ISRCTN12109108 https://doi.org/10.1186/ISRCTN12109108

Treating severe paediatric asthma: the TREAT trial

Submission date 13/01/2020	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 21/01/2020	**Overall study status** Ongoing	
Last Edited 06/03/2025	**Condition category** Respiratory	

Plain English summary of protocol

Background and study aims
2-5% of children with asthma have repeated hospital admissions with asthma attacks, school absences and poor quality of life despite being prescribed maximal doses of treatment. A period of treatment monitoring using an electronic device can distinguish patients that have improved control when they take their inhalers properly from those who remain poorly controlled despite taking their treatment; severe therapy-resistant asthma (STRA).
Apart from high-dose steroids, which result in severe side effects, there are two medications licensed as add-on treatments in children with STRA. Both are given as regular injections in hospital. Omalizumab can currently only be used in about 60% of children with STRA because prescribing is limited by a blood test called IgE that is related to allergies and also the child's weight. Of those in whom omalizumab can be tried, only about half respond. Mepolizumab was licenced for use in children in 2018. Although safety and the doses have been evaluated, no studies have assessed whether it helps children with STRA. The aim of this study is to determine whether mepolizumab is as efficacious as omalizumab in reducing asthma attacks in children with STRA and refractory DA.

Who can participate?
All recruiting sites have a specialist severe asthma service for children. All school-age children aged 6-16 years referred with poor asthma control despite being prescribed maximal asthma inhaler therapy are eligible for the run-in and screening for adherence. In addition, children already attending the clinics at each site that have not yet been prescribed additional medications, or who may have had a previous failed trial of omalizumab, are eligible for the run-in as well.

What does the study involve?
The researchers first check that children with severe asthma are taking their inhalers using electronic monitoring. All children that have poor control despite taking their inhalers (STRA), and those who fail to take their inhalers regularly despite our best efforts to achieve this (these children are at high risk of asthma death), are eligible. The following tests are done at each visit (once a month):
1. Lung function tests (spirometry and exhaled nitric oxide): blowing and breathing tests. These are done routinely at every clinic appointment

2. Symptoms questionnaire: any asthma attacks in the last 4 weeks
3. Quality of life questionnaire: the impact of asthma on the child's activity and emotions

The following tests are done at the first visit, then at one month and 4 months:
1. A blood test (about one teaspoon, or 5 ml) to look at the number of eosinophils
2. A sputum (phlegm) test
3. Throat swab for infection
4. A urine sample (about one teaspoon, or 5 ml) is taken and tested for cigarette smoke exposure
5. A pregnancy test - before receiving the study treatment, a pregnancy test is done but only for children who are of potential child-bearing age
The following tests are done only once at the beginning of the study:
1. Blood tests (about one teaspoon, or 5 ml) and skin tests to assess allergy status
2. Bronchoscopy samples (ONLY to be taken from children who need a bronchoscopy as part of their routine care)
2.1. This includes washings from the airways (broncho-alveolar lavage) and bronchial biopsies (tiny pieces of tissue taken from the airway wall using forceps)
2.2. There is one extra test if a child is having a bronchoscopy. This test involves taking some cells that line the walls of the airways including the nose using a special brush through the bronchoscope (for the lower airways). This test is performed routinely in children as part of normal clinical care. The brushing may cause a very small amount of bleeding. These tests will be performed at the end of the procedure and are just for research. They will take about 3 minutes.

What are the possible benefits and risks of participating?
Participants may receive a newly licenced treatment for severe asthma that not many centres in the UK can currently prescribe. Their eligibility for omalizumab will not be restricted by the current NHS guidelines, as all children will receive at least one treatment, regardless of the current NHS rules.

The monitoring period, many of the assessments including bronchoscopy and omalizumab are part of routine clinical care. There may be some side effects from omalizumab, but these cannot be predicted, and in the researchers' experience of using it in children so far, there have been no side effects that have caused significant harm. Omalizumab can rarely cause discomfort in arms and legs, may make a patient feel dizzy or tired, result in a rash, or pain in the ears. The most common side effects known about for mepolizumab are that it can cause headache, skin reactions where the injection was given, back pain and tiredness. However, the researchers are not aware of all of the potential side effects of mepolizumab in children as it has not been used very much at all in children. It is also possible that the treatment will not benefit participants' asthma, but this cannot be predicted and would be the same even if a patient was not in the study.

