry cough that doesn't go away
- Severe and continuing diarrhoea, vomiting or stomach pains
- Inflammation (swelling and soreness) or ulcers of the vagina

There may sometimes be side effects that are not listed above. If you notice anything unusual and are concerned then you should contact your study team.

What medicines/products should I avoid while taking methotrexate?

There are some medications/products that can change the way that methotrexate acts in your body, potentially resulting in higher levels of the medication, making the above side effects more likely. If you are in the methotrexate group we ask that you do not use the following medications/products:

- Oral antibiotics e.g. Penicillin
- Vitamins that contain folic acid
- Ibuprofen – if taken with methotrexate, the body can have trouble breaking down methotrexate and this can result in serious harmful effects. Paracetamol can be taken unless your doctor has told you not to.
- Live vaccines: measles, mumps, rubella (MMR), polio, rotavirus, typhoid, yellow fever, varicella (chickenpox), varicella-zoster (shingles), and nasal flu (influenza) vaccine.

If you do take any of the medicines/products listed above it may cause serious harmful effects and you should contact your study team.





What are the possible risks of taking part? (continued)

Ciclosporin

Ciclosporin is also used for some types of kidney disease and in patients who have received an organ transplant. When used in this way, this is usually at a higher dose and for a longer time. Many of the side effects you may read about are more likely when used at a higher dose. Side effects are much less likely when ciclosporin is given at the lower dose we use in our study, most are mild when they occur and are reversible when the treatment is stopped.

Side effects with Ciclosporin		
Very Common (in at least 1 in 10 people)	Common (in at least 1 in 100 people)	Other possible side effects (unknown frequency in children)
Headache	Change in blood count (fewer white blood cells being made). This can mean that you may get tired more easily and that you are at a higher	Infections
Tremor (shakiness)	Higher blood pressure	Sensitivity to sunlight
	Muscle cramps and muscle pain	Irregular periods (females)
	*Nausea (feeling sickly)	**Convulsions (fits)
	*Vomiting (being sick)	
	*Abdominal discomfort (tummy pain)	
	*Diarrhoea.	
	Swollen or painful gums. This usually settles with good dental hygiene.	
	Stomach ulcer	
	Abnormal liver and kidney function	
	Flushing of the skin	
	Acne	
	Increased facial or body hair growth	
	Pins and needles	
	Fever	
	Tiredness	

**These might occur when you first start taking Ciclosporin but should wear off after 2 weeks.*

*** These have not been described in adults or children with eczema.*



What are the possible risks of taking part? (continued)

As mentioned in the tables, you may be more sensitive to sunlight whilst taking either treatment. For this reason, whilst outdoors, you are advised to keep your skin covered, wear a hat and to use high factor sun screen (at least SPF 30), especially in the summer.

There are certain possible side effects that we would like you to tell the research team about straight away (if it is out of office hours, then please get in touch with your usual local NHS out of hours services). These are as follows:

- Infections
- Fever (above 38^{oC}), with a sore throat or a cough
- Unusual bleeding that is difficult to stop
- Severe bruising
- Headaches and visual disturbance

There may sometimes be side effects that are not listed above. If you notice anything unusual and are concerned then you should contact your study team.

What medicines/products should I avoid while taking ciclosporin?

There are some medications/products that can change the way that ciclosporin acts in your body. If you are in the ciclosporin group we would like to ask you not use the following medications/products:

- St John's wort
- Grapefruit products
- Live vaccines: e.g. measles, mumps, rubella (MMR), polio, rotavirus, typhoid, yellow fever, varicella (chickenpox), varicella-zoster (shingles), and nasal flu (influenza) vaccine.

If you do take any of the medicines/products listed above it may cause serious harmful effects and you should contact your study team.

Monitoring throughout the study

Your research team will monitor you throughout the study (through blood tests, blood pressure and physical examinations), and they will ask you if you are experiencing any side effects. You may not feel certain side effects such as higher blood pressure and change in kidney function, however these



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side effects will be picked up by the research team monitoring your blood tests and blood pressure. If they note any problems the research doctor will discuss them with you and agree any changes to your medicine that may be needed. The research team will also ask if you have experienced any side effects. If there are any side effects, they usually return to normal when treatment is stopped.

Pregnancy

It is possible that if the study treatment is given to a pregnant female it will harm the unborn child. This applies to methotrexate and we are unsure whether ciclosporin can also harm an unborn child, as there is not enough information available. Pregnant females must therefore not take part in this study; neither should women or young adults who plan to become pregnant during the study.

