The 3TR Molecular PAthobiology and PRecision Therapy iN EaRly Rheumatoid Arthritis Study (3TR-PARTNER-RA Study)

IRAS 1008435

You are being invited to take part in a research study called the 3TR-PARTNER-RA study. Before you decide whether or not to participate, it is important to understand why the research is being conducted and what it will involve for you.

Please take your time to carefully read this patient information sheet. You may also want to discuss it with friends or family members. This sheet explains the study and aims to answer some of the questions you may have. If anything is unclear or if you need more information, you can ask the research team directly or contact the study team by phone or email.

If you decide to participate, you will be asked to sign and date a consent form. A copy will be given to you for your records. There is no rush—you can take as much time as you need (at least 24 hours) to consider the information before signing the form.

As part of the study, you will need to self-inject the study medication once a week. Detailed instructions will be provided to help you with this process. If you are not comfortable self-injecting, a family member, carer, or relative can help administer the injection for you. The study team is also available to assist with any questions or concerns you may have about the injection process.

This study is part of the 3TR consortium, a large-scale public-private partnership that aims to understand why some medications work better than others in treating seven immune-mediated diseases. These diseases include Chronic Obstructive Pulmonary Disease (COPD), Asthma, Crohn's Disease, Ulcerative Colitis, Multiple Sclerosis, Systemic Lupus Erythematosus (SLE), and Rheumatoid Arthritis.

The project will study over 50,000 patient samples across 50 clinical trials to improve disease management. A total of 69 academic and commercial partners from 15 European countries are participating in this effort. Further information about 3TR can be found here: https://www.3tr-imi.eu

Contents

Abbreviation

csDMARDs	conventional synthetic Disease Modifying Anti Rheumatic Drugs
bDMARDs	biological Disease Modifying Anti Rheumatic Drugs
MTX	Methotrexate
RA	Rheumatoid Arthritis
TNFi	Tumor Necrosis Factor inhibitors
RA	Rheumatoid Arthritis

Glossary

For all key terms, please find the glossary at the end of this information sheet.

1. What is the purpose of this study?

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease that affects 0.5-1% of adults in industrialized countries, with 5-50 new cases per 100,000 people each year. If RA is not well-controlled, it can cause joint damage, disability, reduced quality of life, and other health issues, such as cardiovascular disease.

There are several treatments available, including conventional synthetic DMARDs (csDMARDs) like Methotrexate, leflunomide, sulfasalazine, and hydroxychloroquine, which have improved outcomes for many patients. However, about 40% of people do not respond to first-line therapy. Biological therapies are available for treating RA, but you usually won't receive them until you've tried at least two csDMARDs.

In this trial, we aim to explore whether starting Abatacept, a biological therapy, as part of first-line treatment can improve your RA and reduce the "trial and error" approach. You will have a 50/50 chance of receiving either Abatacept and Methotrexate or placebo and Methotrexate. At the end of the trial at 16 weeks, we will let you know whether you received Abatacept or placebo. If you received Abatacept, it's important to note that this drug is not considered routine care at your current stage of RA. Therefore, continuing the medication as part of your ongoing care after 16 weeks will not be available except where local guidelines permit. Methotrexate will be prescribed for your RA during the study and may continue afterward, depending on discussions with your clinician.

You will also undergo a biopsy, where small pieces of tissues will be taken from one of your joints. This sample will be analysed in the lab to see if it can help predict how your RA responds to the treatment. The goal of this study is to better understand how the immune system contributes to early RA and gather data that could help identify biomarkers to predict treatment response in the future.

2. Why have I been invited?

You have been invited to participate because you have been diagnosed with early rheumatoid arthritis (symptoms less than 12 months duration) and are suitable to start csDMARD therapy. csDMARD stands for Conventional Synthetic Disease Modifying Anti Rheumatic Drugs, and includes medications such as Methotrexate, sulfasalazine, hydroxychloroquine and leflunomide. In this trial, all participants will receive Methotrexate treatment.

3. Do I have to participate?

No, participation in this study is entirely voluntary. If you decide to take part, you will be given this patient information sheet to keep. You will be asked to sign an informed consent form, but you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care you receive or count against you in any way. If you decide not to take part, your Rheumatologist will be happy to talk through alternative options. Your treatment and care will not be affected in any way.

4. What are the alternatives to taking part in this study?

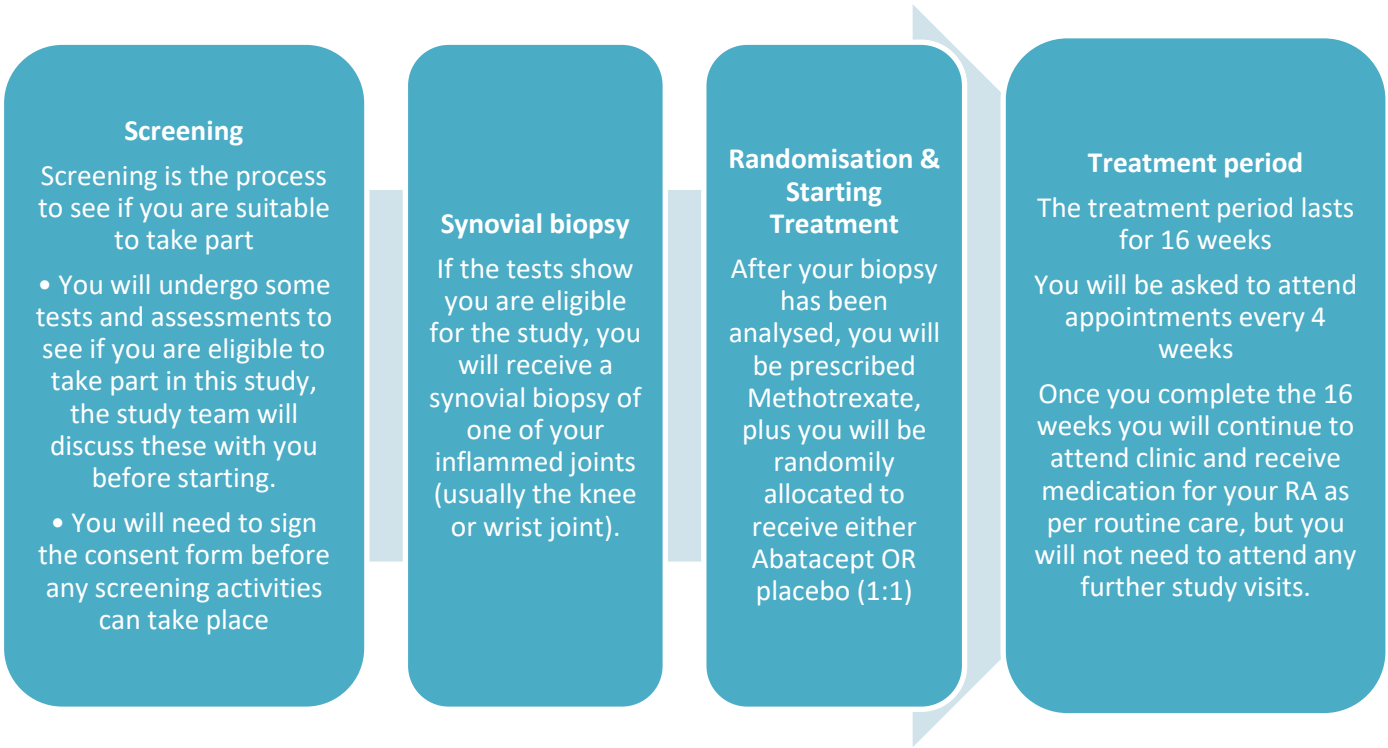
If you decide not to take part you will still receive routine csDMARD therapy, as decided by your rheumatologist. You will not have to undertake any of the additional study activities.