Where is the study run from?
1. Royal Brompton & Harefield NHS Foundation Trust (UK)
2. Manchester University NHS Foundation Trust (UK)
3. University Hospital Southampton NHS Foundation Trust (UK)
4. University Hospitals of North Midlands NHS Trust (UK)
5. University Hospitals of Leicester NHS Trust (UK)
6. NHS Lothian (UK)
7. Alder Hey Children's NHS Foundation Trust (UK)
8. Birmingham Women's and Children's NHS Foundation Trust (UK)
9. King's College Hospital NHS Foundation Trust (UK)

10. Brighton and Sussex University Hospitals NHS Trust (UK)
11. NHS Greater Glasgow and Clyde (UK)
12. Imperial College Healthcare NHS Trust (UK)

When is the study starting and how long is it expected to run for?
August 2019 to January 2027

Who is funding the study?
NIHR Efficacy and Mechanism Evaluation Programme (UK)

Who is the main contact?
Claire Streatfield
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Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2019-004085-17

Integrated Research Application System (IRAS)
252084

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
CPMS 44294, IRAS 252084

Study information

Scientific Title
Treating severe paediatric asthma: a randomised controlled trial of mepolizumab and omalizumab (TREAT trial)

Acronym
TREAT

Study objectives
2-5% of children with asthma have repeated hospital admissions with asthma attacks, school absences and poor quality of life despite being prescribed maximal doses of treatment. A period of treatment monitoring using an electronic device can distinguish patients that have improved control when they take their inhalers properly from those who remain poorly controlled despite taking their treatment; severe therapy-resistant asthma (STRA).
Apart from high-dose steroids, which result in severe side effects, there are two medications licensed as add-on treatments in children with STRA. Both are given as regular injections in hospital. Omalizumab can currently only be used in about 60% of children with STRA because prescribing is limited by a blood test called IgE that is related to allergies and also the child's weight. Of those in whom omalizumab can be tried, only approximately half respond.
Mepolizumab was licenced for use in children in 2018. Although safety and the doses have been evaluated, no studies have assessed whether it helps children with STRA.
In this trial the researchers will first check that children with severe asthma are taking their inhalers using electronic monitoring. All children that have poor control despite taking their inhalers (STRA), and those who fail to take their inhalers regularly despite our best efforts to achieve this (these children are at high risk of asthma death), will be eligible. They will have routine clinical tests e.g. breathing tests, blood tests, and bronchoscopy (look inside the lungs with a fibreoptic camera under general anaesthetic) and will be randomly assigned to either receive omalizumab or mepolizumab for 1 year. The researchers want to know whether mepolizumab is at least as good as omalizumab in reducing asthma attacks in children with severe asthma over the year they are taking the treatment and also what features may predict a good response to either treatment.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 29/01/2020, Berkshire Research Ethics Committee (Easthampsted Baptist Church, South Hill Road, Bracknell RG12 7NS, UK; Tel: +44 (0)207 104 8360, +44 (0)2071048046; Email: nrescommittee.southcentral-berkshire@nhs.net), REC ref: 19/SC/0634

Study design
Randomized; Interventional; Design type: Treatment, Process of Care, Drug, Management of Care, Active Monitoring

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Severe paediatric asthma

Interventions
The trial will be undertaken at 11 specialist paediatric asthma centres across the UK. All children who are referred to the centres with poor asthma control despite being prescribed maximal inhaled therapy (this maximal dose has been defined by the British Thoracic Society Guidelines for managing asthma) will be eligible for entry into the run-in phase of the trial. Children that are already being seen in the clinics who are on maximal treatment, but have poor control, will also be eligible. The lead consultant for the trial at each centre will identify children who are eligible. Their details will be given to the research nurses who will be recruiting, and the nurses, or the doctors will give the parents/legal guardians and the child the information sheets about the trial. The family will be given at least 24 hours, they can have longer if needed, to decide whether they are interested and would like to take part. The nurse will contact the family to answer any questions, provide clarity, and if agreeable, she will book them to come in for a screening visit for the run-in period. That visit can be combined with the family's next routine clinic appointment, or it can be an extra visit at a time that is most convenient to the family.

