ATT-Heart:

An open label, single-centre dose escalation trial, investigating the safety and feasibility of Autologous Thymus derived regulatory T cell treatment for the prevention of cardiac allograft vasculopathy in children receiving Heart transplant.

ATT-Heart

PARENTS / GUARDIANS INFORMATION SHEET

Chief Investigator: Professor Michael Burch

We invite your child to take part in a research study:

- We would like to invite your child to take part in a clinical trial (also called a research study).
- This research study plans to test the safety of a potential new medicine containing regulatory T cells (also known as 'Treg treatment'). This is a bespoke medicine made for each child from their own tissue which can be collected at the time of heart transplant surgery.
- Before you decide whether they would like to take part in the trial, it is important for you and for your child to understand why the research is being done and what it would involve for you all.
- Please take some time to read the information carefully, and discuss with your family, friends and doctor, if you would like to.
- Please ask us, if anything is not clear, or you would like some more information.

Thank you for taking the time to consider your child taking part in the **ATT-Heart** Study.

How to contact us:
Local Research Team Contact: **Email:** **Telephone Number:**

Key information:

Your child has been invited to participate as he/she is on the heart transplant waiting list.

Your child does not have to take part; participation is entirely voluntary and you and your child can decide to stop taking part at any time, without giving a reason. If you do not wish to take part, this will not affect the care your child receives from your doctors or other health care professionals.

This will involve collection of some of your child's tissue which can be done at the same time during heart transplant surgery. Using this tissue, the ATT-Heart trial team can make a medicine containing regulatory T cells (also called Tregs) for your child to receive later on (after they have recovered from transplant surgery).

If you both decide to take part, you can keep this sheet and you will be asked to sign a consent form. Your child will be asked to sign an assent form (age-dependant). By signing these forms, you both will be confirming your willingness to take part.

The study will take place at Great Ormond Street Hospital (GOSH), London.

Research is vital to the continuing improvement in survival rates of children undergoing heart transplant and this study is looking at ways to prevent to a leading cause of death called Cardiac Allograft Vasculopathy (CAV) in children who survive after transplant.

By participating in this study, your child will help us build up the knowledge about potential treatment options for CAV which is an important long-term complication of heart transplant.

The potential risks and benefits are included in this information sheet.

Why is this study needed?

Heart transplantation is a lifesaving procedure, however the long-term success of this involves careful life-long monitoring and adhering to daily immunosuppressants to prevent rejection.

Cardiac Allograft Vasculopathy (also known as CAV) is a disease than can affect the new (donor) heart. All patients after heart transplant surgery continue to be at risk of developing the disease despite good management with immunosuppressant medications.

CAV is due to inflammation caused by the recipient's immune system towards the donor heart, which results in a progressive narrowing of blood vessels that supply oxygen and nutrients to the new heart muscle and eventually, this can result in the weakening of the new heart muscle pump.

The process of CAV is complex and though immune cells and rejection plays a part, traditional cardiac risk factors such as high blood pressure, high cholesterol and diabetes also contribute.

Recent statistics show that 10 years after heart transplantation, approximately a third of children will have signs of CAV.

After transplantation, your clinical team will manage your child's immune response towards the new heart with immunosuppressant medications to prevent rejection and also monitor blood pressure and try to manage other risk factors like high cholesterol to reduce the risk of developing CAV in the future.

Once CAV has become established, it cannot be reversed using conventional medical or surgical approaches so there is a pressing need to prevent the onset of CAV in the first place. Our study team is looking at new ways to do this, so that we can try and improve the longevity of the heart transplant and keep patients who receive a heart transplant healthy for longer.

The ATT-Heart study is looking at a new type of potential treatment to prevent CAV using expanded regulatory T-cells (Tregs) cell therapy.

Who is organising and funding the study?

The study is funded by the British Heart Foundation. The trial is sponsored by Great Ormond Street Hospital.

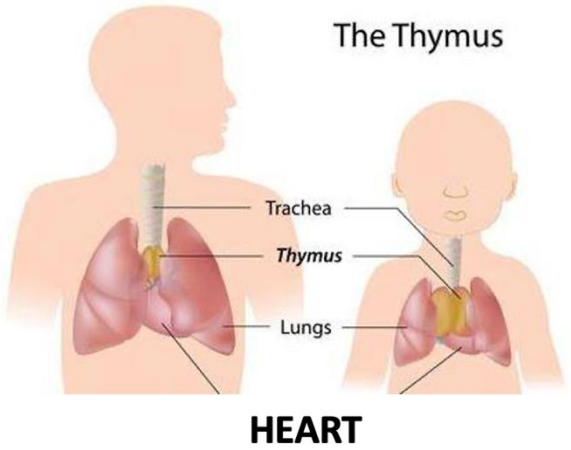
The lead investigator for the study is Professor Michael Burch.

What is the potential therapy being tested?

Regulatory T-cells (Tregs) are naturally produced by our immune system and their job is to regulate other cells in the immune system and prevent them from attacking our own tissues and organs. Tregs and other T cells are produced by the thymus gland which sits in front of the heart and major blood vessels. Most of the thymus gland's work is done before birth, so once born babies will have all the T cells they need for a functional immune system.

Due to the position of the thymus (in front of the heart and major blood vessels), it is usually necessary for the surgeon to remove most of its tissue at the time of open-heart surgery, including during heart transplant.

If you and your child agree to enter the trial, the thymus will be collected from your child during heart transplantation surgery or during the time of having a pump assist device fitted in (which may need to occur before the transplant surgery itself). Thymus tissue will be transferred to a specialist laboratory unit at Guy's and St Thomas' NHS Foundation Trust to be processed.



