The ASTUTE study

Adalimumab vs placebo as add-on to Standard Therapy for autoimmune Uveitis: Tolerability, Effectiveness and cost-effectiveness: a randomized controlled trial.

This is a summary of the study.
More information can be found in the Patient Information Leaflet on page 2.

Why is the research being done?

Many patients with inflammatory eye diseases (uveitis) find their disease does not respond to or tolerate usual treatments, or they have considerable side effects including from high dose steroids. We want to look at how effective a drug called adalimumab is at treating people with uveitis. We also want to find out how uveitis and medications used to treat it impact patients and their quality of life. *See page 2.*

What would taking part involve?

Adalimumab is injected under the skin every 2 weeks. You would receive training on how to do the injections yourself.

This study has two stages. Everyone who joins the study will take part in stage one. This stage is a '**trial run**' for 16 weeks to see if you respond to adalimumab.

If you respond to adalimumab, you will be invited to take part in stage two, the **'main trial'**. In stage two you will be allocated to receive either adalimumab or a placebo (dummy treatment).

You will have some tests which you would receive as part of normal care if you were taking adalimumab in the NHS. We would also ask you to complete some questionnaires about your quality of life and the drug side effects. We will also ask you to donate some **optional** extra blood samples that we will store for future studies to understand better who responds to adalimumab and why. *See page 6.*

Why have I been invited?

You have been invited to take part because your eye doctor has diagnosed you with uveitis. *See page 3.*

What are the benefits?

The information we get from this study may help improve the treatment and lives of people with uveitis. *See page 10.*

What are the risks?

You may be allocated to the placebo. There is a very small risk of serious side effects from adalimumab but they are rare and you will have frequent hospital visits to monitor your safety. Adalimumab has been shown to be safe in the vast majority of patients. *See page 11.*

Taking part is voluntary

You are free to stop taking part at any time and this decision will not affect your ongoing treatment. *See page 13.*

If you are interested in learning more about the study, please continue to read the patient information leaflet.

<Trust Logo>

The ASTUTE study
Patient information leaflet

You are being invited to take part in a research study. Before you decide whether to take part or not, you need to understand why the research is being done, and what it would involve for you. Taking part in research is voluntary; it is up to you to decide whether to join the study. You are free to withdraw at any time, and if you choose not to take part or to withdraw from the research, you do not have to give any reason for your decision. Nobody will be upset, and the standard of care you receive will not be affected if you decide not to take part.

Please take the time to read the following information. One of our team will go through this information leaflet with you, explain the study in more detail, and answer any questions you have. If anything is not clear or you would like more information, don't hesitate to ask a member of the local research team (see contact details on page 19). Talk to others about the study if you wish, such as friends or relatives, and take time to decide. If you would like to take part, you will be asked to confirm by signing a separate consent form and will be given a copy for your records.

You can also read this information leaflet online at
https://bristoltrialscentre.blogs.bristol.ac.uk/details-of-studies/astute/
On the website, you will need to click on the "*ASTUTE-Patient-Information-Leaflet-V5.0_website*" link that can be found under the "*Patient Information Leaflet*" heading.

What is the purpose of the study?
Autoimmune non-infectious uveitis (uveitis) is a term for several rare eye diseases in which the body's own immune system causes inflammation to the retina and tissue at the back of the eye. The usual treatment for sight-threatening uveitis involves steroid tablets and additional drugs to reduce inflammation. Unfortunately, many patients do not respond to usual treatments for uveitis, or they have considerable side effects. Sometimes, they need high dose steroids to control the uveitis. In the short term, steroids can have side effects such as increased risk of infection and blood clots. In the long term, steroids can cause bone fractures, diabetes, heart problems such as heart attack, stroke or heart failure, diabetes, gastrointestinal problems, cataracts, glaucoma and can have negative impacts on your

mental health and quality of life. For these reasons, treatments for uveitis which reduce or prevent the need for steroids could be beneficial.

Adalimumab (Imraldi™) targets chemicals in the body which are released by inflamed tissues and neutralises them. In 2017 adalimumab was recommended by the NHS to treat uveitis but it is only available for people who have 'active' uveitis. This means people whose condition is not controlled by steroids and other medications. People with 'inactive' uveitis whose condition is controlled by steroids and other medications are not eligible for adalimumab on the NHS even if these treatments cause side effects.

What question are we trying to answer?
This study aims to look at how effective adalimumab is at treating people with either 'active' or 'inactive' uveitis. We do know that adalimumab is not effective for everyone with uveitis so this study will first identify people who are most likely to benefit from adalimumab ('trial run'). We then aim to find out whether adalimumab is better at preventing recurrence of uveitis than placebo (identical to adalimumab in every way but contains no active ingredients) – 'main trial'. We are using a placebo because we don't know whether adalimumab is better than standard treatment for all people with uveitis.

