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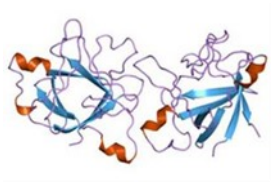
SCIL TRIAL PARTICIPANT INFORMATION FOR PATIENT



We are inviting you to take part in the **SCIL Trial**.

Full trial title: Does Interleukin-1 Receptor Antagonist Improve Outcome following aneurysmal Subarachnoid Haemorrhage (aSAH)? Short trial title: (SC-ILRa in SAH).

This leaflet provides some information about the clinical trial. One of our research team will go through the information sheet with you and answer any questions you may have. Please feel free to share this with your relatives or friends.

This information is divided into two parts:

- **Part 1** explains what would be expected of you if you decided to take part in the trial
- **Part 2** explains the trial in more detail.

Please feel free to ask if anything is unclear or if you would like more information.

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Part 1

Why are we doing the trial?

We are an experienced research group from the University of Manchester and we have shown that subarachnoid haemorrhage (SAH) is associated with inflammation which can lead to further complications.

A protein, made by the body, called interleukin-1 (IL-1) is the main cause of this inflammation. We have shown that this protein can be blocked by another naturally occurring protein, called interleukin-1 receptor antagonist (IL-1Ra). There is a man-made version of IL-1Ra called Kineret®. We are testing Kineret® to see if it improves long term symptoms after SAH. We are testing it by comparing the symptoms experienced by people 6 months after SAH who received Kineret® with those experienced by people who received an identical dummy drug (placebo). Neither the participant nor the research team administering the trial drug will know which treatment the participant is receiving to ensure that we can make a fair comparison.

What is Kineret® and how does it work?

Kineret® (approved name Anakinra®) is the man-made form of IL-1Ra (interleukin-1 receptor antagonist). It prevents the protein IL-1 from attaching itself on to cells, and so prevents it from worsening inflammation. **Kineret®** has been used clinically in many patients with rheumatoid arthritis and other inflammatory diseases and by NHS researchers in stroke and SAH.

SCIL TRIAL TEAM:

Chief Investigating Team Contact: 0161 206 5755

Trial Website: *https://sites.manchester.ac.uk/scil/*

Local Team Contact Details:

Contact name: ……

Telephone: ……..

MANCHESTER 1824
The University of Manchester

NHS National Institute for Health Research

Data storage and usage

The trial will confirm whether giving Kineret® as a subcutaneous injection to patients with SAH improves outcome.

The trial is funded by the National Institute for Health Research (NIHR) and the Chief Investigator's team will follow the recognised guidelines regarding the sharing of trial data. This means that the anonymised data from the trial will be available to others.

Organisation of the trial

The trial is led by the Chief Investigator, Professor Andrew King at The University of Manchester, together with Manchester Clinical Trials Unit, who will oversee the running of the trial at all trial centres. The trial is Sponsored by the University of Manchester.

Who has reviewed the trial?

Independent researchers in the field of stroke and neurosurgery have reviewed the trial positively. All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This trial has been approved by the Health Research Authority (HRA). This includes being given a favourable opinion by a Research Ethics Committee and has received approval from the Medicines and Healthcare products Regulatory Agency (MHRA).

Contact for further information

If you have any queries or questions relating to the trial please contact the research staff at the centre you were recruited from (details overleaf).

THANK YOU FOR READING THIS INFORMATION

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Why have I been asked to take part in this trial?

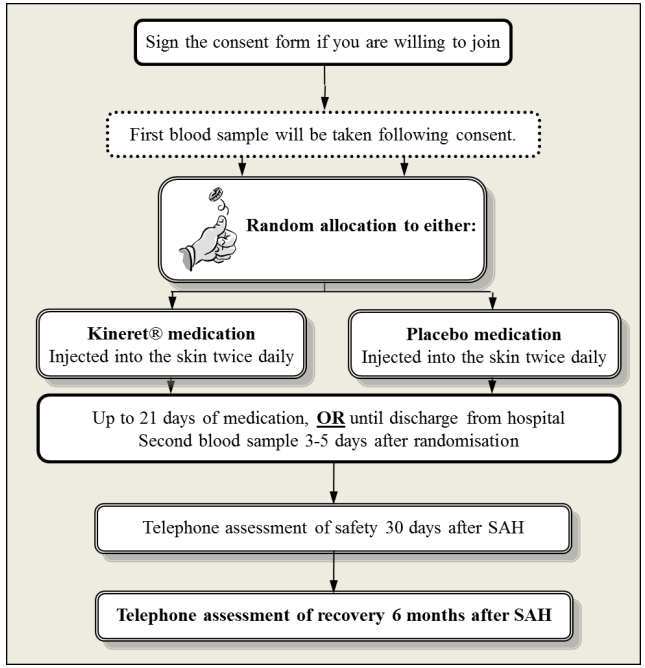
You have been asked to consider taking part in this trial because you have been admitted with SAH.

Do I have to take part in this trial?

No, you do not have to take part in this trial. If you decide that you want to take part you will be given this information to keep and asked to sign a consent form. You are free to withdraw from the trial at any time. You do not have to give a reason for doing so and this will not affect the care you receive.

What will happen if I decide to take part in this trial?

If you decide to take part, the treatment you receive will be identical to that received by anyone not taking part in the trial, with the addition of the trial procedures described here.



If you decide to take part, we will ask you to sign a **consent form** before a **blood sample** is obtained (10ml; 2 teaspoons).

You will be randomly allocated by computer to receive the **Trial Drug**, which will be Kineret® or a placebo (dummy drug). The Trial Drug will be given **twice-daily** as an injection under the skin for a **maximum of 21 days** from the time of your SAH or until you are discharged from the neurosurgical centre. A **further blood sample** (as above) will be taken **3-5 days after randomisation** to check levels of inflammation in the blood. You will be monitored by the research team during your stay in the neurosurgical centre and for **30 days after SAH**.

The trial coordinating team based at the University of Manchester will contact you by telephone at **6 months after the SAH** to ask you some questions about how you are getting on. More detail about the process is described in this leaflet.

Everyone with SAH undergoes a procedure (angiography) to find out if there is a weakness in one of the arteries supplying the brain (an aneurysm) which may need urgent treatment. People who do not have aneurysm do not have the same long term problems as people with aneurysm. If you are found after recruitment into the trial not to have an aneurysm, you will be withdrawn from the trial. You will be followed up for 30 days to make sure you have not had any problems with any trial drug you received before withdrawal, but you will not need to undergo the 6 month assessment.

Whether or not you decide to take part, you will continue to be under the care of your neurosurgical team

The genetic analysis will not affect you directly and you can participate in the trial without agreeing to this. Not all participating hospitals have the facilities to retain the blood cell pellet, but if your site does and you are willing, you will be asked to sign the separate consent. With your permission we would like to treat the blood samples that you give as a gift. After the trial has finished, the Chief Investigator's team would like to keep components of your blood samples indefinitely. Your blood samples will be transferred to a Research Biobank at the Chief Investigator's institution. Blood samples will not be identified using names (see section on Confidentiality) and once the trial has completed, the link between your name and the ID code will be broken so your information will become anonymous. If new knowledge about inflammation becomes available in the future, such as the discovery of a new measure of inflammation this will allow the samples to be used and avoids repeating studies where there are existing samples that can be used to investigate new research questions. The Chief Investigator's team would also like to be able to use remaining components of the sample you give to check the quality and consistency of the tests they carry out, and to develop new tests. You are under no obligation for your samples to be used in this way and you will be asked for your consent to allow your samples to be used for these purposes. If you are withdrawn from the trial because you are found not to have an aneurysm, your samples will still be used in this way (provided you gave consent for this). Your samples would only be used for research relating to inflammation and brain injury and would not be used to investigate other disorders.

Data Sharing

The Chief Investigator's team may wish to share your anonymised data (all identifiable data will be removed) with other research groups conducting research into subarachnoid haemorrhage. For the future, this is a useful way of advancing our knowledge about SAH and its treatment. If this happens, the information about you may be passed to other researchers, but it will be coded so they would not be able to identify you.

What will happen to the results of the trial?

The results of the trial will be submitted for publication to medical journals and at conferences. The results will also be submitted to authorities who are responsible for the development of new drugs to ensure they have all relevant information about the trial drug and the conduct of the trial. The results will also be sent to Swedish Orphan Biovitrum AB, who is also supporting this trial. The results will be completely anonymised and your name or personal details will not be included. If you wish, to receive information about the results of this trial, these will be available on the trial website once the trial is complete in approximately 2023.

Storage of blood samples and usage

The blood samples you give will be prepared for analysis and temporarily stored by research staff at your hospital, before they are transferred to the Chief Investigator's laboratories at the University of Manchester for analysis. We would also like to retain the blood cell pellet left over after sample preparation. This pellet would otherwise be discarded but we would like your permission to keep this to allow analysis of genetics and outcome after SAH in the future.

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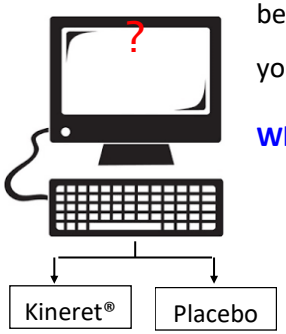
The Consent Process

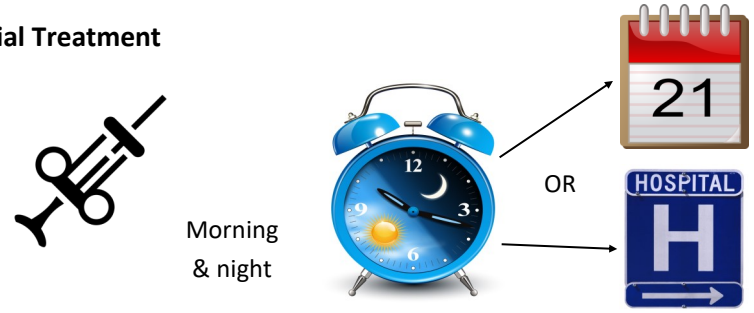
Before you give your consent to taking part in the trial, the research team at your hospital must confirm you are eligible for it and you will be asked to give verbal consent for them to check this. The research team may ask you and/or your family questions but they may also need to check your medical records or speak to your general practitioner (GP). You may be ineligible to participate if you have had certain vaccinations in the last month or if you take some treatments for inflammatory conditions such as rheumatoid arthritis, ulcerative colitis or Crohn's disease. Please tell the researcher if you think you are taking any of these medications. If you are female and of child-bearing age, it will also be necessary to confirm you are not pregnant (see below). If you are eligible and willing to participate, you will be asked to sign a consent form.



What is randomisation?

In order to find out whether a possible new treatment really works, we need to know that the people who receive the new treatment are better than they would have been if they had not received it. This is achieved by conducting a **randomised controlled trial**, in which patients are allocated randomly to receive the treatment being tested or a dummy drug (placebo) treatment. Randomisation is organised by people **independent of the research team.** In this trial half the participants will receive Kineret® and the others will receive placebo (dummy-drug) which will be identical in appearance to the Kineret®, so no-one directly involved in the trial will know which treatment you receive until the trial has completely finished.

Trial Treatment



You will continue to receive injections of the Trial Drug twice daily, morning and evening, for a **maximum of 21 days** from the date of your SAH or until you are discharged from the neurosurgical centre (whichever is earlier).

After this administration period and when you have finished participating in the trial you will no longer have access to the trial drug. Participation in the trial will not delay any aspect of your routine clinical care or your discharge. After completion of the trial your routine clinical care will continue as normal.

Between days 3 to 5 after randomisation, a repeat research blood sample (10ml) will be taken to measure levels of inflammation in your blood.

As part of trial participation, the research team at your hospital will **collect information about you**, your illness and how you are progressing. The first assessment will be performed after consent and will include details of your SAH, past medical history and current medications. The next assessment will be performed at the same time as the repeat blood sample and will record details of your current treatment. The third assessment will be performed on the day of the last injection of the Trial Drug.

Your medical notes and research record may also be seen by authorised people who are not directly involved in your care in order to check the conduct of the trial. This may include representatives from the Manchester Clinical Trials Unit (who are managing this trial), The University of Manchester, regulatory authorities (Medicines and Healthcare Products Regulatory Agency (MHRA) or from your local NHS Trust. In order to complete the final outcome assessment, it will be necessary for the researchers at your hospital to provide a limited amount of personal information (including name, address, telephone number and general practitioner details) to the Chief Investigator's team at the University of Manchester. This information will be held securely and will only be accessed by individuals involved in conducting the final assessment. When the final assessment has been completed, this information will be securely disposed of in accordance with the University's policies and procedures.

Contacting your GP

Your GP will be informed that you are taking part in this trial. This is standard practice and will ensure that your GP continues to be involved in your care.

The University of Manchester is the sponsor for this study based in the United Kingdom. We will be using information from you and your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. The collected personal data will be processed by the Manchester-CTU and will act as the data processor for this study. The legal basis or reason in data protection law which allows us to use your personal data is "public interest task" and "for research purposes" for the sensitive information collected. For more information about the way we process your personal information and comply with data protection law please see our Privacy Notice for Research Participants at the following link http://documents.manchester.ac.uk/display.aspx?DocID=37095, via the SCIL trial website, and by contacting the trial team (0161 206 5755).

The University of Manchester will have access to identifiable information about you for 25 years after the study has finished. The Manchester-CTU will only keep your data until the trial is closed-out and archived by sponsor.

Your rights to access, change or move your information may be limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible. http://documents.manchester.ac.uk/display.aspx?DocID=37095, which can be accessed via the SCIL trial website, and by contacting the trial team (0161 206 5755).

Details of your identity will only be retained by the research team at your hospital. Researchers at your hospital will also require access to your hospital notes and other health records in order to collect and verify your clinical data.

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Follow-up Assessments

As with all clinical drug trials, it is necessary to confirm the **safety** of the Trial Drug being investigated. Members of the research team at your hospital will record everything that happens to you during your in-patient stay and again at 30 days after randomisation. If you are still an in-patient at the neurosurgical centre on this date, this assessment will be performed face-to-face by a member of the research team at your hospital. If you have been discharged home or returned to your local hospital, the researcher will perform this assessment by telephone with you, your relative or your local healthcare provider.

Six months after your SAH the **final outcome assessment** will be performed. This will be conducted by members of the research team in Manchester. You or your relative will be **contacted by telephone** and the researcher will complete a series of questionnaires based on the answers you provide. The questionnaires are all used routinely to **assess recovery after SAH**, so you may have been asked these on a previous occasion by your clinical team.

The first questionnaire (modified Rankin Scale) will assess your level of recovery and **return to normal life** and will include details about self-care, mobility, leisure and social activities and return to work.

Three further questionnaires will assess your **mood** and level of **fatigue** as well as your overall **quality of life**. Completion of all questionnaires will take **no more than 30 minutes**.

If you prefer, you will be offered the opportunity to complete the questionnaires yourself **on paper** and returned by post. The questionnaires will **not record your name** or any personal identifiable information. If you are unable to answer the questionnaires yourself, the researcher may ask for assistance from your relative/friend, your general practitioner or another healthcare provider in completion of these questionnaires. The information obtained at this assessment is **very important**, as it allows the research team to assess whether reducing inflammation after SAH does improve recovery, so please do let us know if you move house or change your phone number. **This assessment will complete your trial participation**.

With your permission, the researchers at your hospital or in Manchester would like to contact your family doctor (GP), Consultant and any other Health Care Professional involved in your care to let them know that you have been a participant and, if necessary, to ask them to provide information about you during trial participation and in particular, at six months if it is not possible to obtain this from you.

Are there any alternative treatments?

No, there are no current alternative treatments to reduce inflammation following SAH.

What are the possible benefits of taking part?

The trial may not have any direct benefits to you, but you will be helping to increase what is known about recovery from SAH, inflammation and new treatments which could improve patient care in the future.

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Part 2

What if new information becomes available?

Sometimes, during the course of a project, new information becomes available relating to what is being studied. If this happens, the researcher at your hospital will tell you about it and discuss if you want to continue in the trial. You may be asked to confirm your willingness to continue by signing a new consent form.

What if there is a problem?

Complaints: If you have a concern about any aspect of this trial, you should ask to speak to the researchers who will do their best to answer your questions. If they are unable to resolve your concerns or you wish to make a complaint regarding the trial, please contact a University Research Practice and Governance Coordinator on 0161 276 7583 or 0161 275 8093 or by email to research.complaints@manchester.ac.uk

Harm: In the event that something does go wrong and you are harmed as a result of your participation in this trial, you may have grounds for a legal action for compensation against The University of Manchester or NHS Trust but you may have to pay your own legal costs. The normal National Health Service complaints mechanisms will still be available to you— please ask a member of your medical or research staff for details of these.

Confidentiality: If you consent to take part in this trial, all information which is collected about you during the trial will be kept strictly confidential as required by Data Protection laws. Once you are registered onto the trial, you will be allocated a unique trial identification number and all research records relating to your participation will use this number to ensure the record is pseudonymised (not easily identifiable).

Pregnancy

The effects of Kineret® on the foetus and nursing child are not known. If you suspect or know you are pregnant or are breast-feeding you cannot take part in the trial so you must inform the trial team. Prior to inclusion in the trial, if you or your representative is not able to reliably confirm you are not pregnant, it will be necessary to perform a pregnancy test. Your verbal consent will be obtained beforehand. If you decline, you will no longer be considered for trial participation. **It is important that you (or if you are male, your partner) avoid becoming pregnant whilst receiving Trial Drug.**

Will I be paid for taking part?

You will not receive payment for taking part in the trial. The research is funded by the National Institute for Health Research (NIHR) and none of the researchers involved in the trial will receive extra payment as a result of your participation.

What else do I need to know?

In some cases of SAH the cause for it cannot be found. One in five patients who present to hospital with SAH is not found to have an aneurysm on brain imaging. These patients are not thought to experience many of the problems associated with raised inflammation. Because of this if, after being included, you are found not to have an aneurysm, you will be withdrawn from the trial (see section on withdrawal).

If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decision.

What are the possible risks/side effects of taking part?

Your well-being and safety is our primary concern. Most of the information about the side effects of Kineret® has been discovered from the treatment of patients with rheumatoid arthritis; many of whom have taken Kineret® for a long time (months or years). In this trial, treatment is much shorter (maximum of 21 days).

Common issues seen in previous trials of Kineret® in SAH:

Injection site reaction: A known side-effect of Kineret® is the appearance of small, red and occasionally itchy patches on the skin where injections have been given. This is more common in people given injections for long periods, but in previous trials where Kineret® was administered for 21 days after SAH, some participants developed these from as early as 10 days. The injection site reaction disappeared when the Trial Drug was discontinued and participants in the previous trial did not request withdrawal because of this. If you experience an injection-site reaction, you can be prescribed medication to relieve itching if necessary. If the injection site reaction is a concern, you may request for the Trial Drug to be discontinued. If you decide to do this, you can choose to continue to participate in the trial without further taking the Trial Drug and outcome information will continue to be collected. You can also choose to withdraw yourself and your data completely (see Withdrawal section below).

Blood Sampling: You may experience some discomfort and bruising caused by blood sampling. Researchers at your hospital will try to combine clinical and research blood sampling to minimise your discomfort.

Final Assessment: While not a side effect of the Trial Drug itself, some people may find the questions and assessments at the 6 month assessment distressing. The researcher performing the assessment is very experienced in completing the assessments and is mindful of the distress this may cause. You can refuse to answer any questions which you find upsetting and you can stop the assessment at any time.

Known risks/side-effects of Kineret® not seen in previous SAH trials:

Infections: Studies that have given Kineret® over short periods (days or weeks) (for severe infections; SAH or stroke) have shown no evidence of increased infections. However, studies in patients with rheumatoid arthritis who have been on Kineret® for a long time (months or years) have shown a slight increased risk of infections; some of which are classed as serious.

People with SAH are also at risk of infections and are monitored extremely closely so that these can be treated rapidly if they occur. Previous studies of Kineret® in SAH have **not shown** an increase in infections.

Antibodies to Kineret®: Previous studies also showed that after long-term use of Kineret®, the body may make antibodies to IL-1Ra (found in Kineret®) with a possible risk of allergy. This is a rare but a potentially serious side effect. If you think you may have received Kineret® (sometimes called Anakinra®) before or a similar drug either as part of your medical care or as part of another research trial, you may be excluded from taking part in this trial. The researcher at your hospital will be happy to discuss this issue.

Withdrawal from the trial

Anyone who takes part in the trial and has received at least one dose of Trial Drug, who is then withdrawn from the trial (for example those who are found to have no aneurysm) will be followed up for at least 30 days. As this is a clinical trial of a drug, we will need to continue to monitor your progress to confirm the safety of the drug. Where possible, the research team at your centre will access information recorded in your medical records, rather than approach you in person.

It is also your right to withdraw yourself from the trial at any point without giving a reason. In this case the research team will continue to access your medical records for 30 days from the day you entered the study to monitor your progress and confirm safety of the drug. The clinical or research team at your centre may also withdraw participants if they consider it to be in their best interests.