Switch
Treatment Options for Refractory Rheumatoid Arthritis

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SWITCH: Clinical Trial for Patients with Rheumatoid Arthritis who haven't benefited from an initial TNF-blocking drug.

PARTICIPANT INFORMATION SHEET AND INFORMED CONSENT DOCUMENT

We invite you to take part in a research study called Switch

- Before you decide whether to take part, it is important for you to understand why the research is being done and what it will involve.
- Please take time to read the following information carefully. Discuss it with friends and relatives if you wish. Take time to decide whether or not you wish to take part.
- You are free to decide whether or not to take part in this research study. If you choose not to take part, this will not affect the care you get from your own doctors.
- Ask us if there is anything that is not clear or if you would like more information.
- Thank you for reading this information. If you decide to take part you will be given a copy of this information sheet and your signed consent form.

Important things that you need to know

- We want to find out the best treatment for those patients with rheumatoid arthritis who haven't benefited from an initial anti-TNF drug.
- We are comparing switching from one anti-TNF drug to another, or switching to abatacept or rituximab.
- This study has three groups or treatment options. Regardless of which treatment group you are in, you will receive treatment for a maximum of 48 weeks. After this, the treatment you receive will be decided by your doctor in line with national and local prescribing policy.
- The study fits into your normal treatment, so there are no extra hospital visits
- None of the drugs we are testing are new. They are all normally used to treat rheumatoid arthritis. However, we are trying to find out which one works best.
- As with any drugs, the drugs used in this study can have side effects. These are detailed in section 4.You can stop taking part in the study at any time, without giving a reason. Your treatment and care will not be affected in any way.

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How to contact us

If you have any questions about this study, please talk to your doctor at:

<<Enter PI, nurse name>>
<<contact details for site>>

1 Why we are doing this study

Rheumatoid arthritis (RA) is one of the most common treatable causes of disability in the Western world. Its symptoms impact heavily on people's ability to perform daily activities at home and ability to undertake work commitments. It is therefore vital to treat this condition effectively as soon as possible.

TNF-blocking (or anti-TNF) drugs have been proven highly effective in the treatment of RA, but some patients do not respond as well for reasons we do not yet fully understand. Initial studies have shown that when a TNF-blocking drug does not work, switching to one of the other TNF-blocking drugs may be effective.

In addition to TNF-blocking drugs, two drugs, rituximab and abatacept, have also been licensed for patients who don't benefit from a TNF-blocking drug. The National Institute for Health and Clinical Excellence (NICE), however, only allows use of rituximab (unless rituximab is contraindicated) which may not be appropriate in all patients. There have been no good studies comparing an alternative TNF-blocking drug or abatacept to rituximab in patients who don't benefit from an initial TNF-blocking drug.

Currently there is not enough evidence to guide clinicians on how best to use these therapies when a patient doesn't benefit from a first TNF-blocking drug.

This study will examine patients who don't benefit from their first TNF-blocker and are then randomised and switched to an alternative anti-TNF drug, abatacept or rituximab (which will be referred to as the standard treatment). The aim is to increase treatment options available to patients.

2 Why am I being asked to take part?

You are being asked to take part in this research study because you have RA and have already been taking an anti TNF-blocking drug. You have either not benefited from that or have lost the initial benefit you had from taking that particular anti TNF-blocking drug. The study is taking place in several other hospitals around the UK and we are hoping that 477patients like you who have rheumatoid arthritis will take part.

3 What will happen to me if I take part?

First we need to make sure that it is safe for you to take part and that you are suitable for this study. To do this you will have some screening tests.

- **Screening:**

Screening may be carried out on the day you sign the consent form or you may be asked to return on a different day.

Your doctor may ask you questions about your medical history and medications you are currently taking. You will have a number of blood and urine tests, a heart trace (ECG), a chest X-ray and a full physical examination of some of your joints. You will also be asked to fill in a short questionnaire about your health.

If you are a woman, and capable of having children, a pregnancy test will be done to make sure you are not pregnant.

These tests are to make sure that it is safe for you to take the drugs in the study.

If these tests show that it is not suitable or safe for you to take part in this study, your doctor will discuss other treatment options

with you. Any information we have collected about you will still be used but you will not continue on the study.

- **Baseline:**

If your screening tests confirm that you are able to take part in the study, further blood tests will be carried out to measure how active your RA is before you start study treatment. You will also be examined thoroughly by your study doctor. You may have x-rays taken of your hands and feet and/or a bone density scan of your back. At this point we will also ask you to fill in some questionnaires.

- **Treatment visits (interventional phase):**

Visits to the hospital will depend on which treatment you are given. During these visits you will also be asked to complete some questionnaires and undergo some blood tests to monitor your disease in line with usual practice

- **Other visits**

As well as any treatment visits you will also be asked to attend your local hospital on a 12-weekly basis over a period of up to 96 weeks (a maximum of 8 occasions) to complete some more questionnaires and undergo further blood tests to monitor your disease, again, in line with usual practice. These visits will take 30-60 minutes. The actual number of visits you will be asked to attend will depend upon when you enter the study. This is because the study is scheduled to end in 2015 which will mean you are involved in the study for at least a minimum of 48 weeks or up to a maximum of 96 weeks.

Everyone who takes part will get one of three treatments

The three different treatments are:

1) **Anti-TNF** (one of a possible 5 drugs)

- Infliximab

You will receive intravenous infusions (drip) at the day unit/ward in your hospital. These will be given at weeks 0, 2, 6 and then every 2 months. Each intravenous infusion takes approximately 2 hours to administer.

- Etanercept

This is given as an injection under the skin every week. Etanercept may be delivered to your home by a home healthcare company as arranged by your hospital. Depending upon your hospital's arrangements, either your specialist nurse or someone from the home healthcare team will teach you how to inject. This may take more than one visit. You, your partner, or another member of your family can learn to give the injections.

- Adalimumab

This is given as an injection under the skin every 2 weeks. Adalimumab may be delivered to your home by a home healthcare company as arranged by your hospital. Depending upon your hospital's arrangements, either your specialist nurse or someone from the home healthcare team will teach you how to inject. This may take more than one visit to the hospital. You, your partner, or another member of your family can learn to give the injections.

- Certolizumab pegol

This is given as an injection under the skin at week 0 and then every 2 weeks. Certolizumab pegol may be delivered to your home by a home healthcare company as arranged by your hospital. Depending upon your hospital's arrangements, either your specialist nurse or someone from the home healthcare team will teach you how to inject. This may take more than one visit to the hospital. You, your partner, or another member of your family can learn to give the injections.

- Golimumab

This is given as an injection under the skin every 4 weeks. Golimumab may be delivered to your home by a home healthcare company as arranged by your hospital. Depending upon your hospital's arrangements, either your specialist nurse or someone from the home healthcare team will teach you how to inject. This may take more than one visit. You, your partner, or another member of your family can learn to give the injections.

2) Abatacept

Abatacept is given as an injection under the skin. These will be given at week 0 and then every week. Your specialist nurse will teach you how to inject abatacept. This may take more than one visit to the hospital. You, your partner, or another member of your family can learn to give the injections.

3) Rituximab

You will receive a total of 1 course of treatment for which you will need to attend the day unit/ward in your hospital. A course consists of 2 doses of rituximab given 2 weeks apart. A steroid injection is usually given first to reduce the risk of reactions to the intravenous infusion (drip). Each intravenous infusion (drip) takes approximately 6 hours to administer. Another course is given when the benefit starts to wear off. This would not be for least 6 months after the first course and in some can be a year or two.

If you are receiving one of the intravenous infusion treatments at your hospital you will undergo some safety checks to make sure it is safe for you to receive the drug and you will be asked how you have been feeling since we last saw you.

If you are receiving one of the treatments given as an injection at home, depending upon your hospitals arrangements, you may be asked to come in for a visit about 4 weeks after your treatment has started to check how you are getting on with your treatment.

What is the standard treatment?

The standard treatment approved by NICE is rituximab. The other treatments being compared are also sometimes available to some patients but this varies from region to region.

How is it decided who gets which treatment?

The best way of finding out whether a new treatment is as effective as standard treatment is in a randomised study. 'Randomised' means that a computer will allocate you randomly (as if by the roll of dice) to receive an alternative treatment. Neither your doctor nor you will choose which treatment you receive. In this way, a fair comparison can be made.

How long does treatment go on?

If you benefit from the treatment, the drug will be continued for the duration of the 48 weeks/1 year study period (interventional phase). If you have been allocated to an anti-TNF drug or abatacept, you might not be able to continue this treatment after week 48 even if you have benefited from it. This would depend on your hospital policy. As mentioned earlier, rituximab is given as a single course and would be repeated if the benefit wears off.

What are the drugs that are being used in this study?

TNF-blocking drugs work by preventing the excessive build-up of a protein called TNF (Tumour Necrosis Factor) that causes inflammation leading to pain, swelling and damage in the joints in RA. Most of them work by helping your immune system to attack the TNF but etanercept works by mopping up excess TNF.

Abatacept works by stopping some of the cells involved in causing inflammation from working together.

Rituximab sticks to and removes a type of cell that is involved in causing the inflammation in RA. Unfortunately some of these cells also make antibodies which are important proteins that the body uses to fight germs, viruses or anything else it sees as foreign or dangerous. However, these cells return after some months.

4 Is it safe?

Unwanted effects of treatment

All the study treatments are approved and licensed for use.

Like the TNF-blocking drug you are already taking, all the drugs used in this study have effects on the immune system (the body's own defense system), and therefore may make you more likely to develop infections. You should tell your doctor or rheumatology nurse straight away if you develop symptoms of an infection such as a sore throat, fever or any other new symptoms or anything else that concerns you.

It is possible that there may be a slightly increased risk of certain types of cancer in patients using such drugs (although rituximab is used to treat a certain type of blood cancer). Such a link has not been proven but is the subject of current research. Please discuss this with your doctor if you are concerned. TNF-blocking drugs have been associated with certain types of skin cancer – these can be readily treated when diagnosed early.

Very rarely, a potentially fatal side-effect called toxic epidermal necrolysis (TEN) that is a side-effect of any drug can occur in patients being treated with these drugs. This appears as a fever and then a rash, most commonly occurring in the mouth and eyes. If this were to occur, your doctor would stop your treatment with the drug thought to be making you ill.

TNF-blocking drugs: Very rarely, people taking TNF-blocking drugs may develop a condition called 'drug-induced lupus', which is usually mild. The symptoms are a rash, fever and increased joint pain. Your doctor will check for this with a blood test. If you develop drug-induced lupus, the TNF-blocking drug will be stopped and the condition usually then disappears.

Abatacept, Etanercept, Adalimumab, Certolizumab & Golimumab: These drugs are given as injections under the skin. Reactions at the injection site (e.g. redness, swelling or pain) may occur. These reactions are usually not serious.

Infliximab & Rituximab: These drugs are given as an intravenous infusion (drip). A small proportion of people have had reactions to the intravenous infusion, with a fever, wheeziness, rash or fall in blood pressure. If you develop any symptoms during the intravenous infusion you should tell the person giving you the infusion straight away, because it may be necessary to slow the intravenous infusion down. Very rarely, reactions are severe enough to need to stop the treatment.

Pregnancy during treatment, information for both women and men: Some of the drugs listed above might harm an unborn baby; therefore you should not take part in this study if you are pregnant. You should not become pregnant or father a child during the study period or for a safety period as indicated by your study doctor after your last study dose.

You must therefore agree to use a reliable form of effective contraception during this time. Your doctor will discuss which methods of contraception are suitable. Combined oral contraceptive pills are often not recommended. If you are using this method of contraception, your doctor may recommend an alternative method, which could include the progesterone-only pill (or the mini pill).

Please note if, as a woman, you are taking hormonal contraceptives to prevent pregnancy you should be aware that herbal products containing St John's wort interact with hormonal contraceptives and can make these contraceptives less effective. This increases the risk of having an unplanned pregnancy. This applies to all hormonal contraceptives except intra-uterine devices. Please talk to your doctor if you have any questions and read the Patient Information Leaflet that comes with your hormonal contraceptive.

If you or your partner does become pregnant during the study, you must tell your study doctor at once who will advise you on the potential risks to your unborn child and the options available to you.

Once you have completed the study or if you withdraw from the study and you become pregnant during the specified safety period after your last dose of study drug, you should still tell your study doctor as soon as possible.

X-rays: During the study you will have a chest X-ray and, depending on the facilities available at your hospital, two X-rays of your hands and feet and a bone densitometry scan of your back and leg. These investigations will expose you to several small doses of ionising radiation. We are all constantly exposed to small amounts of ionising radiation in our daily lives due to natural background radiation in our environment. Rocks, building materials, food and drink, and cosmic radiation from space, all provide a radiation dose that we can't avoid. The small radiation dose from the examinations during your participation in this study will add a maximum of the same as about 10 days of natural background radiation.

For the X-ray and scan you will be asked to remove some of your clothes and to wear a gown. The chest X-ray will only be carried out at the start of the study (screening). The other tests, if available at your hospital, will be carried out before the start of study treatment (baseline) and at week 48 of the study.

5 What are the benefits and disadvantages of taking part?

All the study treatments are already approved and licensed for use but currently, only Rituximab is widely available.

The aim of this study is to compare the other treatments with the standard one in a large group of patients to see which ones give the best benefits to which groups of patients.

Taking part in this research study involves time and commitment such as regular hospital visits, although no more than if you were receiving these treatments outside of a research study setting. It is not expected that you will need to stay in hospital overnight, but occasionally this may be

necessary to treat any side effects. For your safety, your study doctor will monitor you throughout the study.

Not all patients respond in the same way to all treatments so we cannot guarantee that the treatment you receive will benefit you directly. However, the results from the study may improve treatments options for patients in the future.

6 What happens to the information you collect about me?

Will my taking part be kept confidential?

If you decide to participate in SWITCH, the information collected about you will be handled strictly in accordance with the consent that you have given and also the 1998 Data Protection Act.

The information needed for study purposes will be collected on paper forms and sent (usually using standard Royal Mail post but in some cases by fax or email) from the hospital to the Clinical Trials Research Unit (CTRU). You will be allocated a study number, which will be used along with your date of birth and initials to identify you on each paper form. Your full name will be included on your consent form and a copy of this will be sent to the CTRU by fax or post. Every effort will be made to ensure that any further information about you that leaves the hospital will have your name and address removed so that you cannot be recognised from it; this information will usually be removed by a member of the study team at your hospital, but may also be removed by the CTRU upon receipt. Your data will be entered onto a secure database held at the CTRU in accordance with the 1998 Data Protection Act. Some of the information will also be sent to the Academic Unit of Health Economics (AUHE) which is also part of the University of Leeds, to enable them to carry out their part of the research.

If you are allocated one of the drugs that may be delivered to you at home the home healthcare company will be given your name, address and possibly your telephone number to enable them to make deliveries to you. This would also be the case if your doctor prescribed you these drugs but you weren't taking part in SWITCH.

Your healthcare records may be looked at by authorised individuals from the research team, the University of Leeds (the study Sponsor), or the regulatory authorities to check that the study is being carried out correctly.

The information collected about you may be shared with other research teams to answer new research questions in the future. Your information will be anonymised (for example; your full name will not be disclosed).

Your data may be passed to other organisations (possibly in other countries where the data protection standards and laws are different to the UK) to monitor the safety of the treatment(s) that you are receiving; this data will have your name removed.

X-rays of hands and feet will be sent for central review to ensure that results / reports are consistent across hospitals. These will be sent via standard hospital processes (such as Royal Mail or courier). Wherever possible, this data will be anonymised and your name removed

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

You may choose to withdraw from the study at any time, without giving a reason. Your decision will not affect the future medical care you receive. You should contact your doctor if you change your mind and decide that you no longer want to take part.

Your doctor may also decide that you are unable to continue in the study if:

- The results of certain tests show that you are not right for this study or for the study drug;
- You get any new health problems during the study;
- You get pregnant or decide that you want to become pregnant;
- The study doctor thinks it is in your best interest to stop

If, for any reason, during the study something happens that means you are no longer able to fully understand information you have been given about your treatment, your doctor will discuss any changes in your treatment with your family/ carer including whether you should be withdrawn from the study. In any event, the SWITCH team will continue to collect data from your clinical care team about your health and any further treatment you might receive until the end of the study at week 96.

If you decide to withdraw from the study, or if your doctor decides it is in your best interest to leave the study, you should give back all unused study medications.

All information collected about you up until your withdrawal will remain on file and will be included in the final analysis of the study. The SWITCH team will also continue to collect data about your health and any further treatment you might receive from your clinical care team until week 96. If you leave the study and do not wish for any further information to be collected about you for the SWITCH study, you should inform your clinical care team of this in order that no further follow-up information is collected from your medical records. However, please note the SWITCH team may be required to continue to collect some limited information about you in the case of any side effects you may have as a result of taking part in the study. This will only be collected if required by the regulatory authorities.

In line with Good Clinical Practice guidelines, at the end of the study, your data will be securely archived for a minimum of 15 years.

Arrangements for confidential destruction will then be made.

What will happen to the results of the research study?

When the study is complete the results will be published in a medical journal, but no individual participants will be identified. If you would like to obtain a copy of the published results, please ask your doctor.

7 What do I do if I have any concerns?

What if the treatment doesn't help?

If the treatment does not help, then, together with your rheumatologist, you may decide to withdraw your treatment but you will continue to be seen by your doctor so we can continue to collect information about what other treatment you might have and the usual assessments of your arthritis. In this case, your rheumatologist will discuss other available treatment options.

How is my condition monitored?

Your arthritis will be monitored in a similar way to what you are used to. You will attend the hospital to see your rheumatologist every 3 months – as well as assessing your joints, you will have blood tests to measure the level of inflammation/disease activity as well as blood tests to ensure it is still safe for you to continue taking the drug.

What happens when the research study stops?

At the end of the study your doctor will discuss available ongoing treatment options with you.

What if there is a problem?

If a medical emergency related to your treatment for this study occurs while you are at home, you should initially try to contact the hospital where you received your treatment. If this is not possible you should go to the Accident and Emergency (A&E) department at your local hospital. If you are unable to get to the hospital you should contact your GP who will already have been informed of your participation in the study.

Harm:

Every care will be taken in the course of this clinical trial. However, in the unlikely event that you are injured as a result of the managing organisation (University of Leeds), compensation may be available and you may have to pay your related legal costs. Your hospital where you receive your treatment has a duty of care to you whether or not you agree to participate in the trial and the University of Leeds accepts no liability for negligence on the part of your hospital's employees. If you wish to complain about any aspect of the way you have been treated please contact your research doctor in the first instance.

Any claims will be subject to UK law and must be brought in the UK.

Complaints

If you remain unhappy and wish to complain formally, you can do this through the NHS complaints procedure (or Private Institution). Details can be obtained from your hospital. Alternatively, you may contact your local Patient Advisory Liaison Office.

If you have private medical insurance, you should tell your insurer that you are taking part in research. They will let you know if it affects your policy.

8 More information about taking part

What if relevant new information becomes available?

Sometimes during the course of a study, new information becomes available. If this happens your doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide not to continue in the study your doctor will continue your care. If you decide to continue in the study you may be asked to sign an updated consent form. Occasionally on receiving new information, your doctor may consider it to be in your best interest to withdraw you from the study.

Who is organising and funding the research?

The SWITCH study is being organised by the University of Leeds through the Clinical Trials Research Unit (CTRU) in collaboration with the Section of Musculoskeletal Disease, Chapel Allerton Hospital, Leeds. The study has been reviewed by the Leeds West Research Ethics Committee and the Research and Development Department situated at your hospital. The study is funded by National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme. Bristol Myers Squibb, a pharmaceutical company, are providing one of the drugs, abatacept, free of charge.

Who has reviewed the study?

To have obtained funding by the NIHR, the study had to go through review by experts who felt this study to be of relevance and importance to patients with rheumatoid arthritis today. It had also been discussed at the Arthritis Research UK Clinical Study Group with consensus that this study would be of significant value to the rheumatology community. The Data Monitoring Ethics Committee (DMEC) and Trial Steering Committee (TSC) will be supervising the study data on a regular basis.

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

We would like to tell your GP that you are taking part in SWITCH and ask for your consent to do this, but otherwise all information about you and your treatment will remain confidential.

What will happen to any samples I give?

Researchers at the local laboratories at your hospital will have access to your blood samples, which will be examine as part of the SWITCH study in accordance with this consent.

The samples will be labelled according to NHS standard practice and will not be anonymised, so that the results can be fed back to your doctor. The laboratories will handle your samples with the same duty of confidentiality as they would for any clinical sample. They will be retained at the end of the study as a record of the completed research study in order to verify the research results, if required.

Additional research

Your samples and data may also be stored, and may provide a resource for future studies in the field of rheumatoid arthritis. If any information from this study is used to develop new research, data protection regulations will be observed and strict confidentiality maintained; your data will have your personal details removed, but will be coded so it may be linked back to your details. You will not be identified in the results of future studies. Ethical approval will be obtained for any future studies involving your data or samples.

There is also the opportunity to donate tissue samples for future research. This involves having additional blood and urine samples taken before you start treatment and then again at weeks 12, 24, 36 and 48. If you wish to take part in the SWITCH Trial BioBank your doctor will provide you with a separate consent form and participant information sheet which are specific to this research. Participation in the additional research is entirely optional, and your decision to participate will not affect your participation in the rest of the study.

Your samples will **not** be used for commercial purposes.

Will any genetic tests be done?

Genetic tests will not be performed in any of the samples you have provided for this study.

If you decide to take part in the additional SWITCH Trial BioBank project then genetic tests may be performed on your samples but this would be subject to appropriate approval from an ethics or scientific committee.

9 Where can I get more information?

If you have any further questions about your illness or clinical studies, please discuss them with your doctor. You may also find it helpful to contact National Rheumatoid Arthritis Society (NRAS), an independent charity (freephone: [redacted]; address: NRAS, Unit B4, Westacott

Business Centre, Westacott Way, Littlewick Green, Maidenhead, Berkshire, SL6 3RT; website: www.nras.org.uk).

If you would like further information about clinical research, the UK Clinical Research Collaboration (a partnership of organisations working together on clinical research in the UK) has published a booklet entitled 'Understanding Clinical Trials'. Contact UKCRC: Tel: [redacted]; website www.ukcrc.org

Another source of independent advice or support is the Patient Advisory Liaison Service (PALS). For more information on PALS or to find your nearest office visit their website at www.pals.nhs.uk or ask your doctor.

You may also like to visit the following website for information on biologic therapies in the treatment of rheumatoid arthritis (a booklet can be requested from NRAS):

http://www.nras.org.uk/help_for_you/publications/publication_detail.aspx?id=a0B80000008XzmxEAC

Local organiser

If you want further information about the study, contact your local organiser/doctor whose details are given on page 1

Thank you for taking the time to consider taking part in this study.