The cells obtained from the thymus of your child are used to create the Treg cell therapy for your own child. Therefore, the Treg cell therapy is unique to each patient and is described as an 'autologous' cell therapy ('*auto*': means, "your own,") where the cell therapy given back to the child consists of *their own* Treg cells.

Tregs will be extracted from the thymus and then expanded. This means that the cells will be grown in the laboratory to reach the dose required for your child. It can take up to 23 days to produce enough cells for the infusion. The cells will be kept frozen until they are ready to be used for treatment. The cells will undergo

various quality control checks to ensure that they are of good quality. This is in line with process which has been approved by the Medicines and Healthcare products Regulatory Agency (MHRA).

How does the potential therapy work?

Our body has an immune system that works to keep us free of infections using a complex system of barriers (for example: skin), cells (for example: white blood cells) and proteins (for example: antibodies). These parts of the immune system can work together to detect and eliminate infections, when they occur.

When our immune system works as it should, it can tell the difference between our own body ("self") and something that shouldn't be there ("non-self," for example: an infection). In other words, the immune system is designed so that it will not attack our own organs.

Tregs regulate other cells in the immune system, and can prevent inflammation directed against our own organs. The aim of the study treatment is to use Tregs to regulate your child's immune system to suppress the potential for their immune system to be directed against the transplanted heart.

The bespoke cell therapy treatment we will produce for each child entering this trial will be known as TR006.

If you and your child agree to take part in the study, your child will receive a single dose of TR006 at least three months after their heart transplant. In the trial, we will begin with a lower dose (1 to 3 million cells per kilogram) to ensure safety before giving a higher dose (5 to 10 million cells per kilogram) to the next cohort of patients.

Have Tregs been used before in patients?

Cell therapy with Tregs has shown promise for patients in different therapeutic areas. Early clinical trials testing the use of Tregs in adult patients with kidney and liver transplants, as well as, adults and children with autoimmune disease such as diabetes have been shown to be safe with some early signs of clinical benefit. A research group in Spain have recently published a report on giving autologous thymus-derived Treg cell therapy to an infant early after heart transplantation. The injection of the Treg cell therapy was tolerated well, with no adverse effects related to the infusion. They demonstrated that the Treg cell therapy boosted the number of Tregs in the child's blood circulation during the 2 year follow up period which is promising for future treatment of moderating the immune response to the new heart. Their clinical trial is currently ongoing with a plan to give Tregs to 10 children.

Data from pre-clinical and animal models have shown that Tregs are important in moderating the immune response against the transplanted heart and can prevent the development of CAV. We believe that Treg cell therapy can prevent CAV developing in paediatric heart transplant recipients and this is the future goal of our trial.

We have included links to these study findings in the final section for further reading.

What type of trial is it?

This study is a Phase I (one) clinical trial. It means the Treg cell treatment described above is primarily being tested for safety purposes.

The aims of the study are:

- To confirm that this potential therapy can be safely given to nine children receiving a heart transplant.
- To discover what happens to these cells after they have been given to children.
- To see how the children's immune system reacts to the cells.
- To determine the optimal tolerated dose of the Treg cell infusion to test the biological activity of the treatment.
- To help us design a larger trial to test this potential therapy further.

Why has my child been invited and what does their contribution mean?

Your child has been invited to take part in this trial because he/she is on the heart transplant waiting list.

By participating in this study, he/she will help us build up the knowledge about the new Treg cell therapies being developed and potentially increase future treatment options for CAV.

Does he/she have to take part?

Your child does not have to take part in this study. Participation is entirely voluntary and her/his clinical care will not be affected regardless of the decision. If you both decide to take part, you will be asked to sign a consent form, and your child will be asked to sign an assent form (age-dependant). By signing these forms, you both will be confirming your willingness to take part.

If you both decide to take part, you are still free to withdraw at any time and without giving a reason. Deciding not to take part or withdrawing from the study will not affect the healthcare that your child receives, or their legal rights.

What are the possible benefits of taking part?

There are no known benefits to the participants taking part in the study. While we hope that the Treg cells will prevent the onset of CAV in your child (as is suggested in pre-clinical studies and data from other early phase clinical trials around the world), this may not happen as this an early phase clinical trial with Tregs which are given at lower doses. Our main aim is to establish safety of this cell therapy in children.

Your child may not directly benefit from taking part in this study, but the information gained from their participation may help towards improving the treatment options available for CAV in the future. Furthermore, evidence from this study could support opening of larger trials in children with heart transplants in the future.

What are the possible risks of taking part in the trial?

Risks associated with thymus removal

Due to the position of the thymus gland in front of the heart, it is usually necessary for the surgeon to remove most of the thymus in order to complete your child's heart surgery (such as heart transplant or placement of a heart pump assist device). Because the thymus gland works mainly before birth and your child will have already developed a full complement of T cells, removal of the thymus at this stage will not cause any problems with deficiency of the immune system. In fact, sometimes a small piece of the thymus tissue may be left in place depending on its position and may grow back after surgery. After the transplant surgery, your child will have to take immunosuppressant medication to prevent their immune cells rejecting their new donor heart. This will be the same treatment schedule whether or not your child is enrolled into ATT-Heart.

Risks associated with the infusion treatment:
This is the first time that these particular expanded Tregs will be tested in children in the UK and so there may be risks we don't know about yet and they could be serious. The safety information we have is based on pre-clinical data and also other clinical trials using expanded Tregs in other conditions.

Your child will be closely monitored for any signs of adverse effects. If they become unwell following treatment infusion, there are medications that can be used to suppress the action of the Tregs.

During the study your child will receive an infusion of their own expanded Treg cells. We anticipate that the risks of cell administration are similar to those of a blood transfusion. Allergic reactions to blood transfusions are caused by the body's immune system reacting to proteins or other substances in the donated blood, but they are uncommon. The Treg cells are made from your child's own cells rather than cells from a blood donor, so the risks are likely to be less than for a blood transfusion.

The symptoms of a blood transfusion allergic reaction are usually mild and occur during or shortly after the transfusion. Common symptoms include: a red, itchy skin rash, swelling of the hands, arms, feet, ankles and legs, dizziness and headaches. Less common symptoms include: high temperature, chills and shivering. These types of reactions can usually be managed by slowing down or stopping the transfusion.

Your child will be given paracetamol and anti-histamine medication (such as piriton) before the Treg infusion to reduce the risk of any reaction. We know that regulatory cells similar to the cells used in this trial have previously been given to 64 children with type 1 Diabetes patients in the USA (Seattle) and to 12 children with diabetes in Poland. In both cases, the patients were monitored very closely and didn't have any immediate reactions to the infusions.

In Madrid, one infant received thymus derived regulatory T cells after heart transplant with no safety issues being reported during follow up for 2 years after the dose. More children have been administered Tregs as part of this ongoing study with follow up data being awaited.

We also have safety information from 2 clinical trials we have run from Guy's Hospital. 12 kidney transplant patients and 9 liver transplant patients were treated with Treg cells. No reactions were reported for the kidney patients. One adverse effect was reported for a patient on the liver transplant trial and this may have been related to the Treg infusion. The patient experienced fever, chills and a decrease in white blood cells count less than 24 hours after having received the infusion. The patient was given intravenous fluid and antibiotics. The adverse effects resolved within 48 hours and the patient felt normal again.

Harm to Unborn Children:
We don't have information about the effects of regulatory T-cells in pregnancy or breast-feeding. Therefore, we need to carry out urine pregnancy tests in any patients of child-bearing potential before receiving the infusion and at various stages during the study, as pregnant or nursing mothers will not be allowed to take part in the trial.

Female participants who could become pregnant during the trial must use an effective method of birth control during the trial. If applicable, the trial doctor will discuss relevant birth control methods with you and your female child.

If your female child becomes pregnant, or thinks she may be pregnant during the trial, please **immediately** contact the trial doctor/team.

Risks can be associated with procedures (such as: blood tests, cardiac tissue biopsies and cardiac vascular imaging) that form part of the routine care for transplant patients. These procedures are not performed specifically for study purposes alone. However, as data from these routine procedures will be used as part of the study, we summarise them briefly below. Please refer to the usual information and consent form given by the Clinical Team regarding these procedures for a full explanation of risks involved. Do ask a member of a study team for further information and we would be happy to go through each procedure (and the respective risks) in more detail with you.

- Blood samples:
During the collection of the blood samples, your child may experience discomfort and there is a risk of bleeding and bruising around the puncture site but this is very rarely serious. We can offer numbing cream or spray to help with this.

Frequent blood monitoring, is standard of care in the post-transplant patient and there is some additional monitoring tests for safety and research with TR006 for those enrolled in the study. Volumes for blood draw will be closely monitored and adjusted accordingly to the weight of your child. Furthermore, the study team will pay particular attention to full blood count trend and will be monitoring for anaemia during study visits.

Where possible and once families are consented, blood tests can be done at the same time as routine medical procedures (e.g. during biopsy procedures when your child receives a general anaesthetic) to minimise discomfort or pain. Additional blood samples for research will be taken at the same time as clinical samples to minimise distress for your child.

- Cardiac tissue biopsies:
This is a medical procedure to collect small pieces of heart tissue for examination under a microscope. These are performed on all patients who have undergone a heart transplant and is part of the usual care post-transplant (not just for study patients).

The test is performed in a catheter laboratory with x-rays. Your child will usually receive a general anaesthetic. This is necessary because the procedure is a little bit uncomfortable, and it is important that the patient stays very still. Once asleep, we put a needle into one of the veins in the neck (or sometimes in the leg), and through that needle we pass a wire towards the heart. This wire allows us to direct a long tube (called the “catheter”) into the heart, through which we pass a small pair of pincers. During this time, we are watching with x-rays to check that the pincers are in the correct place. Once there, we take three or four samples from the inside of the heart, which we send to the lab.

Samples will be checked under the microscope for rejection as is usual. However, if you agree, the research team would also like to check the samples taken for cells pertaining to the study to see how TR006 affects the cardiac muscle itself before and after the infusion.

- Cardiac Vascular imaging:
Intravascular ultrasound (IVUS) and cardiac angiography using a dye (contrast) are specialist imaging tests that look more closely at the coronary arteries (blood vessels that supply the heart muscle with oxygen and

nutrients). In CAV these vessels can become narrowed and inflamed which affects the supply of the heart and affect its pumping function. Both of these tests are performed whilst your child is asleep (under general anaesthetic) in a similar way using catheter tubes as in a cardiac biopsy procedure.

These are also a routine tests performed by the transplant team at 3 months (at the same time as the cardiac biopsy) and at 12 months after the heart transplant. The data from this will be collected for the study purposes to check for CAV development.

Coronary angiograms and X-ray guided cardiac biopsies are part of your child's routine care. If your child takes part in this study they will not undergo any additional angiograms or biopsies. These procedures use ionising radiation to form images of their body and provide the doctor with other clinical information. Ionising radiation may cause cancer many years or decades after the exposure. The chances of this happening to your child are the same whether they take part in this study or not.

What are the alternatives for treatment?

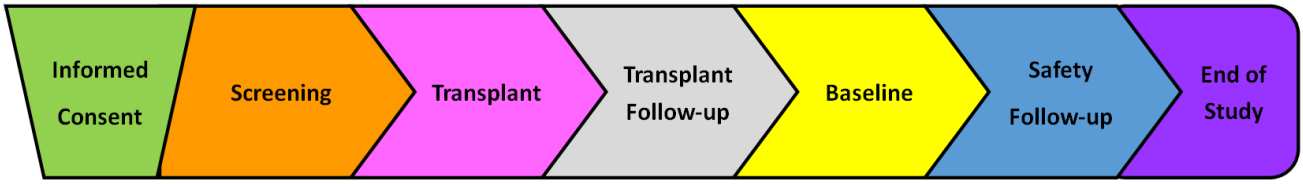
If you and your child decide not to participate in this study, your doctor will discuss your treatment options with you.

At this stage of development, it is not possible to offer further Treg infusions after the end of the study. Further testing will be needed in a larger group of people to see if the potential therapy works and is safe to receive.

What would taking part involve?

If you and your child agree to take part in the study, formal consent will be taken whilst they are on a heart transplant waiting list. This will occur before any research takes place. We have designed our trial visits around the usual transplant pathway appointments that your child would expect to have before, during and after the heart transplant in order to make the visit schedule and investigations as streamlined as possible. The main additional step is the administration of the regulatory T cell infusion, around which we will have to do some extra monitoring and investigation for safety purposes.

Here is a summary of the stages of the study:



We have summarised the time line of events you and your child can expect during the trial, in the table below. Please turn to page 12 to section, "Study Schedule (detailed)," for a detailed explanation for each individual stage.

Table of Study Schedule:

Visit	Clinical and Study Procedures
Enrolment / **Screening**	• Enrolment into ATT-Heart. • Medical history review. • Clinical blood tests (including virology testing).
Day of Transplant (When a donor heart becomes available)	• Medical history review. • Medical observations (vital signs, height and weight measured). • Clinical blood tests (including virology testing). • Research blood samples. • Urine pregnancy test.† • **Heart transplant.** • **Thymus taken to laboratory facility to generate cell therapy.** • Potential overnight stay in hospital.
Transplant Day 1 (Day after transplant)	• Medical review (including physical examination). • Medical observations (vital signs measured). • Cardiac assessments (ECG and echocardiogram). • Clinical blood tests. • Research blood samples.
Transplant Follow-up Day 14 (14 days after heart transplant) (+/- 1 week)	• Medical review (including physical examination). • Medical observations (vital signs, height and weight measured). • Cardiac assessments (ECG and echocardiogram). • Clinical blood tests. • Routine cardiac biopsy. • Research blood samples.
Transplant Follow-up 1 Month (1 month after heart transplant) (+/- 1 week)	• Medical review (including physical examination). • Medical observations (vital signs, height and weight measured). • Cardiac assessments (ECG and echocardiogram). • Clinical blood tests.
Transplant Follow-up 2 Month (2 months after heart transplant) (+/- 1 week)	• Medical review (including physical examination). • Medical observations (vital signs, height and weight measured). • Cardiac assessments (ECG and echocardiogram). • Clinical blood tests.
Transplant Follow-up 3 Month (3 months after heart transplant) (+/- 1 week)	• Medical review (including physical examination). • Medical observations (vital signs, height and weight measured). • Cardiac assessments (ECG, echocardiogram, intravascular ultrasound* and coronary angiography*). • Clinical blood tests (including virology testing). • Urine pregnancy test.† • Routine cardiac biopsy. • Research blood samples.
Transplant Follow-up 4 Month (4 months after heart transplant) (+/- 3 days) **Visit may not be required if the patient is ready for TR006 after the Transplant Follow-up 3 Month study visit.**	• Medical review (including physical examination). • Medical observations (vital signs, height and weight measured). • Cardiac assessments (ECG and echocardiogram). • Clinical blood tests (including virology testing). • Urine pregnancy test.† • Research blood samples.
Transplant Follow-up 5 Month (5 months after heart transplant) (+/- 3 days)	• Medical review (including physical examination). • Medical observations (vital signs, height and weight measured). • Cardiac assessments (ECG and echocardiogram). • Clinical blood tests (including virology testing). • Urine pregnancy test.†

Visit may not be required if the patient is ready for TR006 after the Transplant Follow-up 3/4 Month study visits.	• Research blood samples.
Infusion Day: Baseline Day 0 (Day of infusion with TR006; this is 3 to 6 months after the heart transplant)	• Medical review (including physical examination). • Medical observations (vital signs, height and weight measured). • Cardiac assessments (ECG and echocardiogram). • Clinical blood tests. • Urine pregnancy test.† • **Infusion of TR006.** • Overnight stay in hospital.
Baseline Day 1 (Day after the infusion with TR006)	• Medical review (including physical examination). • Medical observations (vital signs, height and weight measured). • Cardiac assessments (ECG and echocardiogram). • Clinical blood tests. • Research blood samples.
Immediate Safety Follow-up (For the 2 to 13 days after infusion with TR006) (+/- 2 days)	• Remote medical review (performed by a daily phone call).
Safety Follow-up Day 14 (14 days after infusion with TR006) (+/- 2 days)	• Medical review (including physical examination). • Medical observations (vital signs, height and weight measured). • Cardiac assessments (ECG and echocardiogram). • Clinical blood tests. • Research blood samples.
Safety Follow-up Day 28 (28 days after infusion with TR006) (+/- 2 days)	• Medical review (including physical examination). • Medical observations (vital signs, height and weight measured). • Cardiac assessments (ECG and echocardiogram). • Clinical blood tests. • Research blood samples.
Safety Follow-up Month 2 (2 months after infusion with TR006) (+/- 1 week)	• Medical review (including physical examination). • Medical observations (vital signs, height and weight measured). • Cardiac assessments (ECG and echocardiogram). • Clinical blood tests (including virology testing).
Safety Follow-up Month 3 (3 months after infusion with TR006) (+/- 1 week)	• Medical review (including physical examination). • Medical observations (vital signs, height and weight measured). • Cardiac assessments (ECG and echocardiogram). • Clinical blood tests. • Urine pregnancy test.† • Cardiac biopsy. • Research blood samples.
Safety Follow-up Month 6 (6 months after infusion with TR006) (+/- 2 weeks)	• Medical review (including physical examination). • Medical observations (vital signs, height and weight measured). • Cardiac assessments (ECG and echocardiogram). • Clinical blood tests. • Research blood samples.
Safety Follow-up Month 9 (9 months after infusion with TR006) (+/- 2 weeks)	• Medical review (including physical examination). • Medical observations (vital signs, height and weight measured). • Cardiac assessments (ECG, echocardiogram, intravascular ultrasound* and coronary angiography*). • Clinical blood tests (including virology testing). • Urine pregnancy test.† • Routine cardiac biopsy. • Research blood samples.