5. What will happen if I participate in the study?

Before you take part in this study, you will be given this patient information sheet and consent form, which we ask you to read in full. You are encouraged to ask as many questions as you would like.

If you decide to take part in the study, you will sign and date a consent form (a copy will be returned to you for your records). You do not need to sign this form today. You can take as long as you need (we recommend at least 24 hours) to consider the information provided and consult with family and friends as you wish.

The study has been broken down in the following diagram to 4 parts:



Self-Injection

You will be given a pre-filled syringe containing the treatment or placebo depending on your allocation. This will need to be administered weekly. You can decide if you would like to self-administer the treatment or ask a relative/caretaker to do so on your behalf. Self-injection teaching sessions will be given at baseline visit by a dedicated member of staff which includes research nurses or clinical fellows.

In more detail:

Visit 1- Screening visit

At your screening visit, you will undergo a clinical assessment, which will include completion of a variety of questionnaires, a full physical examination of all your joints, an ultrasound assessment, blood tests maximum of 20 mL (3-4 teaspoons), vital signs such as height, weight, blood pressure, pulse rate and temperature, a chest x-ray, ECG, and a urine pregnancy test if you are a person of child-bearing potential. The doctor or nurse will record your medical history, any allergies you may have, and any medications you are taking or have recently taken. This appointment will take approximately 1 hour.

It is possible, that following the screening tests, your doctor identifies that it may not be appropriate for you to be entered into the study. If this happens your doctor will not carry out any further activities relating to the study, and you will receive routine care for your RA.

Visit 2- Biopsy

If the tests show that you are suitable for the study and you still agree to take part, you will undergo a synovial biopsy of one of your inflamed joints and blood tests (maximum of 40 mL (6-8 teaspoons)). This is an essential part of the study and is required to progress into the study. If on the day you do not have a joint suitable for biopsy you will be withdrawn from the study.

At this visit, you will also undergo an ultrasound and an x-ray of the hands and feet (if you haven't already). This study visit will take approximately 1-2hrs.

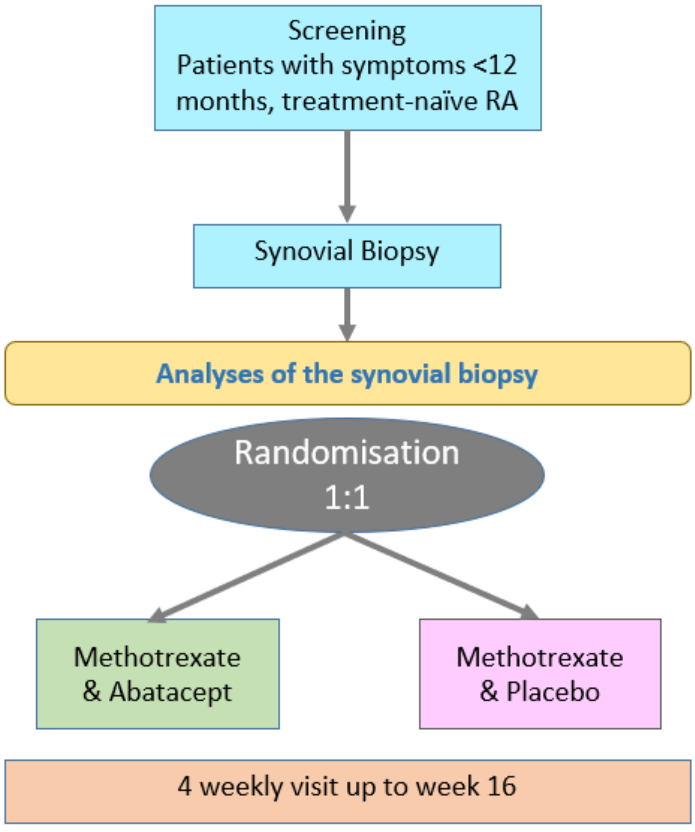
Randomisation

Randomisation involves using a computer to allocate you to randomly receive either the study drug Abatacept or a placebo (Injection in pre-filled pen) (see diagram below). This means that neither your doctor nor you can predict or choose which treatment you receive. You will have a 50/50 chance to receive the drug or the placebo. You and your clinical team will have no idea (double-blinded) if you are receiving the study drug or the placebo as both will be given in syringe form with no identification of their content.

All patients in this trial will receive a drug to treat Rheumatoid Arthritis called Methotrexate, which is used as a standard care treatment in early RA. Abatacept would be considered “additional” to what is routinely prescribed to patients with early RA who have not received treatment previously.

What does a double-blinded trial mean?