Many patients say that the usual uveitis treatments have a negative affect on their lives, yet the impact of uveitis and its treatments on patients' well-being and their work has never been studied before. This study will find out this information for the future benefit of all uveitis patients.

This study has been designed in collaboration with a uveitis patient group to ensure it is fair and acceptable for everyone taking part.

Why have I been invited?
You have been invited to take part because your eye doctor has diagnosed you with uveitis. We aim to recruit 400 people with uveitis into this study. The study has about the same number of visits you would make to the uveitis department for your normal care.

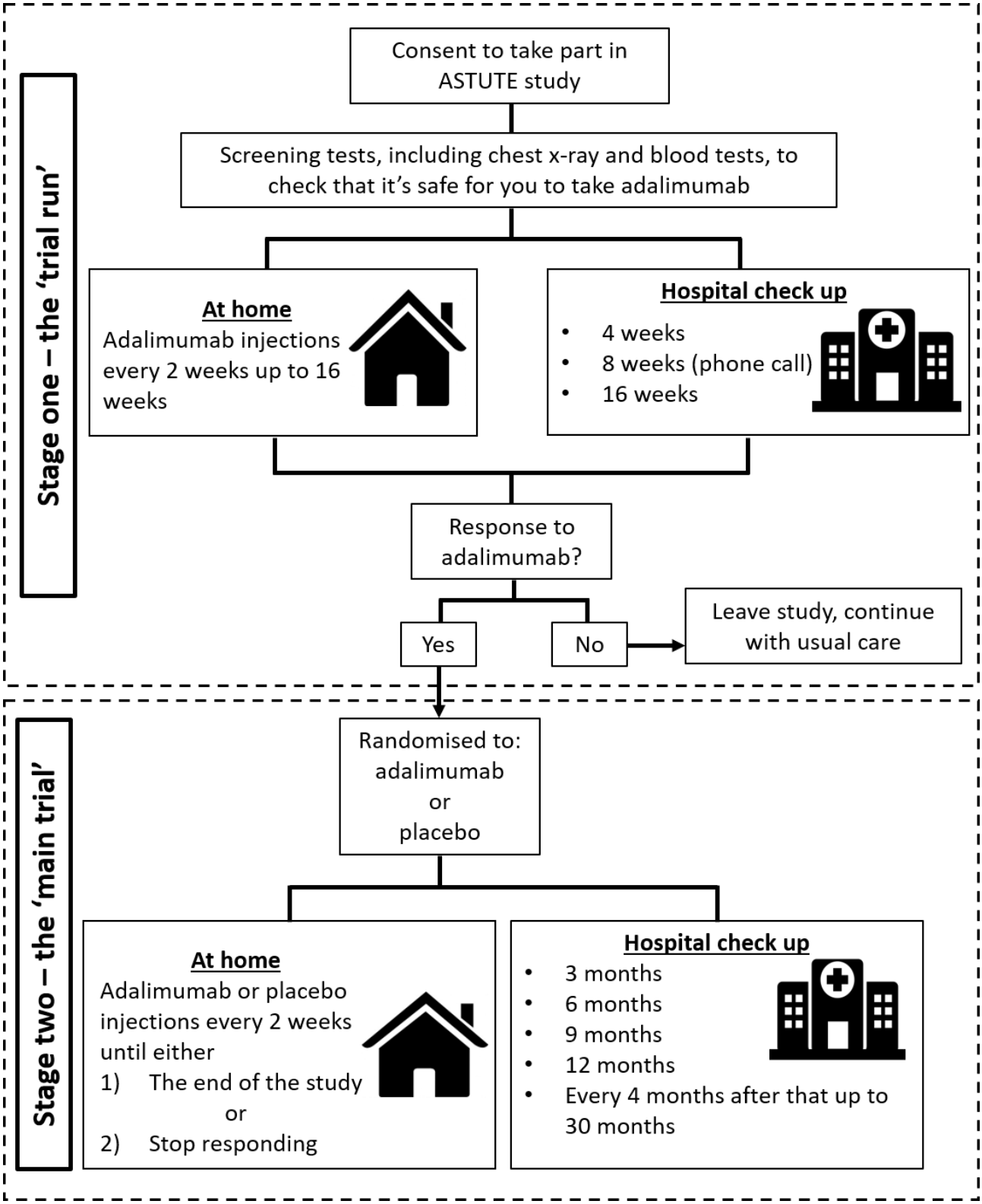
What will happen to me if I take part?
This study has two stages (see the ASTUTE study pathway on page 5). Everyone who joins the study will take part in stage one which involves taking adalimumab for up to 16 weeks. This is a '**trial run**' to see if you respond to adalimumab treatment. If you do not show a response to adalimumab after 16 weeks you will leave the study and continue with normal NHS care because adalimumab is not likely to be of benefit to you. If you do respond to

adalimumab after 16 weeks you will be invited to take part in stage two, the '**main trial**'.