All participants (males and females) should use reliable methods of contraception for the whole time they are in the study, and for 6 months after they have stopped taking their study medicines.

Any female who finds that she is pregnant while taking part in the study should immediately tell her research doctor. Similarly, if any male participant has a partner that becomes pregnant they should also immediately tell their research doctor.

All pregnancies will be monitored by the researchers.



Do I have to take part?

If you do not wish to take part in the study you do not have to give a reason and you will receive the routine treatment used by your hospital.

The standard of care you receive now or in the future will be the same whether you take part or not.

What happens if I change my mind?

If at any point you decide to stop taking part in the study, you do not have to offer a reason. A decision not to take part or to leave the study will not affect the standard of care you receive. All information collected up until the time of withdrawal will be included in the study analysis, unless you request that it is removed.

Will my participation be kept confidential?

Yes. We will follow ethical and legal practice and all information which is collected about you during the course of the study will be kept strictly confidential. With your consent, we will send a letter to your GP to let them know you are taking part.

Your named data (consent form) will be transferred to the coordinating centre for the study (the Medicines for Children Clinical Trials Unit in Liverpool). This will only be accessed by people working on the study or people working to ensure the study is being run correctly.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak with one of your research team who will do their best to answer your questions.

If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital. If you are harmed by taking part in this research project, there are no special compensation arrangements.

If you are harmed and this is due to someone's negligence, then you may have grounds for a legal action for compensation against the NHS Trust where you are being treated but you may have to pay for your legal costs. The normal National Health Service complaints mechanisms should be available to you.

Additional information about the study

The study is funded by the Department of Health (Efficacy and Mechanism Evaluation Programme) and is supported by the NIHR Clinical Research Network: Children (www.crn.nihr.ac.uk) as well as the UK Dermatology Clinical Trials Network (UK DCTN).

The study is being run in your hospital, and the day to day running of the study is being carried out by the Medicines for Children Clinical Trials Unit, part of the University of Liverpool. This research has been approved by a research ethics committee, who has agreed that this study is being conducted in an appropriate manner.

This trial is co-sponsored by King's College London and Guy's and St Thomas' NHS Foundation Trust. The sponsors will at all times maintain adequate insurance in relation to the study. King's College London, through its own professional indemnity (Clinical Trials) and no fault compensation and the Trust having a duty of care to patients via NHS indemnity cover, in respect of any claims arising as a result of clinical negligence by its employees, brought by or on behalf of a study patient but you may have to pay your legal costs. As mentioned earlier, the normal National Health Service complaints mechanisms will still be available to you.

Thank you for taking the time to read this information. We hope you will find it useful, and we hope that this research will be of interest to you. If you would like to talk to someone about this study please see Page 1 for contact details.





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<Trust address 1>
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Consent Form for 16 Year Old

To be filled in by the patient

Once you have read and understood each statement please tick (✓) and initial

No.	Statement	Tick ✓	Initial
1	I have read and understood the information leaflet (version 4.0 dated 29/03/2016) for the above study. I have had the opportunity to ask questions and have these answered satisfactorily.		
2	I understand that participation is voluntary and that I am free to withdraw at any time, without giving a reason, and without my care or legal rights being affected.		
3	I give permission for urine and additional blood samples to be collected for the study.		
4	I give permission for the genes in my saliva/blood to be looked at for the study.		
5	I give permission for skin cells to be removed from my skin using a special tape.		
6	I understand that my anonymised data will be retained for a maximum of 15 years at site/or at the Medicines for Children Clinical Trials Unit (MC CTU) and that they will be stored in a confidential manner.		
7	I understand that relevant sections of my hospital records and any data collected during the study may be looked at by authorised individuals from the research team, MC CTU, Regulatory Authorities, Co-Sponsors or the NHS Trust. I give permission for these individuals to access my records.		
8	I agree to my GP being informed of my participation in the study.		
9	I give permission for a copy of my consent form which will include my name to be sent to the MC CTU for the administration of the study.		
10	I understand that it may be harmful for me to take ibuprofen whilst taking methotrexate. If randomised to the methotrexate arm I agree to abstain from taking it during the study.		
11	I agree to take part in the above study.		

Name (please print)		Your Signature		Today's Date	dd-mm-yy
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Researcher Name (please print):

Researcher Signature: Date d d m m y y

When completed, 3 copies need to be made: the original should be kept in the investigator site file, 1 copy for the participant, 1 for the patient notes and 1 copy of the **consent form only** for the coordinating CTU (fax to 0151 282 4721)