Screening visit for run-in
The nurse or doctor will go over the information sheet again with the child and parents and will ensure any concerns/questions are addressed. Consent for run-in will then be taken. The child will undergo lung function tests (routine clinical breathing tests), the family will answer a questionnaire which includes information about asthma control and current prescribed medication and the nurse will go over inhaler technique to ensure the child is taking their inhaler properly and will issue the family with an electronic monitoring device which fits on to the regular inhaled steroid inhaler that the child should be using. She will tell the family it will record every time the child takes their inhaler, and that we want to ensure 80% adherence before we will randomise for the add-on treatments.

8-12 weeks – end of run-in visit
The child and family will be asked to return at the end of at least 8 weeks monitoring, this visit will also be combined when possible with a routine clinic visit, therefore the return can be between 8-12 weeks as these children are routinely seen 3 monthly in clinic. The family will complete a questionnaire about asthma control and again repeat the lung function tests. The data from the monitor will be downloaded and related to control, if the child has taken their inhaler at least 80% of the time and control has improved, they will not move into the

randomisation phase, as maintaining good adherence will allow them to maintain asthma control. Poor adherence, but good control will also not continue, as that child may have been overprescribed treatment. If the child has poor adherence and poor control, they will be given a different monitoring device, which not only records doses taken, but also includes a way of checking technique, that an inhalation was taken and reminder functions. Children will also have a period of directly observed therapy (DOT) during which their inhaler treatment will be given while supervised by teachers in school. This is to aid improved adherence before randomisation, this will be done for a further 8 weeks. They will return after enhanced monitoring, if at that stage they still have poor control, they will move onto the randomisation phase, regardless of adherence as they are at high risk of very severe attacks. Children who have good adherence, but poor control will be eligible to move on to the randomisation phase.

Clinical bronchoscopy visit
All children who are due to be randomised will undergo clinically indicated bronchoscopy (this is current clinical practice prior to starting an add-on therapy). The bronchoscopy is a test undertaken under general anaesthetic during which a fibreoptic camera is passed down into the lungs and enables samples to be collected to make sure there is no infection and also that the cells in the lungs fit with those seen in severe asthma. Informed consent is routinely taken for the procedure, and for this trial, additional consent will be sought for additional research samples to be taken, or if parents do not want that to be done, then any surplus samples to be used for this study. There are some samples that we would like to take just for research and we will only take those with consent. Blood tests are also taken during the bronchoscopy, the researchers will ask for consent to take some extra blood for research to measure the IgE level and eosinophils. They will also ask for consent for blood to be taken for a genotype - as there are now several genes that have been identified and associated with severe asthma in children. The researchers want to know whether the response to the medications to be used is determined by the child's genotype.

Randomisation visit and subsequent visits
Within 4 weeks of the bronchoscopy, the child and family will attend for their randomisation visit and initiate the study treatment. At this visit consent will be obtained to confirm participation in the interventional part of the trial. Clinical tests will be undertaken (lung function tests, questionnaires), and an additional test to obtain a sample of sputum (phlegm) will also be undertaken during this visit. The researchers will not use the current prescribing guidance to decide eligibility for either of the interventional drugs. All children will be randomly allocated to one or the other medication regardless of their IgE levels, or their eosinophil counts. This is because the researchers want to use this trial to decide the best prescription criteria for children. After randomisation, the child will receive their first dose of the trial medication at this visit. The frequency of attending for the trial medication is determined by the drug. If omalizumab is to be given, the frequency of injections (2 or 4 weekly) is determined by the dose. Mepolizumab is always 4 weekly. All children will attend 4 weekly for the medication and as per routine clinical practice, at each visit, they will have lung function tests and complete questionnaires about symptoms and asthma control. The total number of doses of the interventional drug is 13, therefore total duration in the randomisation phase of the trial is 52 weeks. At 4 weeks, 16 weeks and 52 weeks two additional tests will be performed for research (with consent, these are not an absolute requirement for participation), an induced sputum test and blood test.