Safety Follow-up Month 12 (12 months after infusion with TR006) (+/- 4 weeks)	• Medical review (including physical examination). • Medical observations (vital signs, height and weight measured). • Cardiac assessments (ECG and echocardiogram). • Clinical blood tests. • Research blood samples.
End of Study Follow-up (24 months after infusion with TR006) (+/- 4 weeks)	• Medical review (including physical examination). • Medical observations (vital signs, height and weight measured). • Cardiac assessments (ECG and echocardiogram). • Clinical blood tests. • Urine pregnancy test.† • Research blood samples.

† Only applicable to female participants who could become pregnant during the trial.
* Only if your child is over 25kg in weight.

What will my child and myself have to do?

You will need to give written informed consent for all study procedures. Where appropriate, your child will also have to provide written informed consent to take part in ATT-Heart (depending on their age). This will include permission for the study team to contact your child's GP to let them know that your child is taking part in the study.

Your child will have to attend the study visits at GOSH for the procedures and tests described in the "What would taking part involve?" Section (of this Information Sheet). Most of these visits are done at the same time as the usual post-transplant follow up appointments and most of the investigations performed are part of the usual standard of care in these patients.

Your child will need to be available for at least one additional overnight stay (Baseline Day 0 for the TR006 infusion) at GOSH in addition to any planned hospital admissions for the heart transplant surgery and subsequent clinical issues. Please see below (on page 14) in the Study Schedule (detailed) for further information.

Whilst your child is taking part in this study, you should both tell your doctor of any medications that your child takes, including over-the-counter medicines and vitamin supplements. Your doctor will discuss any drugs that your child should not take during the study.

Please contact the clinical or study team at GOSH if your child is feeling unwell and report any side effects/reactions when your child attends the hospital for the trial visits.

You and your child will also be given a patient information card with details of the study. Please carry this with you at all times, especially to any medical visits, to make healthcare professionals aware that your child is a study patient. It will also have contact details for the study staff should you or your healthcare professionals wish to contact us for anything over the duration of the trial.

What will happen with my child's samples?

Some of your blood samples collected will be analysed by the local laboratory at GOSH. These samples will be part of the clinical care and will be used to monitor your child's vital functions and identify any potential safety concerns.

The research blood samples and some of the biopsy samples will be transferred to labs at GOSH and/or Guy's Hospital and/or King's College London for analysis and storage. If there are any leftover clinical blood samples, these also may be sent to labs at GOSH and/or Guy's Hospital and/or King's College London for analysis and storage. If there are any cells remaining from the manufacturing process that makes the dose of the TR006 treatment, these may be retained by the study team members at Guy's Hospital and/or King's College London to further investigate this new type of treatment.

Your child's biological samples will be stored securely in accordance with the Human Tissue Act and according to national and local NHS Research Governance guidelines. Any details that can identify your child will be removed and the samples will be labelled only with a unique study identification number.

An external academic team or commercial company may be involved with the analysis of some of the research samples which will be pseudo-anonymised. This means that the study team will keep a list of people, along with the codes used on the research samples. Only the coded samples will be sent for analysis. The analysis may be carried out outside the UK. The same confidentiality rules will apply to samples sent outside the UK.

If your child is a girl who has started her period, a urine pregnancy test will be done routinely (even if they are not sexually active) at multiple time points during the study. This is mainly for safety purposes to exclude the possibility of pregnancy in patients who will receive the cell therapy and also prior to routine investigations such as X-rays which are not recommended during pregnancy. This has been agreed with the Research & Development Team at GOSH who oversee the safety and conduct of all studies carried out within GOSH. If applicable to your child, these will occur at the following visits:
- Day of heart transplant.
- Three months post heart transplant.
- Day of TR006 infusion (also known as Baseline Day 0).
- Safety Follow-up Month 3 (which is 3 months after infusion with TR006).
- Safety Follow-up Month 9 (which is 9 months after infusion with TR006).
- End of Study Follow-up (24 months after infusion with TR006).

Will my child's samples be used for future research?

Leftover samples may be made available for further analysis or for use in future research studies as long as you and your child agree to this. We will prioritise research with investigators who have received the necessary ethical and regulatory approvals. This research could be in or outside the UK, and could be with academic or commercial partners. DNA analysis may be performed on the stored samples. Nobody will know who your child is from your samples because the samples will be pseudo-anonymised (as described above).

If you and your child agree to the use of the samples in this way, please discuss this with the Study Team and you will have the choice to opt in during the study consent process.

What happens if we don't want to carry on with the study?

You and your child are free to withdraw from this study at any time. Your participation is entirely voluntary. This will not affect your future treatment options or the standard of care you receive from your doctors and nurses.

As a study of a potential new therapy, it is important that participants are monitored after dosing and over a longer period of time. We would like to check how your child is feeling after receiving the therapy for up to two years. If your child decides to withdraw, we will ask them to carry on visiting the hospital for safety visits.

Data or tissue that has already been collected with consent before withdrawal will be retained and used in the study. No further data or tissue would be collected as part of the trial. No further research study procedures would be carried out on your child.

What if relevant new information becomes available?

Sometimes during the course of a research project, new information becomes available about what is being studied. To ensure your child's safety, an independent committee of experts will review the results regularly during the study. They will also look at the results of other relevant studies. They can stop the study early if they see any unfavourable results.

If new information becomes available, your study doctor will tell you and your child about it and discuss everything with both of you. They will explain to you both any potential change to your child's normal care and discuss whether they want to, or should, continue in the study. Your study doctor can take your child out of the study at any time if it is in their best medical interests to stop their participation. The study sponsor also has the right to direct your study doctor to take your child out of the study at any time.

If the study is stopped for any other reason, you and your child will be told why, and your child will receive normal standard of care.

What will happen to the results of the research study?

The study is expected to take around two years to complete, starting in 2024. We are hoping to publish the results through medical publications shortly after completing the study. At this point we will be happy to send you a summarised version of the study results at your request.

Any study results or published reports using the data will be anonymised prior to publication, so that it is not be possible to identify participants. Your child will not be identifiable in the report.

What medical care will my child receive at the end of the research study?

Once your child's involvement in the study is over, they will continue to receive their usual care (and continue to see their doctor on a regular basis). The study doctor will discuss treatment options with you both.

Study Schedule (detailed):

Informed Consent:	Screening:

Once the consent forms have been signed, the study team we will invite you and your child to a screening process where a study Doctor will talk to you and your child and you will be asked about your child's general health, medical history and the medications they take. Routine clinical blood tests will be performed to ensure it is safe for your child to enter the study. The blood tests and screening visit can be done at the same time as your planned visit at GOSH in order to avoid multiple trips or investigations.

One of these blood tests will be for infection with HIV (Human Immunodeficiency Virus), Hepatitis B and C, Human T-lymphotropic virus and syphilis. These blood tests are already done as part of the usual transplant assessment process. If your child has any of these infections they won't be able to take part in the study because Tregs cannot be prepared safely under these circumstances. These tests will be repeated again at various time points as outlined in the study.

During this visit, we will need to take up to 10ml of blood (less than two and a half teaspoons of blood) for routine tests.

Transplant:

Once a heart becomes available for your child, they will be admitted into hospital to prepare for the heart transplant operation. As part of this visit, the recent medical history for your child will be reviewed and up-to-date bloods tests, including virology tests, will be performed as is usual prior to surgery.

We will measure your child's vital signs (blood pressure, heart rate, respiratory rate, temperature and oxygen saturation) as well as your child's height and weight.

During these visits, we will need to take up to 10ml of blood at each visit (less than two and a half teaspoons of blood) for routine tests.

If you are still both happy to take part in the study, some additional blood samples taken will be sent off to look closely at the immune cells as well as their genetic code and other investigations of immune function (up to 11ml more blood per visit, which is less than two and a half teaspoons of blood). The research blood samples will be taken for comparison with bloods taken after receiving the cell therapy. This will help us to understand how your child's immune system reacts to Tregs and what happens to the expanded Tregs in their body.

At the time of the heart transplant surgery, the thymus is removed and transferred to a specialist laboratory at Guy's and St Thomas' NHS Foundation Trust where it is processed to make TR006. Once the TR006 has been made it will be it is ready to be used for treatment.

After the heart transplant operation, your child will be kept in the hospital whilst they recover and will also have routine clinical examinations and clinical investigations such as regular blood tests, heart scans and close monitoring to make sure that everything is okay with the heart transplant. Results of the following tests will be shared with the trial team:
- ECG (electrocardiogram): A type of heart tracing that can detect electrical signals produced by your heart. This is done by attaching a number of sticky sensors to your child's skin. The ECG is a painless test but your child might feel some discomfort when the sensors are removed (a bit like removing a plaster).
- Echocardiogram: A jelly scan used to look at the heart and nearby blood vessels that uses sound waves to create images of the heart.

For research purposes specifically, we will take some blood samples at the same time as routine clinical blood tests to look at the genetic code of the immune cells and perform other investigations of immune function (up to 3ml, less than one teaspoon of blood) to monitor the immune system once the new heart is in place.

After the heart surgery, it is usual practice for the transplant team to do a cardiac tissue biopsy to check for any early signs of rejection in the new heart. In addition to the standard clinical tests that are performed on the heart tissue to check for rejection, if you and your child are happy, the samples will also be looked at by the research team to see how the immune cells are functioning in the new heart tissue.

Once the Clinical Team are happy with the progress of the heart transplant, your child will be discharged from the hospital.

Transplant Follow-up over 3 months (4 visits) (potentially up to 5 months (6 visits)):

Your child will be seen in the outpatient clinic at GOSH as required and advised by the clinical team. These visits do vary between children but can be fairly frequently occurring up to once every 2 weeks. For the study purposes, we will co-ordinate with their planned clinic visit schedule and see your child at: day 14 post-transplant, then at: one, two and three months post-transplant. There is the chance that extra study visits may be carried out at the same time as your planned clinic visit schedule at four and five months post-transplant too.

All of these visits will include a medical review and general assessment of your child along with their vital signs and height and weight being measured. There will also be cardiac assessments (ECGs and echocardiograms) carried out with clinical samples being taken for routine monitoring. Repeat virology blood tests will be taken at month three post-transplant.

During these visits, we will need to take up to 10ml of blood at each visit (less than two and a half teaspoons of blood) for routine tests.

At month three post-transplant, there will be another routine cardiac biopsy taken from your child to check the state of the transplanted heart. If you and your child are happy, some clinical samples taken (for example: cardiac biopsies) may be used for research purposes.

Furthermore, at day 14 and month three post-transplant, during the planned cardiac biopsies there will also be some additional blood samples taken for our genetic and other investigations of immune function (up to 11ml more blood for these visits only, which is less than two and a half teaspoons of blood per visit). These tests can be done at the same time as any routine blood tests ahead of the procedure or when your child is in theatre to minimise any discomfort.

Additionally, if your child weighs over 25kg, there will be a couple of additional clinical cardiac assessments done at the same time as the cardiac biopsy procedure and at one year after the transplant surgery (and these are done primarily to monitor for early signs of CAV):
- An intravascular ultrasound: An imaging test that creates images of the heart and blood vessels from the inside of the body.
- A coronary angiography: A heart test performed using dye that looks at the blood supply of the heart and in particular the coronary vessels to check for any narrowing that can happen in CAV.

These procedures are carried out to help monitor your child's health after their heart transplant and to make sure that everything is safe in order for them to carry on their participation in the study.

Baseline (two consecutive days: Baseline Day 0 and Baseline Day 1):

> Infusion Day: Baseline Day 0:

If screening and the transplant stage was successful, your child will begin the trial phase and attend Walrus ward (at GOSH) in preparation for the TR006 treatment on the morning of Baseline Day 0.

The study Doctor will talk to you and your child and you will be asked again about your child's general health, medical history and the medications they take.

Upon admission, we will perform a clinical examination and clinical blood tests for your child to make sure everything is okay to proceed with receiving the dose of TR006.

We will measure your child's vital signs and also carry out a couple of cardiac assessments (ECG and echocardiogram).

Your child will then receive a dose of TR006. It will be administered through a cannula (needle) in their arm by a Doctor or a Research Nurse. It should take around 30 minutes to complete.

A study Doctor will monitor your child closely before, during and after the infusion during the day. The team will measure your child's vital signs at regular intervals after the infusion (up to 6 hours post-dose).

Another set of clinical blood tests will be taken at 6 hours post-dose to allow us to monitor possible side effects by giving information on how organs such as liver, kidneys, heart, bone and bone marrow are working.

In total, we will need to take up to 5ml of blood over the whole visit (that is including before and after the infusion which is less than one and a half teaspoons of blood) for clinical monitoring after the infusion.

Your child will need to stay overnight in GOSH for monitoring purposes to make sure that everything is well after the infusion.

> The Day After Receiving the Infusion: Baseline Day 1:
A study Doctor will review your child to check how they are feeling. The study team will also take clinical blood tests, measure your child's vital signs and also carry out a couple of cardiac assessments (ECG and echocardiogram).

During this visit, we will need to take up to 3ml of blood for the whole visit (less than one teaspoon of blood) for monitoring purposes.

There will also be some additional research blood samples taken which will give us information about how your child's immune system reacts to Treg cells and what happens to the expanded T-cells in their body (up to 6ml more blood taken, which is less than two teaspoons of blood).

Your child will then be discharged from hospital 24 hours after the infusion as long as they are feeling well. The study doctor may ask your child to stay for longer observation if they have experienced any side effects.

Follow-Up After Discharge from Hospital After Receiving the TR006 Dose: Safety Follow-up:

> Immediate Follow-up (Days 2-13 post-infusion):

A study Doctor will give you a phone call every day (from days 2 to 13 post-infusion) and perform a remote medical review for your child to check if there have been any side effects and to ask about their general health.

> Outpatient Visits Over 12 Months (7 visits):
We will ask your child to visit GOSH at days 14 and 28 post-infusion and then months 2, 3, 6, 9 and 12, as an outpatient. These visits will be conducted at the same time as your visits to GOSH for the routine post-transplant follow up care in clinic to minimise any inconvenience to your family.

All of these visits will include a medical review and general assessment of your child along with their vital signs and height and weight being measured. There will also be cardiac assessments (ECGs and echocardiograms) carried out with clinical samples being taken for routine monitoring. Repeat virology blood tests will be taken at month two post-infusion.

During these visits, we will need to take up to 10ml of blood at each visit (less than two and a half teaspoons of blood) for routine tests.

At month three post-infusion, there will also be a routine cardiac biopsy taken from your child to check the state of the transplanted heart. Again, if you and your child are happy, some clinical samples taken (for example: cardiac biopsies) may be used for research purposes.

Furthermore, additional research blood samples will be taken at each study visit at the hospital (except at month two post-infusion). The highest amount of extra blood taken in a single visit for research purposes will be 11ml, which is less than two and a half teaspoons of blood per visit).

If your child weighs over 25kg, there will be a couple of additional clinical cardiac assessments (intravascular ultrasound and coronary angiography) carried out at the visit nine months post-infusion (approximately a year post heart transplant).

Final Study Follow-up (Month 24 post-infusion):

At month 24 post-infusion (two years after the dose of TR006 was administered), we will ask your child to visit GOSH as an outpatient to be seen by the study team.

This will include a medical review and general assessment of your child along with their vital signs and height and weight being measured. There will also be cardiac assessments (ECGs and echocardiograms) carried out with clinical samples being taken for routine monitoring.

During this visit, we will need to take up to 5ml of blood during the whole visit (less than one and a half teaspoons of blood) for routine tests.

The last set of research blood samples will be taken at this study visit at the hospital (up to 11ml additional blood for this last visit, which is less than two and a half teaspoons of blood).

Your child will then revert to their normal clinical schedule and will be seen by your Paediatric Cardiologist for routine standard-of-care clinical visits.

MORE INFORMATION ABOUT TAKING PART IN ATT-HEART

Who has reviewed the study?

This research has been reviewed by an independent group of people, called a Research Ethics Committee, to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given a favourable opinion by: XXXXX.

The study has also been reviewed by the UK Regulatory Authority, the MHRA (the Medicines and Healthcare products Regulatory Agency). The MHRA is part of the Department of Health with the responsibility to regulate clinical trials of medicines in the UK.