In stage two you will be allocated to receive either adalimumab or placebo. You, your doctor and the study team will not know whether you are taking adalimumab or placebo. This is so we can fairly assess whether adalimumab is an effective treatment for uveitis without influencing the results of the study.

During both stages of the study you will continue to take any other medications you normally take as prescribed by your doctor.

The ASTUTE study pathway



Consent and Screening

If you agree to take part in the study, you will be asked to sign a consent form and you will receive a copy. Before you take part in the study your eye doctor will need to look for any medical reason that you cannot take adalimumab. They will arrange for you to undergo some tests, including blood tests and a chest x-ray, which you would normally have if you were going to start taking adalimumab in the NHS. Some people may also have an electrocardiogram (an ECG to check your heart health) and/or an MRI scan of the brain. Not everyone will have all of these tests; your doctor will decide what tests you need based on your medical history and current symptoms. Your doctor will discuss the tests with you and what they involve.

If you are fit and well enough to take adalimumab you will start stage one of the study.

Stage One: the **trial run**

You will be prescribed an initial dose of 80 mg adalimumab (Imraldi™) followed by 40 mg of adalimumab every 2 weeks, starting one week after the initial dose, for up to 16 weeks.

You will attend an outpatient appointment at the hospital 4 weeks and 16 weeks after starting adalimumab so your eye doctor can review your progress and make sure it is safe for you to continue taking adalimumab. The hospital visits may take up to 3 hours. Eight weeks after starting adalimumab your eye doctor or study nurse will phone you to check on your wellbeing.

A number of tests will be done at each hospital appointment and some less often. You may already have had some of these tests as part of your usual care:

Sight test

You will be asked to read letters from a chart under normal light levels with your distance glasses or contact lenses if you use them.

Eye exam

The pressure in your eyes will be checked. Your pupils will be dilated with eye drops. An examination light and special lenses will be used to look at the back of your eye under magnification. Please note that you must not drive until the effect of the eye drops on your vision has worn off. This can be several hours for some people. Therefore, it is better for you not to drive to your appointments.

Optical coherence tomography (OCT) images

This procedure is used to examine the eye with beams of safe laser light. This test shows the thickness of the tissue layers inside the eye, and any fluid swelling. It is like having a picture taken of your eye.

Colour fundus and autofluorescence images
Photographs of the retina (a light-sensitive layer of tissue lining the inner surface of the eye) are taken using a special camera. You will be asked to sit very still and not to blink when the photo is taken so the photograph is not blurry. The bright flash during the photograph may cause you momentary discomfort if you are sensitive to light.

Fundus fluorescein angiogram images
This test allows the study doctor to examine the blood vessels in your eyes. Your study doctor will inject a special dye (fluorescein) into a vein in your arm or hand and take several eye pictures as the dye passes through blood vessels in your eyes. Rarely, some people may have an allergic reaction to fluorescein (rash, mouth swelling); very rarely the allergic reaction may be serious and require emergency treatment.

Questionnaires
We will ask you to complete a questionnaire booklet. The booklet contains 4 questionnaires to assess your quality of life and whether you have had any side effects from the study treatment.

Data collection
As well as collecting data from the tests carried out, we will check your pulse and blood pressure and record your weight. You will be asked about any medications you are taking and whether your have had any illnesses, hospital admissions, GP attendances or experienced any side effects since your previous hospital visit.

Blood tests
We will take some blood samples for routine blood tests to monitor for possible side effects and make sure you are well.

At the 16 week hospital visit your eye doctor will assess whether you have responded to adalimumab or not. If you haven’t responded you will leave the study at this stage and continue with normal NHS care. Your eye doctor will discuss your treatment options with you.

If you do respond to adalimumab you will be invited to continue in the study and take part in stage two. Stage two will start at your 16 week visit.

Optional research blood samples

At the start of stage 1 **(**the **trial run)** we will also ask for additional small blood samples (two tablespoons) from you before you start taking adalimumab and at the end of the trial run. If you continue to the main trial we will also ask for an additional blood sample at 12 months and 24 months after you start the main trial and at any point that you stop responding to the treatment.
We will store a component of the blood called 'serum' which contains proteins and chemicals and we will also store genetic material (DNA). The samples will be stored in a biobank at the University of Oxford and used for future ethically-approved research into uveitis. As the samples will only be used for future research purposes and the people doing the research will not be able to identify you from the samples, it will not be possible to inform you of any findings from your samples.
Taking part in this aspect of the study is completely **optional**. You can still take part in the ASTUTE study without providing blood samples that will be stored for future research.

Stage two: the **main trial**

You will be allocated to receive either adalimumab or placebo. We will use a computer system to chose which group you'll be in. You'll have an equal chance of being in either group and it will not be possible for you or your local study team to guess which group you'll be put in. You and your doctor will not know which group you are in. This is to ensure that the trial results are not affected by the 'placebo effect' (when a patient's condition improves because the patient belives that a treatment will improve their condition) and that the local study team are not subconsciously influenced by knowing if you are taking adalimumab or not. However, in an emergency the study team will be able to find out which group you are in, if required.

You will take 40 mg adalimumab or a placebo every 2 weeks for at least a year and continuing up to the end of the study. The end of the study is when the last person to start stage 2 (the **main trial**) has been in the study for one year. The minimum time you will be in the main trial is 12 months and maximum time is 30 months.

You will attend the hospital for study visits 3, 6, 9 and 12 months after starting stage 2 and every 4 months after that (i.e. 16 months, 20 months, and so on). At the study visits you will have the same assessments as you had in stage 1 (the **trial run**) and we'll collect the same data as described above for stage 1.

Again, some of these assessments may take place at each appointment and some less often.

If you stop responding to the study treatment you will stop the study treatment you are on, and re-start stage one (the **trial run**). This means you will be prescribed adalimumab for 16 weeks. If you again respond to adalimumab you will continue with stage two (the **main trial**) but you will be switched from your original group (adalimumab or placebo) to the other group. You and your doctor will still not know which group you are in. You can re-start stage one and switch groups up to two times.

If you do not respond to adalimumab after repeating stage one you will leave the study and continue with usual NHS care. You will be asked if you are willing to continue with study visits so we can continue to monitor your progress up to the end of the study. As the study visits are scheduled to take place approximately as often as your normal care for uveitis this shouldn't require you to attend more hospital visits than usual.

During stage one and stage two of this study you should continue to take any other medications you are on as prescribed by your doctor. Please follow your doctors advice before starting or stopping any medications.

<u>Taking adalimumab or placebo</u>
Adalimumab comes as a liquid in a pre-filled injectable pen. The placebo comes in an identical pen; during stage two of the study you will not be able to tell it apart from the adalimumab pen. The pens will be delivered to your home by a company called Sciensus/Healthcare at Home.
Sciensus/Healthcare at Home works with the NHS to deliver prescriptions to people's homes and provide information and training on taking medications. If you join the study, Sciensus/Healthcare at Home will send you a welcome leaflet with general information about their service. A healthcare professional from Sciensus/Healthcare at Home will arrange a convenient time to visit you at home to show you how to give yourself the injections. They will also deliver the pens to your home in a refrigerated van throughout the study as the pens need to be stored in the fridge (between 2°C - 8°C). This means that someone will need to be at home to receive the prescription deliveries approximately once a month.

<u>Communication from the ASTUTE study team</u>
If you take part in the study, the ASTUTE study team at the Bristol Trials Centre, University of Bristol, will be in touch either via SMS text message or email to send reminders about taking the treatment. You will also be sent a short questionnaire every two weeks, which we will ask you to complete to confirm whether you have taken the treatment and the date you took it.

The study team may also send SMS text message or email reminders about going to hospital visits. You will not need to reply to these messages.

The study team may also need to phone you if they do not receive a reply to the short questionnaire about your treatment, or to help the Sciensus/Healthcare at Home team schedule training sessions and prescription deliveries.

The study team will post or email occasional newsletters to keep you up to date on how the study is going.

You can opt out of receiving different types of communication from the study team at the Bristol Trials Centre at any time; just let your local hospital study team know. It is really important that the study team are able to contact you by SMS message, email or phone call so please take this into consideration when deciding to join the study.

In addition to communication from the ASTUTE study team, you can sign up to Sciensus/Healthcare at Home's SMS text message system to receive delivery confirmation messages and updates on delivery timeslots. You will also have the option to provide Sciensus/Healthcare at Home with contact details of a friend or family member to help you organise and receive deliveries if you would find it helpful, but this information will not be passed on to the study team at the Bristol Trials Centre.

What alternatives are there to taking part in the study?
If you decide not to take part in the research study, then you will receive the normal treatment for uveitis at this hospital.

What are the possible benefits of taking part?
We cannot promise to help you but the information we get from this study will help improve the treatment of people with uveitis. If you are not currently eligible for adalimumab on the NHS you could benefit from being prescribed it as part of this study. You might be able to reduce your dose of corticosteroids if taking adalimumab. It is possible, but cannot be guaranteed, that you will eventually be able to stop taking at least one of the immunosuppression medications that you are currently taking.

What are the possible disadvantages and risks of taking part?
If you progress to stage two of the study there is an equal chance that you will be in the placebo group after showing a response to adalimumab. There is a small risk of permanent eye damage from uveitis if you are allocated to the placebo group, although the risk is the same as if you were receiving normal NHS care only. To minimise this risk, you will be closely monitored. Hospital visits are frequent enough that if your condition relapses it should be picked

up by your eye doctor before permanent uveitis damage occurs. If your condition relapses in stage 2, you will be able to re-start stage 1. If you respond to adalimumab again during stage 1, you will continue in the study but switch to the other group.

Whether or not you are having adalimumab or placebo you will be giving yourself injections under the skin every two weeks. These are mildly sore, and you can get a reaction at the injection site.

There is also the risk of serious side effects from adalimumab but such events are rare and you will have frequent hospital visits during stage one to monitor your safety.

What are the side effects of taking adalimumab?
Like all medicines, adalimumab can cause side effects, although not everybody gets them. Most side effects are mild to moderate. However, some may be serious and require treatment. Side effects may occur up to 4 months or more after the last adalimumab injection.

The most common side effects of adalimumab (affecting more than 1 in 10 people) are:

- Injection site reactions (including pain, swelling, redness or itching)
- Respiratory tract infections (including cold, runny nose, sinus infection, pneumonia)
- Headache
- Abdominal (belly) pain
- Nausea and vomiting
- Rash
- Pain in the muscles
- Low blood measurements for white blood cells
- Low blood measurements for red blood cells
- Increased lipids in the blood
- Raised liver enzymes

For a full list of all reported side effects please refer to appendix 1 at the end of this leaflet.

The symptoms described below can be signs of the side effects that have been observed with adalimumab. If you suffer these or any other symptoms during the study please contact your local study nurse or doctor as soon as possible using the contact details on page 19, unless it is serious, in which case seek immediate medical attention.

Seek medical attention <u>urgently</u> if you notice any of the following:

- Severe rash, hives or other signs of allergic reaction
- Swollen face, hands, feet
- Trouble breathing, swallowing
- Shortness of breath with exertion or upon lying down or swelling of the feet

Tell your doctor as soon as possible if you notice any of the following:

- Signs of infection such as fever, feeling sick, wounds, dental problems, burning on urination
- Feeling weak or tired
- Coughing
- Tingling
- Numbness
- Double vision
- Arm or leg weakness
- A bump or open sore that doesn't heal
- Signs and symptoms suggestive of blood disorders such as persistent fever, bruising, bleeding, paleness.

Certain vaccines contain weakened but live forms of disease-causing bacteria or viruses, and these vaccines should not be given while receiving adalimumab. Check with your doctor before you receive any vaccines.

Ionising radiation (medical exposure)
Before you take part in this study you will have a chest x-ray to see if you have tuberculosis . The x-ray will help your doctor decide if you can take adalimumab. You would have this assessment if you were going to take adalimumab even if you weren't part of this study. This procedure uses ionising radiation to form images of your body and provide your doctor with other clinical information. Ionising radiation can cause cell damage that may, after many years or decades, turn cancerous. We are all at risk of developing cancer during our lifetime. The normal risk is this will happen to about 50% of people at some point in their life. There is only a very small chance that taking part in this study will increase the risk of this happening to you.

For women only
Anyone who is pregnant or planning to get pregnant during the study will not be able to take part. You will be asked to take a pregnancy test before taking part in the study. If you become pregnant during the study you must inform your doctor immediately. If you agree to take part in the study you must be willing to use contraception, be surgically sterile or be post-menopausal.

What will happen to any samples I give?

The optional blood samples described on page 8 are in addition to your normal care. The blood samples will be transferred to a laboratory at the University of Oxford where they will be processed to separate out parts of the blood called ‘serum’ and ‘DNA’. The serum and DNA will be frozen and stored securely for future research studies. Only authorized personnel will have access to the samples. It will not be possible to identify you from your blood samples. Any future studies which use the samples will be required to have approval from an independent research ethics committee.

What will happen if I don’t want to carry on with the study?
You are free to stop taking part in the study at any time without giving a reason and this decision will not affect your rights. You may decide to stop taking the adalimumab or placebo but continue with study visits so we can continue to collect information and monitor how you are doing, or you may want to stop taking part in the study completely. This will be discussed with you if you decide to stop taking part in one or more aspects of the study. There is also a possibility that your doctor may decide that it is not in your best interests to continue. If you decide not to carry on with the study you will be asked to return to the hospital all used and unused study medication.

You can let the study team know about your decision in writing, by telephone, or in person by contacting your hospital study team or the study coordinating centre.

Before deciding whether to take part in this study it is important to know that the people who designed the study have carefully calculated how many participants are needed for the results of the study to be meaningful. This means if too many people stop taking part in the study the results might not be meaningful or reliable.

Your rights to access, change or move the research data about you are limited, as we need to manage this information in specific ways in order for the research to be reliable and accurate. This means that we won’t be able to let you see or change the data we hold about you. If you stop taking part in any part of the study, we will keep and use the information about you that we have already obtained.

If you choose to stop taking part in the study, we would like to continue collecting information about your health from your hospital records, without contacting you. If you do not want this to happen, tell us and we will stop. To safeguard your rights, we will use the minimum personally identifiable information possible. We will continue to store blood samples that you donated for the study to be used in future studies unless you ask us to destroy them. You can ask for your samples to be destroyed at any time by contacting your hospital study team.

You can find out more about how we use your information or how to make a complaint about how we handle your data at:

http://www.uhbristol.nhs.uk/research-innovation/for-patients-and-public/how-we-use-your-information-(gdpr)

and/or by contacting: InformationGovernance@UHBristol.nhs.uk

What happens when the research study stops?
At the end of the study you will continue with NHS care. Your eye doctor will discuss your treatment options with you.

Will my taking part in the study be kept confidential?
University Hospitals Bristol and Weston NHS Foundation Trust (UHBW) is the sponsor for this study. UHBW and The Bristol Trials Centre (BTC) at the University of Bristol are the joint data controllers for this study based in the United Kingdom. Your local study hospital will collect information from you and your medical records for this research study and will transfer it securely to the BTC. This information will include your:

- Name
- Date of birth
- NHS number
- Address
- Phone number
- Email address

People will use this information to do the research or to check your records to make sure that the research is being done properly. Your name and contact details will only be seen by people who need this information to carry out the study. You will be given a unique study code number. People who do not need to see your personal information but need to see the other information we collect from you, such as those analysing the data, will only be able to see your unique study code number. All information about you will be kept safe and secure.

BTC and your hospital research team will share your name and contact details securely with Sciensus/Healthcare at Home so as they can contact you to arrange training visits and delivery of your prescriptions. Sciensus/Healthcare at Home will also notify your hospital care team if you make them aware of any illnesses you've had or difficulties you've experienced with the study medication. This is their normal practice for NHS patients who are taking adalimumab.

The images of your eyes (described in 'Stage one – the **trial run**) will be transferred by a secure network to a specialist centre for analysis (Central Angiographic Resource Facility, Queen's University Belfast). The images will be labelled with your unique study code number so that no one looking at the images will be able to identify you.

With your consent, your GP will be informed that you are taking part in the study. Your GP may be asked for information from your records which is required for the study.

What will happen to my information once the study has finished?
Once we have finished the study, BTC will keep identifiable information about you on an NHS server for 15 years. Only authorised staff at the BTC will be able to link your personal identifiable data to the other data collected from you for the study.

After 15 years the data will be anonymised and kept indefinitely by the BTC on a secure University of Bristol server. This means that no one will be able to identify you from this data.

With your consent your data, including the images of your eyes, may be used for future studies that have been approved by a research ethics committee but your personal identifiable data will never be shared.

You can find out more about how we use your information at:

www.hra.nhs.uk/patientdataandresearch

If you would like a paper copy please ask your local hospital team who will be able to provide you with one. Or you can ask the BTC research team by emailing:

astute-trial@bristol.ac.uk or calling 07929 845 247.

The data protection officer for this study based at University Hospitals Bristol and Weston NHS foundation Tust can be contacted by emailing:

InformationGovernance@UHBW.nhs.uk

What will happen to the results of the research study?
The results of the research will not be known until some time after the last person has entered the study (about 4 years after the start of the study). During the course of the study we will ask you if you would like to receive a summary of the results by post or email after the research has finished. The results may be reported in medical journals or presented at meetings. We will

report the results in a way that no-one can work out that you took part in the study.

What if relevant new information becomes available?
Sometimes we get new information about the treatment being studied. For example, other research may show additional side effects associated with adalimumab. If this happens, your eye doctor will tell you and discuss whether you should continue in the study.
If you decide not to carry on, your eye doctor will make arrangements for your care to continue.
OR
If you decide to continue in the study they may ask you to sign a form outlining the discussion.
OR
In light of the new information, your eye doctor might consider you should withdraw from the study. He/she will explain the reasons and arrange for your care to continue.
OR
If the study is stopped for any other reason, we will tell you and your eye doctor will arrange your continuing care.

Expenses
The ASTUTE study will not be able to reimburse any travel expenses for taking part in this study. Hospital visits have been scheduled to be the same or a very similar frequency to that of normal NHS care for uveitis patients. Hospital visits should also take a similar amount of time as normal but your parking expenses may be reimbursed if a study visits takes much longer than a normal eye hospital visit because you are taking part in this study.

Insurance
Before participating you should consider if this will affect any insurance you have and seek advice if necessary.

What if there is a problem?
If you have any concerns or questions about this study, please contact the study team listed on page 19 of this leaflet. Please feel free to ask any further questions before deciding to take part in the study, or at any time during the study.
If you have concerns about the way you have been approached or treated during the course of the study, you may wish to contact:

<local PALS details here>

We have no reason to believe that you will be placed at any greater risk by taking part in this research study. However, if something goes wrong and you are harmed during the research study there are no special compensation arrangements. The University Hospitals Bristol and Weston NHS Foundation Trust cannot offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

If anything goes wrong as a consequence of taking part in the trial because negligence has occurred, University Hospitals Bristol and Weston NHS Trust, who is sponsoring the trial, will compensate you. Negligence would include, for example, a situation in which injury is caused by a researcher not following the study protocol. Your legal right to claim compensation for injury where you can prove negligence is not affected. If you are harmed and this is due to someone's negligence then you may have grounds for a legal action against the University Hospitals Bristol and Weston NHS Trust, but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

The University of Bristol holds professional negligence insurance to cover the legal liability of the University as the employer of staff engaged in the research (Bristol Trials Centre staff) for harm to participants arising from the design of the research, where the research protocol was designed by the University.

Who is organising and funding the research?
The research is funded by the National Institute for Health Research Health Technology Assessment programme (NIHR-HTA). University Hospitals Bristol and Weston NHS Trust has overall responsibility for conduct of the study. The research is being organised and run on their behalf by the Bristol Trials Centre, University of Bristol.

Who has looked at the study?
All research in the NHS is looked at 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 the South Central – Oxford B Research Ethics Committee.

Further information

You can obtain **general advice on uveitis** and its treatment from the Royal National Institute of Blind People (RNIB)
https://www.rnib.org.uk/eye-health/eye-conditions/uveitis
Tel: 0303 123 9999

You can obtain **general information on clinical research** from the UK Clinical Research Collaboration (UKCRC) who produce a booklet called "Understanding Clinical Trials". This provides in-depth information on the design and conduct of clinical trials and aims to answer the questions of those considering taking part.

Electronic copies can be downloaded from the UKCRC website:
https://www.ukcrc.org/public-awareness-of-clinical-research/information-resources-on-clinical-research/

Printed copies can be requested by emailing:
crncc.info@nihr.ac.uk

Or contacting:

UK Clinical Research Collaboration,
Woburn House
20 Tavistock Square
London
WC1H 9HD
Tel: 020 7419 5494

IRAS ID: 271051

Contact details

ASTUTE Study Team
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Bristol. BS2 8HW
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Thank you for taking the time to read this leaflet.

General information about research can also be found at www.uhbristol.nhs.uk/research-innovation

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Appendix 1
Possible side effects of adalimumab

The following potential side effects are common (may affect up to 1 in 10 people):

- Serious infections (including blood poisoning and influenza)
- Intestinal infections (including gastroenteritis)
- Skin infections (including cellulitis and shingles)
- Ear infections
- Mouth infections (including tooth infections and cold sores)
- Reproductive tract infections
- Urinary tract infection
- Fungal infections
- Joint infections
- Benign tumours
- Skin cancer
- Allergic reactions (including seasonal allergy)
- Dehydration
- Mood swings (including depression)
- Anxiety
- Difficulty sleeping
- Sensation disorders such as tingling, prickling or numbness
- Migraine
- Symptoms of nerve root compression (including low back pain and leg pain)
- Vision disturbances
- Eye inflammation
- Inflammation of the eyelid and eye swelling
- Vertigo (sensation of the room spinning)
- Sensation of heart beating rapidly
- High blood pressure
- Flushing
- Haematoma (a solid swelling with clotted blood)
- Cough
- Asthma
- Shortness of breath
- Gastrointestinal bleeding
- Dyspepsia (indigestion, bloating, heart burn)
- Acid reflux disease
- Sicca syndrome (including dry eyes and dry mouth)
- Itching
- Itchy rash

- Bruising
- Inflammation of the skin (such as eczema)
- Breaking of finger nails and toe nails
- Increased sweating
- Hair loss
- New onset or worsening of psoriasis
- Muscle spasms
- Blood in urine
- Kidney problems
- Chest pain
- Oedema (a build up of fluid in the body which causes the affected tissue to swell)
- Fever
- Reduction in blood platelets which increases risk of bleeding or bruising
- Impaired healing
- High blood measurements for white blood cells
- Low blood measurements for platelets
- Increased uric acid in the blood
- Abnormal blood measurements for sodium
- Low blood measurements for calcium
- Low blood measurements for phosphate
- High blood sugar
- High blood measurements for lactate dehydrogenase
- Autoantibodies present in the blood
- Low blood potasium

The following potential side effects are <u>uncommon</u> (may affect up to 1 in 100 people):

- Opportunistic infections (which include tuberculosis and other infections that occur when resistance to disease is lowered)
- Neurological infections (including viral meningitis)
- Eye infections
- Bacterial infections
- Diverticulitis (inflammation and infection of the large intestine)
- Cancer, including cancer of the lymph system (lymphoma) and melanoma (a type of skin cancer)
- Immune disorders that could affect the lungs, skin and lymph nodes (most commonly as a condition called sarcoidosis)
- Vasculitis (inflammation of blood vessels)
- Tremor
- Neuropathy (nerve damage)
- Stroke

- Hearing loss, buzzing
- Sensation of heart beating irregularly such as skipped beats
- Heart problems that can cause shortness of breath or ankle swelling
- Myocardial infarction
- A sac in the wall of a major artery, inflammation and clot of a vein; blockage of a blood vessel
- Lung diseases causing shortness of breath (including inflammation)
- Pulmonary embolism (blockage in an artery of the lung)
- Pleural effusion (abnormal collection of fluid in the pleural space)
- Inflammation of the pancreas which causes severe pain in the abdomen and back
- Difficulty in swallowing
- Facial oedema
- Gallbladder inflammation, gallbladder stones
- Fatty liver (build up of fat in liver cells)
- Night sweats
- Scar
- Abnormal muscle breakdown
- Systemic lupus erythematosus (including inflammation of skin, heart, lung, joints and other organ systems)
- Sleep interruptions
- Impotence
- Inflammations
- Elevated bilirubin measurement

The following potential side effects are <u>rare</u> (may affect up to 1 in 1,000 people):

- Leukaemia (cancer affecting the blood and bone marrow)
- Severe allergic reaction with shock
- Multiple sclerosis
- Nerve disorders (such as inflammation of the optic nerve to the eye, and Guillain-Barré syndrome, a condition that may cause muscle weakness, abnormal sensations, tingling in the arms and upper body)
- Cardiac arrest
- Pulmonary fibrosis (scarring of the lung)
- Intestinal perforation
- Hepatitis
- Reactivation of hepatitis B
- Autoimmune hepatitis (inflammation of the liver caused by the body's own immune system)
- Cutaneous vasculitis (inflammation of blood vessels in the skin);

- Stevens-Johnson syndrome (early symptoms include malaise, fever, headache and rash)
- Facial oedema associated with allergic reactions
- Erythema multiforme (inflammatory skin rash)
- Lupus-like syndrome
- Angioedema (localized swelling of the skin)
- Lichenoid skin reaction (itchy reddish-purple skin rash)
- Low blood measurements for white blood cells, red blood cells and platelet count

The following potential side effects are have been reported but the frequency is not known from the available data:

- Hepatosplenic T-cell lymphoma (a rare blood cancer that is often fatal)
- Merkel cell carcinoma (a type of skin cancer)
- Kaposi's sarcoma (a rare type of cancer)
- Liver failure
- Worsening of a condition called dermatomyositis (seen as a skin rash accompanying muscle weakness)
- Weight increased

There may also be side effects that have not been identified yet. You should report anything untoward even if it is not listed in this leaflet.

If you experience these or any other side effects during the study please contact your local study nurse or doctor as soon as possible using the contact details on page <X>, unless it is serious, in which case seek urgent medical attention.