A double-blind study is a type of research where neither the participants nor the clinical team know who is getting the active treatment. This method is considered the "gold standard" for clinical trials because it helps prevent bias, such as when people expect a certain result, which can influence outcomes. By keeping everyone unaware of who is receiving the treatment, the study ensures that the results are more reliable. The data from both groups – those receiving the real treatment and those receiving the placebo – are compared to see if the treatment had any real effect. A placebo is an injection that does not contain any active drug but is designed to look like the study drug.



Visit 3 – Baseline Visit

At this visit, you will undergo some similar assessments to visit 1 to record your disease activity (how “good” or “bad” your rheumatoid arthritis currently is) prior to starting treatment. By collecting this

information before you start treatment, it will allow the researchers to see how well your RA responds to the drugs.

Your doctor will then prescribe you Methotrexate therapy at this visit as well as Abatacept OR placebo. Neither you or your doctor will know if you are receiving Abatacept or placebo, as they will both look the same.

The questionnaires you will be given are the:

1. **Health Assessment Questionnaire (HAQ)** - to assess physical function and disability.
2. **FACIT-Fatigue Questionnaire** - to evaluate fatigue levels.
3. **SF-36 Questionnaire** - to measure overall health-related quality of life.
4. **Epworth Sleepiness Scale** - to assess daytime sleepiness.
5. **EQ-5D-5L Questionnaire** - a standardized instrument to evaluate the general health status.

This visit will take approximately 1.5-2 hours to complete.

Treatment period / Follow-up visits (Visits 4-7)

After your baseline visit where you will be prescribed your RA treatment, you will need to visit your clinic for follow-up visits every 4 weeks for a total of 16 weeks (i.e. 4 further visits). During the treatment period, you will need to self-inject one a week. These follow up visits are expected to last approximately 1 hour.

We may ask for your permission to perform an additional biopsy at 16 weeks, however, you do not have to agree to this and it will not change your treatment or follow-up within this study.

You will also be contacted by telephone approximately 30 days after your last hospital visit to check how you are feeling after completing the trial.

A summary of study-specific investigations [that would be additional to your normal routine care] in taking part in this study is below. The "X" means the corresponding activity will be performed at that visit. Please note that in line with routine care for patients taking csDMARDs you will undergo some additional assessments not listed here.

The results from diagnostic tests given in clinic (such as routine blood tests, ultrasound examination and x-rays) will be documented in your medical records and used as part of the study to monitor your safety.

If you are currently taking other medications for other conditions that you may be suffering from, you can usually continue these during the study. Your doctor will discuss these with you in more detail. **Throughout the trial you should always discuss any new medications that you start, or old ones that you stop, with your doctor.**

Specifically, we ask you to inform your study team if your GP, or any other doctor, commences or increases your current dose of Prednisolone (a steroid medication) or plans to give you a steroid injection, as this may interfere with the study assessments.

You will be able to claim back any reasonable travel expenses (Taxi, train, public transport, private mileage) up to 50 pounds and lunch for yourself and your carer up to 15 pounds each when attending study visits during your time on the trial If your expenses go beyond the limit, please contact your local team to discuss. If there are any additional or specific reimbursement requests, please discuss with your study team. For all expenses, we ask that you please provide receipts. The expenses will be reimbursed via [bank [transfer/cash – Delete as appropriate]

Visit number	1	2	3	4	5	6	7	Post-treatment visit/call
Timeline (weeks)	-6 – -1 weeks	-3 – -1 weeks	0	4	8	12	16	Last dose + 30 days
Deviation window (days from scheduled visit)	N/A	N/A	N/A	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	N/A
Visit type	Screening	Biopsy & Randomisation	Baseline	Follow-up	Follow-up	Follow-up	Follow-up	Follow-up
Informed Consent	X							
Study specific blood tests		X		X	X	X	X	
Pregnancy test (if applicable)	X		X	X	X	X	X	
HAQ Questionnaire	X	X	X	X	X	X	X	
Study questionnaires (FACIT-fatigue, SF-36, Epworth Sleepiness scale, EQ-5D-5L)			X	X	X	X	X	
Pre-Biopsy Assessment*		X					X*	
Post-Biopsy Assessment*		X						X*
Synovial Biopsy*		X					X*	
Ultrasound assessment		X					X	
X-ray of hands & feet			X**				X	
Chest x-ray	X							
Urine collection (optional)			X	X		X	X	
Saliva collection (optional)			X	X		X	X	
Stool collection (optional)			X	X		X	X	

* Baseline biopsy is mandatory. Patient will be re-assessed at week 16 prior the second biopsy and decide to consent or opt-out.

** the x-ray of hands & feet at baseline (visit 3) is considered routine care.

Stool, Urine and Saliva collection

As part of the 3TR project, there are wider objectives spanning all the disease areas. There is a stool, urine and saliva collection study, which is not included in the objectives of the 3TR PARTNER-RA trial but is an overall 3TR objective. This allows patient samples to be compared across 7 different disease areas. **Collections of these samples are optional.** If you are happy to donate stool, urine and/or saliva, you will be asked to donate 3 samples- one at baseline, one at week 4 and one at week 16.

For the stool collection: Depending on your centre, you will either be provided with pre-addressed envelopes to send the samples to the lab for analysis yourself or will be asked to bring the sample in the pack to your appointment, for the research team to send. The samples will be sent to the Institute of Clinical Molecular Biology at Kiel University and/or Andalusian Public Health, Granada, Spain for analysis.

For the urine collection - You will be asked to donate the sample in your hospital clinic before your appointment. This is because your sample needs to be processed a few hours after collection. If you consent to the collection, you will be provided with clear instructions on collecting the sample.

For the saliva collection- You will be asked to donate the sample whilst in your hospital clinic. If you consent to the collection, you will be provided with clear instructions on collecting the sample.

The urine and saliva samples will be sent to Andalusian Public Health, Granada, Spain for analysis.

The purpose of the urine analysis is to look at “metabolites” –waste products produced by the body and how they might differ across the 7 diseases in 3TR. The stool and saliva analysis will be used to investigate your microbiome. Your microbiome is the bacteria that is naturally found in your gut and they affect your health in many ways, including your immune system. Again, a comparison will be performed across the 7 3TR disease areas.

6. What is the drug or/and the procedures being tested in this study?

There are no experimental drugs involved in this study. Any drugs you are prescribed during this study are licensed for treatment of Rheumatoid Arthritis or are a placebo.

Abatacept is licensed for use in patients with RA after they have already tried Methotrexate. In this study Abatacept (or a matching placebo) is being used outside this license to see what the effect is when it is used at the same time as MTX in people who have not had any previous treatment for their RA.

Methotrexate

Methotrexate (MTX) is licensed and currently is being used in routine clinical practice to treat patients with rheumatoid arthritis. MTX is an immune-system suppressant and a chemotherapy agent. MTX is widely used as a disease-modifying treatment for rheumatoid arthritis and other autoimmune diseases (psoriasis, psoriatic arthritis, reactive arthritis, enteropathic arthritis, myositis, systemic sclerosis, lupus, sarcoidosis, Crohn's disease, eczema and multiple forms of vasculitis).

MTX is a so-called "antimetabolite" of a physiological metabolite called "folate". When incorporated into our blood cells and metabolized into its active form, MTX competes with folate and prevents it from being used when it is needed, for example during the synthesis of DNA molecules. As a consequence, active MTX can act as a potent inhibitor of the proliferation of the cells in our body.

MTX has also been suggested to act as an inhibitor of our immune system by preventing the communication between immune cells by binding to and inhibiting one of their key receptors called "interleukin-1 receptor".

Importantly, MTX has been used widely over the last 30 years since its approval in 1988 by FDA. It has a known and predictable safety profile.

For more information refer to the Versus Arthritis Information website leaflet: https://versusarthritis.org/about-arthritis/treatments/drugs/Methotrexate/

Abatacept

Abatacept (known commercially as ORENCIA) is licensed and currently is being used in routine clinical practice in combination with Methotrexate. It is a type of drug called biological therapy. It targets the cause of your inflammation and reduces the activity of your immune system. It's an effective treatment for many people living with arthritis. It will be administered as an Injection in a pre-filled pen. It is indicated for:

- the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who responded inadequately to previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) including Methotrexate (MTX) or a tumour necrosis factor (TNF)-alpha inhibitor.
- the treatment of highly active and progressive disease in adult patients with rheumatoid arthritis not previously treated with Methotrexate.

Abatacept works by reducing the activity of these T-cells, which in turn reduces inflammation, pain, swelling and joint damage. A reduction in the progression of joint damage and improvement of physical function have been demonstrated during combination treatment with Abatacept and Methotrexate.

Importantly, Abatacept has been used over the last 19 years since its approval in 2005 by FDA. It has a known and predictable safety profile.

For more information refer to the Versus Arthritis Information website leaflet: https://versusarthritis.org/about-arthritis/treatments/drugs/Abatacept/

Placebo

A placebo is a drug that is designed to have no therapeutic effect and contains no active ingredients. It might be a sugar pill, a water or salt water (saline) injection; in this trial, it will look just like an Abatacept syringe. A placebo is used in clinical trials to act as a "control" – meaning the drug being investigated can be compared against it to see if there is a difference between the two groups.

Synovial biopsy procedure

The synovial biopsy procedure used in this study is not considered a part of routine rheumatoid arthritis management due to the investigational nature of the study. However, the procedure is routinely used in clinical practice outside of other contexts. The technique is very well tolerated in patients and the physicians performing the procedure are fully trained. At the beginning of the trial, you will receive a synovial biopsy of an inflamed joint as previously described. You will undergo one of two types of biopsy procedure as described below:

1. Ultra-sound guided needle biopsy

A needle is placed into the joint under local anaesthetic guided by ultrasound scanning. A number of biopsies (small pieces of tissue of approximately 1-2 mm^2) are taken from the lining of the joint. This is performed in a sterile setting.

2. Arthroscopic biopsy

An arthroscope (a viewing instrument) is inserted into the joint through a small cut in the skin. A number of biopsies are taken from the lining of the joint. This is also performed under local anaesthetic but is not guided by ultrasound scanning.

We may ask for your permission to perform a further biopsy at 16 weeks from recruitment however this is additional and not mandatory as previously described.

The samples of tissue and synovial fluid obtained from the biopsy procedure are then taken to the laboratory and used for the research purposes described.

Your Rheumatologist will discuss the type of biopsy that will be performed in more detail with you and this will be prior to obtaining your consent to participate in the study.

[You will attend _____~insert site name~_____ for your biopsy.] *Please delete if not applicable at your site.*

7. What are the possible benefits of taking part?

There are no direct benefits to participating in the study. However, the trial will give us essential information, which could be of benefit to others in the future. The medication you are prescribed during the study are routine medications used to treat RA, however Abatacept would not usually be prescribed at this stage of your disease (i.e. before trying at least 2 cDMARDs). If you are randomised to receive Abatacept, you may see an improvement in your disease that you might not have seen if you were prescribed Methotrexate only, however we cannot be sure of this and neither you nor your doctor will be able to decide whether you receive Abatacept or placebo.

The results of the research and analyses obtained from this study might contribute to the development of new therapies or diagnostic products of commercial use.

You will not derive any financial benefit or other claims for the provision and use of your biological samples and your clinical and personal data, or from the commercial use of the results obtained, or from any pharmaceutical products developed.

8. What are the possible risks or discomforts of taking part?

Being involved in a research study involves a degree of commitment such as regular hospital visits and additional tests and surveys. There are no specific advantages to you as the patient, however future patients may benefit from the research by allowing a more tailored approach to their treatment.

The main additional procedure involved in this study is the synovial biopsy procedure as described above. Most patients have no adverse reaction to the procedure, and it is generally very well tolerated. However, there are a few possible complications such as infection of the joint or skin, bleeding, pain and rarely nerve or tendon damage (less than 1: 10,000 risk).

Unwanted effects of treatment

The drugs you will be prescribed during this study are medications that would be prescribed on the NHS for treatment and management of rheumatoid arthritis. However, as with any medication, there are always associated risks, which your doctor will discuss with your prior to starting. You will be given a Patient Information Leaflet with your prescribed medication which lists everything you will need to know about the medication. If you have any questions, do not hesitate to get in touch with your doctor and/or the research team.

<u>Methotrexate</u>

Methotrexate can sometimes cause side effects, which may include feeling sick, headaches, vomiting, diarrhoea, shortness of breath, mouth ulcers, minor hair loss and hair thinning and rashes.

Because your condition and Methotrexate affect the immune system, you may be more likely to get infections.

Often, people say Methotrexate upsets their tummy or makes them sick. Your doctor will probably give you folic acid tablets to help reduce any unpleasant effects caused by your weekly dose of Methotrexate. They will tell you when to take the folic acid.

Severity	Side effects
Uncommon (may affect up to 1 in 100 people)	• Loss of appetite • Feeling or being sick • Stomach pain or indigestion • Diarrhoea • Headaches • Feeling tired or drowsy • Hair loss
Serious side effect (may affect 1 in 10,000 people)	• Yellowing of the whites of your eyes, or yellowing of your skin although this may be less obvious on brown or black skin – these may be signs of liver problems • A persistent cough, chest pain, difficulty breathing, or you become breathless – these may be signs of inflammation of your lungs • Swollen hands, ankles or feet, changes to how often you pee or not peeing at all – these may be signs of kidney problems • A high temperature, chills, muscle aches, sore throat – these may be signs of an infection • Bleeding gums, blood in your pee, vomiting blood or unexplained bruising – these may be signs of a blood disorder

Abatacept

Most people do not experience side effects. Some side effects can happen around the time of the injection. They aren't usually serious, but if you have severe side effects or are concerned about your symptoms contact one of the healthcare professionals in charge of your care.

Some of the side effects can include dizziness, tiredness, headaches, feeling sick or vomiting, and diarrhoea.

In very rare cases people can be allergic to Abatacept. This could be in the form of swelling or a rash, or you may feel short of breath. This is very rare, but if you do develop these symptoms, or any other severe symptoms, during or soon after a dose of Abatacept you should seek medical advice immediately.

Because Abatacept affects your immune system, you may be more likely to pick up infections.

Severity	Side Effects
Very Common (may affect more than 1 in 10 people)	• Infections of the upper airway (including infections of the nose, throat, and sinuses)
Common (may affect up to 1 in 10 people)	• Infections of the lungs, urinary infections, painful skin blisters (herpes), flu • Headache, dizziness • High blood pressure • Cough • Abdominal pain, diarrhoea, nausea, upset stomach, mouth sores, vomiting • Rash • Fatigue, weakness, injection site reactions • Abnormal liver function tests
Uncommon (may affect up to 1 in 100 people)	• Tooth infection, nail fungal infection, infection in the muscles, bloodstream infection, collection of

	pus under the skin, kidney infection, ear infection • Low white blood cell count • Skin cancer, skin warts • Low blood platelet count • Allergic reactions • Depression, anxiety, sleep disturbance • Migraine • Numbness • Dry eye, reduced vision • Eye inflammation • Palpitation, rapid heart rate, low heart rate • Low blood pressure, hot flush, blood vessel inflammation, flushing • Difficulty breathing, wheezing, shortness of breath, acute worsening of chronic obstructive pulmonary disease (COPD) • Throat tightness • Rhinitis • Increased tendency to bruise, dry skin, psoriasis, skin redness, excessive sweating, acne • Hair loss, itching, hives • Painful joints • Pain in extremities • Absence of menstruation, excessive menstruation • Flu-like illness, increased weight

Rare (may affect up to 1 in 1,000 people)	• Tuberculosis • Inflammation of uterus, fallopian tubes and/or ovaries • - Gastrointestinal infection

X-Rays

One of the procedures involved in this study is an X-ray of your hands and feet at the baseline visit and at week 16 (visit 7).

You would normally receive X-rays of your hands and feet every 12 months as part of your normal routine care, to look for joint damage, which can occur in patients with rheumatoid arthritis.

You will also need to receive a chest x-ray to ensure you are suitable to start taking a biological therapy such as Abatacept, to ensure no respiratory symptoms are present which could affect your suitability to take this drug. If any symptoms are present which would exclude you from taking part in the trial, they will be followed up accordingly with your clinical care team.

If you take part in this study, you will have X-rays of the hands/wrists and feet and possibly a chest x-ray as well. Some of these will be extra to those that you would have if you did not take part.

These procedures use ionising radiation to form images of your body and provide your doctor with clinical information. Ionising radiation may cause cancer many years or decades after the exposure. We are all at risk of developing cancer during our lifetime. 50% of the population is likely to develop one of the many forms of cancer at some stage during our lifetime. Taking part in this study will add only a very small chance (0.0001%) of this happening to you.

Venepuncture

Before starting any of the medications you will need to have blood tests to ensure that it is safe for you to start these medications. We will also need regular blood tests while you are on the medications.

Blood samples are obtained by inserting a needle into a vein which can cause discomfort and may result in bruising, clotting, or, rarely, infection. Both discomfort and bruising should disappear in a few days.

Pregnancy

We will perform a pregnancy test when you agree to participate in this study (if you are a person of child-bearing potential). If you are pregnant, you will be excluded from the study. It is not known

whether the intervention drug of the study (Abatacept) can harm a foetus if given to a pregnant woman. It is also not known whether Abatacept passes into breast milk. In order to prevent any damage to an unborn baby it is in your interest not to become pregnant or father any children whilst you are in this study.

For Female Participants:
If you are a woman of childbearing potential, you must agree to use a reliable and effective form of contraception during the study and for 3 months after your last treatment. Acceptable methods of contraception for women include:

- Hormonal contraceptives (e.g., oral pills, patches, vaginal rings, injectables, or implants)
- Intrauterine devices (IUDs) or intrauterine hormone-releasing systems (IUS)
- Barrier methods (e.g., condoms with spermicide, diaphragms with spermicide)
- Bilateral tubal occlusion (surgical sterilization)
- Sexual abstinence, if it aligns with your usual lifestyle

For Male Participants with Partners of Childbearing Potential:
If you are a male participant with a partner who is of childbearing potential, you must agree to use a reliable form of contraception during the study and for 3 months after your last treatment. Acceptable methods of contraception for men include:

- Condoms with or without spermicide during sexual intercourse
- Vasectomy, provided it has been confirmed effective
- Sexual abstinence, if it aligns with your usual lifestyle

Additionally, it is recommended that your female partner also uses an effective method of contraception during this time.

Please discuss any questions or concerns about contraception with the study staff to ensure you select the most appropriate method for your situation.

If you become pregnant during your participation in this trial, you must inform the trial doctor immediately and you will be withdrawn from the trial. One of the study doctors will meet with you to discuss this and arrange further investigations or referrals as required.
If your partner become pregnant during your participation in this trial or within 3 months after your last treatment, you must inform the trial doctor immediately. We will ask your pregnant partner to consent for the clinical team to collect information about their health and their pregnancy. This is

optional and if your pregnant partner agrees, clinical team will contact them after they have given birth to your baby asking you about their pregnancy and delivery and the health of their baby.

9. Will my participation in the study remain confidential?

If you decide to participate in this study, the information about you will be kept strictly confidential. Information needed for study purposes will be collected in a secure electronic database. The information entered into the database will be pseudo-anonymised so that you cannot be identified. No identifiable information will leave the hospital site where you are being treated. You will be given a unique identifier number (study ID), which will be used to track all clinical data and laboratory samples taken during the course of the study.

All samples and data, including data generated through the processing of the samples collected during the study, will be dealt with in strict confidence. They will be used for the purpose of the study as well as future research projects and only in pseudonymised form. No identifiable information will leave the hospital site where you are being treated. The co-ordinating site and the Sponsor will not hold any patient identifiable data (except for year of birth and initials). Therefore, they cannot be linked to you personally. The measures to guarantee your confidentiality have been given a favourable opinion by the **South Central - Hampshire B Research Ethics Committee**

Authorised individuals from the research team, the hospital, the study sponsor, the study funders or the regulatory authorities may inspect relevant medical records. This is to check the study is being carried out correctly.

When the study is complete the results will be published in a peer-reviewed medical journal, but no individual patients will be identified.

Involvement of the General Practitioner/Family Doctor (GP):

We do need to let your general practitioner and hospital consultants know you are taking part in this study. If any clinically relevant information is obtained due to your involvement in the study, we will discuss this with you. If you choose to participate in this trial, you will need to consent to relevant information about your participation being shared with your GP and any relevant doctor involved in your care.

10. What happens if relevant new information becomes available?

Sometimes we get new information about the treatment being studied during the time you are on the study. If this happens your research doctor will tell you and discuss whether you should continue in the study. If you decide not to carry on, your doctor will make arrangements for any ongoing treatment. If you decide to continue in the study, you may be asked to sign another consent form.

On reviewing new information, your doctor might consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons and arrange for your care to continue.

If the study is stopped for any other reason, we will tell you and arrange for your ongoing care.

11. What will happen if I don't want to or can't carry on with the study?

You may withdraw from the study at any time without specifying reasons. If you choose to revoke your consent, you must notify your medical doctor or nurse. If you withdraw consent for any further collection of your data or attendance at study visits, your data and samples already collected will remain on file and will be included in the final study analysis. We will continue collecting only data related to the safety of the treatment received as part of the study. Alternatively, you may choose to only withdraw from continuing the trial treatment and can continue to attend the study visits only. This would be helpful to the researchers in order to collect important data for the trial analysis.

If you become unable to take part in the study due to another illness, or if your doctor feels it is no longer appropriate for you to continue taking part, they may decide to stop your trial treatment. It is important for your own safety that you undergo a normal follow-up examination. This usually consists of a physical examination as well as laboratory tests.

By consenting to participate in this trial, you are consenting to your synovial tissue and blood samples being stored at the Biobank facility at Experimental Medicine and Rheumatology, Charterhouse Square, Queen Mary University of London, as described in Section 14 of this information sheet. Optional samples (urine/stool/saliva) will be sent to and stored at the the Institute of Clinical Molecular Biology at Kiel University and/or Andalusian Public Health System Biobank, Centro de Investigación Biomédica, Avda. del Conocimiento s/n, 18016, Granada, Spain. If in the future you change your mind and wish for your samples to be destroyed, you will need to contact your local research team to request this, who will send the request to the relevant Biobank team (or consortium member, if relevant - see Section 14).

12. What if something goes wrong?

Every care will be taken during the trial. If you have a concern about any aspect of this trial, please discuss this with your medical doctor or nurse who will try their best to answer your questions. If there are any concerns about your safety and your doctor needs to know whether you are taking Abatacept or placebo, there is a process in place to "unblind" you, i.e. to reveal which drug you have been taking. In most cases, patients who are unblinded during their participation in the trial will be withdrawn from continuing trial treatment.

If you must visit another doctor, please make sure you tell them that you are taking part in this study so that they can contact your study doctor if necessary. You can show them a copy of this information sheet.

If you need to speak to a doctor urgently you can do so by contacting ~insert contact person eg 'rheumatology department on-call registrar'~ on the telephone number ~insert number~.

Queen Mary University of London has agreed that if you are harmed as a result of your participation in the study, you will be compensated, provided that, on the balance of probabilities, an injury was caused as a direct result of the intervention or procedures you received during the course of the study. These special compensation arrangements apply where an injury is caused to you that would not have occurred if you were not in the trial. These arrangements do not affect your right to pursue a claim through legal action.

Please contact ~insert Independent contact, e.g. Patient Advisory Liaison Service (PALS)~ if you have any concerns regarding the care you have received, or as an initial point of contact if you have a complaint.

Please telephone ~insert number~, or email ~insert email address~ you can also visit PALS by asking at any hospital reception.

Participants with Personal Medical Insurance are advised to contact their companies and inform them that they intend to take part in the trial.

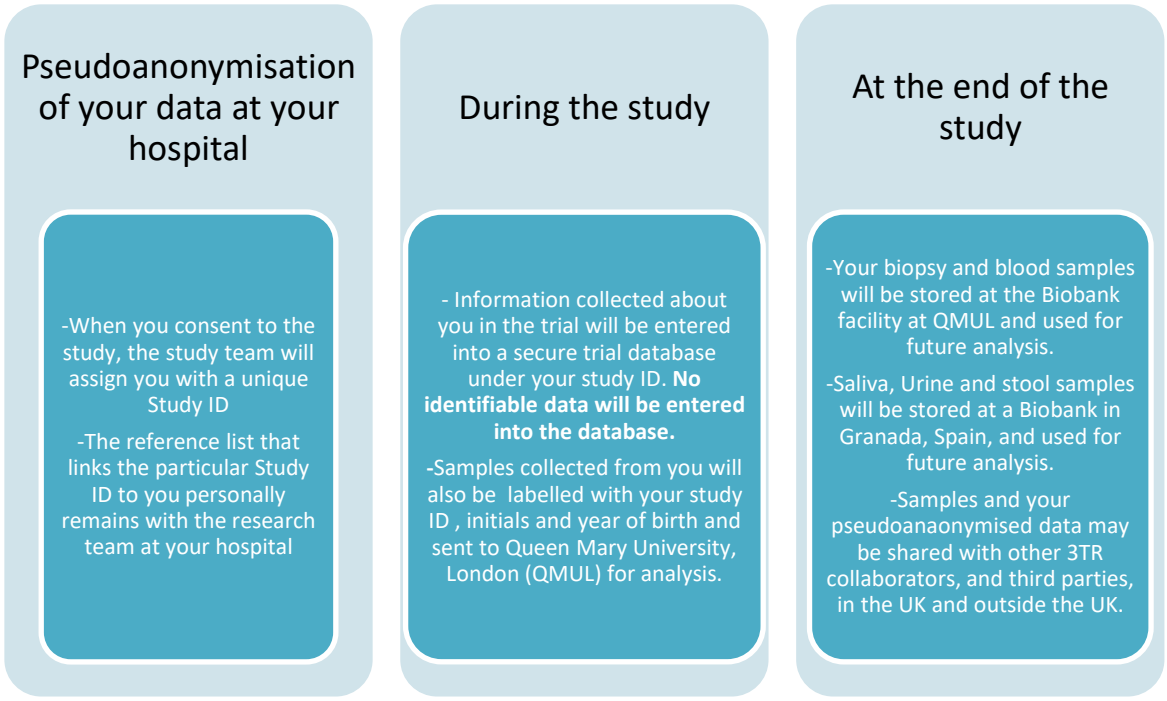
13. Will I be informed about the results of the study?

The results of this trial will be analysed by the Experimental Medicine and Rheumatology department at Queen Mary University of London and will be presented at 3TR and other rheumatology-associated meetings and published in associated journals. You will not be identified in any report or publication about this study.

This study is part of the wider 3TR consortium, which sole purpose is to investigate the mechanisms underlying different autoimmune, inflammatory and allergic diseases, to develop diagnostic methods for these diseases and to support the development of new treatments/medicinal products in this field. This is a lengthy process. The results from this study will provide us with detailed information about the disease at a biological level. ‘ . They will very probably not yield any information which has a direct influence on decisions relating to your current disease treatment. The results from the trial and the analysis of your samples will not be shared directly with you and will not be included in your routine medical care records, as they are solely for research purposes. They will be analysed by the 3TR consortium and presented to the scientific community at various conferences and through publications in scientific journals. You will not be identified in any of those.

The results of the trial are likely to be published on the QMUL and/or the 3TR website which can be found at the following links: https://www.qmul.ac.uk/whri/emr/clinical-trials-emr/ and https://3tr-imi.eu/

14. What will happen to my samples and data? Who has access?



The biological samples collected for the study such as synovial tissue, blood, saliva (optional), urine (optional), and stool (optional), and the associated personal (DOB, sex, ethnicity) and clinical data relating to you will be encoded ("pseudonymised"). This means that your personal identifying characteristics (such as name and address) will be replaced with a numerical code (study ID) so that your identity remains confidential. The reference list that links the study ID to you personally remains with your medical doctor or the research team managing the study in your hospital.

Your pseudonymised data will be saved in a secure electronic database for 25 years. The database will be hosted in the Bart's Cancer Institute, QMUL ITS Safe Haven datacentre. Access to the database will be strictly controlled and restricted to authorised personnel. All the computers and servers storing patient data must meet special security arrangements.

All synovial tissue and blood samples obtained for the study from all participating clinical centres will be sent and stored at the Biobank facility at Experimental Medicine and Rheumatology department for 25 years, Charterhouse Square, Queen Mary University of London. These samples will be used to investigate markers of response to the treatments used in this study, to better understand the mechanisms which lead to rheumatoid arthritis/other disease areas in the 3TR consortium, and potentially new treatment targets. Optional samples (urine/stool/saliva) will be sent to and stored at the the Institute of Clinical Molecular Biology at Kiel University and/or Andalusian Public Health System Biobank, Centro de Investigación Biomédica, Avda. del Conocimiento s/n, 18016, Granada, Spain. The samples and your data may also be used for future analysis in other projects, the nature of which is currently undefined. These samples will be considered as a gift to Queen Mary University of London and will be stored securely by them for up to 25 years. If you decide to participate in these

studies, you agree to give your sample/s and data to the researchers who will be free to use your sample/s for academic and/or commercial research purposes. The samples may be sent to other researchers in the 3TR consortium for analysis, and third parties in the UK and/or outside the UK, including service providers (e.g. contract laboratories). You will not own the results generated using your sample/s and you will not be entitled to any interest in or share of any profit that might arise from research using the sample/s.

The biological samples together with your clinical diagnosis, sex, and year of birth will be forwarded to the commercial and non-commercial Consortium Members for commercial and non-commercial research purposes in accordance with the study. These Consortium Members may use and keep the pseudonymised samples and data for the purposes of the study, as described in this patient information sheet, during the term of the study. If necessary, your pseudonymised samples and clinical data will also be forwarded to third parties including service providers (e.g. contract laboratories) for specific tests and analyses. All the results obtained in connection with the tests and analyses will be generated, collected and saved in a pseudonymised form in a secured centralized database managed by the Consortium Members.

The 3TR consortium is made up of multiple different beneficiaries, including both academic and industry partners. By agreeing to provide samples as part of this trial, you agree that they may be shared anonymously with our academic and commercial partners, including for commercial use (for example, for the development of new drugs).

Your pseudonymised biological samples, data and results can be made available to and used by the aforementioned authorised entities within and outside the UK.

The treatment, communication and transfer of your samples and personal data will at all times comply with the provisions of the UK Data Protection Act even if some aspects of the research are conducted outside of the UK..

In line with Good Clinical Practice guidelines and the Sponsor's research policies, at the end of the study, your data will be securely archived for at least 25 years. Arrangements for confidential destruction will then be made.

15. Will any genetics tests be done?

DNA, RNA and proteins will be extracted from white blood cells in your blood and from cells in the lining of your joint (synovium) that we obtained from your synovial biopsy. DNA will be sequenced and genes in particular associating with response or resistance to treatment will be examined. DNA analysis for antibody production and development will be performed as this is an important aspect of how your arthritis continues to affect you, and how your treatment may improve your symptoms.

Your samples will be identified by a study number only, before any genetic tests are performed. Any test results will therefore not be available individually and will only be reported anonymously on a group basis.

16. What happens at the end of the study?

During the 16-week treatment period, the medications given during the trial will be continued if they are not giving you any negative side effects. At the end of the study, your treatment will be "unblinded", meaning the researchers will reveal whether you have been received Abatacept or placebo during the trial. As Abatacept is not considered routine care at this stage of your disease, whether you have been taking Abatacept or placebo during the trial, it might not be guaranteed that you can receive it as part of your continued care within the NHS/hospital system.

As Methotrexate will be prescribed for your rheumatoid arthritis during this study as per best practice, you may continue receiving Methotrexate after your participation in the study ends, if it is working well for you and your doctor feels it is appropriate. At the end of the study your clinician will discuss the best treatment option for you.

If you are responding well to your treatment, you may be eligible to participate in CReMSIA, which is a research database collecting long term data on patients with rheumatoid arthritis. Your study doctor will discuss this with you if it a possibility (some hospitals may not be participating in CReMSIA).

If your treatment is not working well and you still have high levels of uncontrolled disease, you may be eligible to participate in another 3TR study called 3TR-Precis-The-RA. If you are suitable for this study and it is running at your hospital, your study doctor will discuss it with you and give you a patient information sheet (like this one) to read.

After the end of the study, your samples and your pseudo anonymised data could still be used by 3TR partners to finish any ongoing analysis or research directly related to the 3TR objectives.

17. Who has organised, reviewed and funded the research and who will be supervising it?

This trial is being organised by the Experimental Medicine and Rheumatology department (Queen Mary University of London) and is being sponsored by Queen Mary University of London. The trial has also been peer reviewed within QMUL and by the 3TR partners who make up the rheumatoid arthritis working group, including both academic and commercial partners. The trial has also been reviewed by two independent peer reviewers (these are experts who are not connected to the trial in any way). The study has also been reviewed and approved in the UK by **The South Central - Hampshire B Research Ethics Committee has given a favourable opinion of the study**. This committee is appointed to determine that research studies are ethical and do not impair the rights or wellbeing of patients. The trial is also reviewed and approved by the national regulator. Lastly the

trial has been reviewed by the local Research and Development Department situated at your hospital. The study doctors and nurses will not personally receive any payment for conducting this research study.

This study is being funded by the Innovative Medicines Initiative. Funds obtained from this grant will reimburse your hospital the cost of conducting the study, but the doctors and nurses will not benefit financially from your participation.

18. If I have any questions, who can I contact?

You can ask all the questions you want and obtain more information about this Study, now or at any time in the course of it. To do this you can contact:

Dr.: _____ Phone: _____

Hospital: _____ email: _____

Thank you for taking the time to read this information leaflet.

19. Further information about how your data will be used

How will we use information about you?

Queen Mary University of London will need to use information from you and from your medical records for this research project. This information will include your initials and year of birth. People will use this information to do the research or to check your records to make sure that the research is being done properly. People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead.

We will keep all information about you safe and secure.

Some of your information may be sent to research collaborators in and outside the UK.. Any information shared with research collaborators both within and outside of the UK will be handled with the same high standards of confidentiality and security as required in the UK, ensuring your personal data is fully protected.. 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 you took part in the study.

What are your choices about how your information is used?

- You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.
- We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

- If you agree to take part in this study, you will have the option to take part in future research using your data saved from this study (see section 15).

Where can you find out more about how your information is used?

You can find out more about how we use your information

- at www.hra.nhs.uk/information-about-patients/
- our leaflet available from **www.hra.nhs.uk/patientdataandresearch**
- by asking one of the research team
- by sending an email to sponsor's data protection team data-protection@qmul.ac.ukor
- by ringing us on [phone number].

Glossary

Arthroscopic biopsy – An arthroscope (a viewing instrument) is inserted into the joint through a small cut in the skin.

bDMARDs – Biologic DMARDs – Biological therapies (also known as biologics) are newer drugs that have been developed in recent years. They target individual molecules and tend to work more quickly than csDMARDs (Conventional Synthetic Disease Modifying Anti Rheumatic Drugs). Some biological therapies are called anti-TNF drugs. They target a protein called tumour necrosis factor, which increases inflammation when excess amounts are present in the blood or joints. Etanercept is an anti-TNF drug. Other biological therapies target different proteins, e.g. Sarilumab targets IL-6.

csDMARDs – Conventional Synthetic Disease Modifying Anti Rheumatic Drugs- include such medications as Methotrexate, Sulfasalazine, Hydroxychloroquine and Leflunomide which your doctor may already have spoken to you about.

Double-Blinded – A clinical trial that is “double-blinded” means that neither the patients on the trial nor their doctors know whether the patient is taking the active study drug or the placebo. This is to avoid any bias when reporting the data or the results. If there are any safety concerns, there is always a process to “unblind” the patient, i.e. reveal which treatment they are taking. A “double-blinded randomised, placebo-controlled trial” is considered the “gold standard” of clinical trials.

MTX – Methotrexate is an immune-system suppressant and a chemotherapy agent. MTX is widely used as a disease-modifying treatment for rheumatoid arthritis and other autoimmune diseases.

Placebo – Placebo is a drug that is designed to have no therapeutic effect and contains no active ingredients. It might be a sugar pill, a water or salt water (saline) injection. It is used in clinical trials to act as a “control” – meaning the drug being investigated can be compared against it to see if there is a difference between the two groups.

RA – Rheumatoid Arthritis is a long-term autoimmune disease that typically causes warm, swollen, and painful joints, most commonly in the small joints in hands and feet and can lead to joint destruction.

RNA signatures – These are found in the genetic material of your body.

TNFi – Tumor Necrosis Factor inhibitors which include medications such as infliximab, adalimumab, etanercept, golimumab, and certolizumab.

Ultrasound guided needle biopsy – A needle is placed into the joint under local anaesthetic, guided by ultrasound scanning whereby small tissues are removed from the synovium which is a thin membrane that lines the inside of your joints

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