The families of patients who have previously had heart transplants and a patient group specialising in paediatric heart disease were involved in reviewing and providing feedback on this Patient Information Sheet, the Patient Invitation Letter, Informed Consent Form and study protocol.

Will my child be paid for taking part in this study?

You or your child will not receive any money for taking part in this study. However, a travel fund is available to help reimburse reasonable travel expenses associated with study visits. We will also cover the costs of overnight accommodation for the night of infusion day (Baseline Day 0) if needed.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions [Professor Michael Burch - Telephone number: 020 7405 9200 Extension: 38532 and E-mail: Michael.Burch@gosh.nhs.uk].

If you remain unhappy and wish to complain formally, you can do this through the GOSH Patient Advice and Liaison Service (PALS):
Telephone number: 020 7829 7862
E-mail address: pals@gosh.nhs.uk

In the event that something does go wrong and you are harmed during the research you may have grounds for legal action for compensation against Great Ormond Street Hospital but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).

How will we use information about your child?

We will need to use information from you, your medical records, your child, your child's medical records and your child's GP for this research project.

This information will include your child's name, NHS number, date of birth and contact details. People will use this information to do the research or to check their records to make sure that the research is being done properly.

People who do not need to know who your child is will not be able to see your child's name or contact details. Your child's data will have a code number instead.

GOSH is the sponsor of this research, and is responsible for looking after your child's information. We will keep all information about your child safe and secure by:

- Ensuring that information that could identify you or your child is held securely with strict arrangements about who can access the information.
- Making sure that all study personnel have undertaken relevant induction and training programmes to ensure that these staff members meet the highest standards in data collection and governance.
- Using clinical data that is stored on password-protected local clinical applications which can only be accessed by delegated clinical staff.
- Making sure that research data is stored electronically on a password-protected database with strict user access.
- Ensuring that any physical medical or research paperwork related to the study is stored securely in filing cabinets in a locked room and is only accessible by the local research team.

We may share data about your child outside the UK for research related purposes to:

- Conduct specialist analysis.
- Understand unique results.

If this happens, we will only share the data that is needed. We will also make sure you or your child can't be identified from the data that is shared where possible. This may not be possible under certain circumstances (for instance: if your child has a rare illness, it may still be possible to identify them). If their data is shared outside the UK, it will be with the following sorts of organisations:

- Universities.
- Organisations or companies involved in health and care research.

We will make sure your child's data is protected. Anyone who accesses their data outside the UK must do what we tell them so that your child's data has a similar level of protection as it does under UK law. We will make sure your child's data is safe outside the UK by doing the following:

- Some of countries your child's data will be shared with have an adequacy decision in place. This means that we know their laws offer a similar level of protection to data protection laws in the UK.
- We use specific contracts approved for use in the UK which give personal data the same level of protection it has in the UK. For further details visit the Information Commissioner's Office (ICO) website.
- We do not allow those who access your child's data outside the UK to use it for anything other than what our written contract with them says.
- We need other organisations to have appropriate security measures to protect your child's data which are consistent with the data security and confidentiality obligations we have. This includes having appropriate measures to protect your child's data against accidental loss and unauthorised access, use, changes or sharing.

Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that your child took part in the study.

We will keep your child's study data for the minimum period of 25 years (as per GOSH policy). The study data will then be fully anonymised and securely archived or destroyed.

You and your child can stop being part of the study at any time, without giving a reason, but we will keep information about your child that we already have.

If you or your child choose to stop taking part in the study, we would like to continue collecting information about their health from central NHS records, local hospital records and their GP. If you do not want this to happen, tell us and we will stop

You and your child have the right to ask us to remove, change or delete data we hold about you/them for the purposes of the study. We might not always be able to do this if it means we cannot use your child's data to do the research. If so, we will tell you why we cannot do this

You can find out more about how we use your child's information, including the specific mechanism used by us when transferring their personal data out of the UK by:

- Contacting Professor Michael Burch (Email: Michael.Burch@gosh.nhs.uk)
- Contacting the GOSH data protection officer at: your.data@gosh.nhs.uk
- Visiting the GOSH Privacy Policy webpage at: https://www.gosh.nhs.uk/privacy-policy
- Visiting: www.hra.nhs.uk/patientdataandresearch
- Discuss this with the study team if you have any questions.

Useful links for further interest of clinical research in Treg therapy

1. The use of thymus derived Tregs infusion in an infant post heart transplantation:

   Summary article outlining the basic science and other centres in the world investigating this therapy (British Columbia (Canada) and Spain- Madrid):
   https://www.bcchr.ca/news/how-thymus-could-stop-transplant-rejection

   Link to full paper of study conducted in Madrid:
   https://rupress.org/jem/article/220/12/e20231045/276370/First-in-human-therapy-with-Treg-produced-from

2. Review article describing the potential of Treg therapy to prevent Cardiac Allograft Vasculopathy (CAV) in children receiving heart transplants:
   Link to review article: https://pubmed.ncbi.nlm.nih.gov/39315099/

3. Use of regulatory T cell therapy in children with type 1 diabetes (American study)
   Link to full paper:
   https://www.science.org/doi/10.1126/scitranslmed.adn2404?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed

4. Use of regulatory T cell therapy in children with type 1 diabetes (Poland)
   Link to full paper:
   https://pubmed.ncbi.nlm.nih.gov/24704576/

5. Regulatory T cells therapy in liver transplantation (ThRIL study)

Link to full paper:
https://pubmed.ncbi.nlm.nih.gov/31715056/

6. Regulatory T cell therapy in kidney transplantation (ONE study)
   Link to full paper on ONE study:
   https://pmc.ncbi.nlm.nih.gov/articles/PMC7613154/

Thank you for taking the time to read this Patient Information Sheet