Intervention Type
Drug

Phase

Not Applicable

Drug/device/biological/vaccine name(s)
Mepolizumab, omalizumab

Primary outcome(s)
Current primary outcome measure as of 10/09/2020:

52-week asthma exacerbation rate; defined as the number of asthma attacks requiring high dose systemic steroids (oral, intravenous, or intramuscular) or asthma related admission to hospital (≥4 hours in hospital) measured at 52 weeks

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Previous primary outcome measure:

52-week asthma exacerbation rate, defined as the number of asthma attacks requiring a short course of high-dose oral steroids (for 3 or more days) or admission to hospital, measured at 52 weeks

Key secondary outcome(s))
Current secondary outcome measures as of 30/07/2024:

1. Asthma severity measured using the composite asthma severity index (CASI) questionnaire at 4, 16, 32, and 52 weeks
2. Quality of life measured using paediatric asthma quality of life (PAQLQ) questionnaire at 4, 16, and 52 weeks
3. Lung function (FEV1, bronchodilator reversibility) measured by spirometry (blowing and breathing tests) at 4, 16, 32, and 52 weeks
4. Exhaled nitric oxide measured by blowing and breathing tests at 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52 weeks
5. Asthma control measured using asthma control test (ACT) questionnaire at 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52 weeks
6. Inhaled corticosteroid dose (dose determined by the manufacturer that makes the inhaled steroid) at 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52 weeks
7. Sputum inflammatory cell count and eosinophil peroxidase measured by sputum test at4, 16, and 52 weeks
8. Patient burden (number of visits and injections) measured using a patient-assessed visual analogue scale at 4, 16, 32, and 52 weeks

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Previous secondary outcome measures as of 10/09/2020:

1. Asthma severity measured using the composite asthma severity index (CASI) questionnaire at 4, 16, 32, and 52 weeks
2. Quality of life measured using paediatric asthma quality of life (PAQLQ) questionnaire at 4, 16, and 52 weeks
3. Lung function (FEV1, bronchodilator reversibility) measured by spirometry (blowing and breathing tests) at 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52 weeks
4. Exhaled nitric oxide measured by blowing and breathing tests at 4, 8, 12, 16, 20, 24, 28, 32, 36,

40, 44, 48, and 52 weeks
5. Asthma control measured using asthma control test (ACT) questionnaire at 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52 weeks
6. Inhaled corticosteroid dose (dose determined by the manufacturer that makes the inhaled steroid) at 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52 weeks
7. Sputum inflammatory cell count and eosinophil peroxidase measured by sputum test at4, 16, and 52 weeks
8. Patient burden (number of visits and injections) measured using a patient-assessed visual analogue scale at 4, 16, 32, and 52 weeks

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Previous secondary outcome measures:

1. Asthma severity measured using the composite asthma severity index (CASI) questionnaire at weeks 4, 16, 52
2. Quality of life measured using paediatric asthma quality of life (PAQLQ) questionnaire at weeks 4, 16, 52
3. Lung function (FEV1, bronchodilator reversibility) measured by spirometry (blowing and breathing tests) 4 weekly during the trial
4. Exhaled nitric oxide measured by blowing and breathing tests 4 weekly during the trial
5. Asthma control measured using asthma control test (ACT) questionnaire 4 weekly during the trial
6. Inhaled corticosteroid dose (dose determined by the manufacturer that makes the inhaled steroid) measured 4 weekly during the trial
7. Sputum inflammatory cell count and eosinophil peroxidase measured by sputum test at weeks 4, 16, 52
8. Patient burden (number of visits and injections) measured using a patient-assessed visual analogue scale at weeks 4, 16, 52

Completion date
31/01/2027

Eligibility

Key inclusion criteria
Current inclusion criteria as of 02/02/2023:

1. Written informed consent given
2. Aged 6 to 16 years
3. Confirmed diagnosis of asthma
4. Poor asthma control despite being prescribed high dose therapy

Inclusion criteria for RCT phase:
1. Written informed consent
2. Children aged 6-17 years
3. Confirmed diagnosis of asthma with one of the following:
3.1. Persistent poor control ≥1 attack after adherence assessment with ≥80% adherence during run-in (STRA) 3.2. Persistent poor control and poor adherence despite optimal efforts to improve adherence, including enhanced monitoring (Refractory DA)
4. Female patients capable of becoming pregnant must agree to use hormonal contraception,

intrauterine device, intrauterine hormone-releasing system, or to complete abstinence for the duration of the trial and up to 100 days after the last dose of IMP

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Previous participant inclusion criteria as of 10/09/2020:

Inclusion criteria for run-in phase:
1. Written informed consent given
2. Aged 6 to 16 years
3. Patients capable of becoming pregnant must agree to use hormonal contraception, intrauterine device, intrauterine hormone-releasing system, or to complete abstinence for the duration of the trial and up to 100 days after the last dose of IMP
4. Confirmed diagnosis of asthma
5. Poor asthma control despite being prescribed high dose therapy

Inclusion criteria for RCT phase:
1. Children aged 6-17 years
2. Confirmed diagnosis of asthma with one of the following:
2.1. Persistent poor control ≥1 attack after adherence assessment with ≥80% adherence during run-in (STRA) 2.2. Persistent poor control and poor adherence despite optimal efforts to improve adherence, including enhanced monitoring (Refractory DA)

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Previous participant inclusion criteria:

1. Confirmed diagnosis of asthma
2. On high dose maintenance treatment (>/=800mcg per day budesonide/equivalent and long-acting beta agonist)
3. At least 4 severe attacks (defined as the need for a short course of oral steroids, or hospitalisation) in the previous 12 months, OR if on maintenance oral steroids then at least 2 severe attacks in the last 12 months
+/-
4. Poor asthma control defined as a score of < 20 on the Asthma Control Test (ACT) [children aged 12-16 years], or childhood Asthma Control Test (cACT) [children aged 6-11 years]

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Child

Lower age limit
6 years

Upper age limit
17 years

Sex
All

Key exclusion criteria
Current participant exclusion criteria as of 10/09/2020:
1. Considered unfit for the study or risk of noncompliance with study procedures by the responsible physician as a result of medical interview, physical examination or screening investigation
2. Known hypersensitivity to Omalizumab or Mepolizumab or to any of the excipients
3. History of drug or other allergy, which, in the opinion of the responsible physician, contra-indicates their participation
4. Pregnant, lactating or within 6 weeks post-partum or breast feeding
5. Participated within 3 months in a study using a new molecular entity, another study investigating drugs or in a study with invasive procedures
6. Significant alternative diagnoses that may mimic or complicate asthma, in particular dysfunctional breathing, panic attacks, and overt psychosocial problems (if these are thought to be the main diagnosis; they can be present in addition to asthma major problem rather than in addition to severe asthma)
7. Significant other primary pulmonary disorders in particular cystic fibrosis, or interstitial lung disease
8. Diagnosis of chronic inflammatory diseases other than asthma (e.g. inflammatory bowel disease)

Previous participant exclusion criteria:
1. As a result of medical interview, physical examination or screening investigation the physician responsible considers the child unfit for the study or has a risk of non-compliance with study procedures
2. The child has a history of drug or other allergy, which, in the opinion of the responsible physician, contra-indicates their participation
3. Participant is female who is pregnant, lactating or within 6 weeks post-partum or breastfeeding
4. The child has participated within 3 months in a study using a new molecular entity, another study investigating drugs or in a study with invasive procedures
5. Significant alternative diagnoses that may mimic or complicate asthma, in particular dysfunctional breathing, panic attacks, and overt psychosocial problems (if these are thought to be the major problem rather than in addition to severe asthma)
6. Significant other primary pulmonary disorders in particular cystic fibrosis, or interstitial lung disease
7. Diagnosis of chronic inflammatory diseases other than asthma (e.g. inflammatory bowel disease)

Date of first enrolment
23/04/2021

Date of final enrolment
30/06/2025

Locations

Countries of recruitment
United Kingdom

England

Scotland

Study participating centre
Royal Brompton & Harefield NHS Foundation Trust
Royal Brompton Hospital
Sydney Street
London
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SW3 6NP

Study participating centre
Manchester University NHS Foundation Trust
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Study participating centre
University Hospital Southampton NHS Foundation Trust
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Study participating centre
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Sponsor information

Organisation
Imperial College London

ROR
https://ror.org/041kmwe10

Funder(s)

Funder type
Government

Funder Name
NIHR Evaluation, Trials and Studies Co-ordinating Centre (NETSCC); Grant Codes: 17/60/51

Funder Name
National Institute for Health Research (NIHR) (UK)

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The anonymised data can be shared with other researchers following the end of the study. The request should be made to the Chief Investigator Prof. Sejal Saglani (s.saglani@imperial.ac.uk).

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		21/08/2024	23/08/2024	Yes	No
HRA research summary			28/06/2023	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes