SAFA (Spironolactone for Adult Female Acne)

A pragmatic multicentre double-blind randomised superiority trial to investigate the clinical and cost-effectiveness of spironolactone for moderate or severe persistent acne in women

We invite you to take part in a research study

- You have been given this information sheet because you might like to take part in the SAFA trial.
- You are being invited because you have experience of acne or spots.
- Please take the time to read this information carefully. You may also wish to discuss it with your family and friends before making up your mind.
- Please feel free to contact us to ask any questions you may still have after reading this information sheet.

Do I have to take part? No. It is entirely up to you if you take part in the trial or not. If you choose not to take part, any future care or treatment you get from your own doctors will not be affected in any way.

If I start the trial, can I stop if I want to? Yes. If you choose to take part in the trial, you are free to stop at any point without giving a reason – your participant rights and routine care will not be affected.

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If you have any questions about this trial or would like to discuss it further, please contact**:**

[local investigator name]

[contact details]

Important things you need to know about SAFA

- The SAFA trial is being run so that we can find out more about a treatment (medicine) that might help women with acne or spots.
- For some women, we think this treatment could replace using antibiotics (taken by mouth) for treating acne. Reducing the use of antibiotics is very important owing to the increased risk of bacteria becoming resistant to antibiotics.
- If you decide to take part in the SAFA trial you will be put into one of two treatment groups and receive the trial medicine (either spironolactone [a drug], or placebo [dummy pill]). Your treatment will be decided by chance, this process is called *randomisation*.

Randomisation: Sometimes we do not know the best way to treat patients. To find out, we need to compare different treatments. We put people into groups and give each group a different treatment; the results are compared to see if one is better. To try to make sure the groups are the same to start with, each patient is put into a group by chance (randomly).

- The trial medicine is a tablet. Each tablet contains 40mg of lactose.
- Everyone in the SAFA trial can use topical treatments (these are treatments you apply to the skin such as creams, gels and lotions) for their acne along with the trial medicine they are given. It would be helpful if you did not change your topical treatment for the first 3 months of the study.
- You must not have started, stopped or changed long-term hormonal contraception (or other hormonal treatment) in the 3 months before starting the study, and you must not start, stop or change hormonal contraception or treatment during the first 3 months of the study.
- You must not have taken antibiotics by mouth for your acne in the month before starting the study, and you must not take them during the first 3 months of the study.
- You must not have taken Roaccutane in the 6 months before the study, and you must not take it during the first 6 months of the study.
- All medication can cause side effects. However, you will be able to report any side effects that you experience to the study team as well as to your GP as usual, and these will be treated appropriately.
- We will need to collect and analyse a small sample of your blood (about 5-10ml, 1-2 teaspoons, each) at your first clinic visit to make sure it is safe for you to remain in the study.
- Women who could become pregnant will need to take a urine pregnancy test before being accepted into the trial. Pregnant women, or women who are breastfeeding, will not be able to take part in the trial.
- Women who could become pregnant **must** be willing to use their usual hormonal or barrier method of contraception for the first 6 months of the study and for 4 weeks (about one menstrual cycle) afterwards.
- You must not donate blood or eggs during the first 6 months of the study.
- You will need to sign a consent form before taking part in the trial to confirm that you have read this information and agree to take part.

1. Why we are doing the SAFA trial?

The SAFA trial is a randomised study looking at how effective a tablet called spironolactone is when taken alongside usual treatments for adult women with acne, compared with usual treatments alone. The trial will include around 434 women.

A third of people who see their doctor for their acne are prescribed a long course of oral antibiotics (antibiotics taken by mouth). There are growing concerns about bacteria becoming resistant to antibiotics and there is a need to find new effective alternative treatments to antibiotics. By carrying out the SAFA trial, we hope that adult women with acne might benefit in the future if this trial is successful.

2. Who is the trial for?

The trial is for adult women (aged 18 years or older) with acne.

3. What will I have to do if I decided to take part?

If you decide to take part in the SAFA trial, you will be asked to sign an Informed Consent form.

After you have given informed consent, you will be asked to give a small blood sample (about 5ml-10ml, 1-2 teaspoons), which will be used to check your blood potassium level and check how well your kidneys work. If your kidneys are not working well, or your blood potassium is high, then the SAFA trial may not be suitable for you and you will be asked to stop taking the trial medicine.

The study team will also look at any other medications you are currently taking.

Women who could become pregnant will need to take a urine pregnancy test to check that they are not pregnant before starting the study. The study team will also ask you to confirm that you are not planning to become pregnant in the next 6 months. You will be given information about appropriate effective contraceptive use during the trial.

This is because the trial medicine should not be taken if you are pregnant and you should avoid becoming pregnant whilst on the study treatment.

You will then be randomised to one of the two treatments in the trial. One group will be given spironolactone and the other group will be given an identical looking *placebo*. Neither you nor your doctor will know which pill you are taking.

Placebo: A placebo is a 'dummy treatment' given to compare its effects with those of a real drug. The placebo in this trial will be made into identical tablets so that it looks like the trial medicine. It will be taken by mouth just like spironolactone, but will contain no active ingredient. Regardless of which group you are allocated to, you will still receive standard treatment for your acne in addition to the trial medicine.

What is the treatment and visit schedule?

If you are eligible to join the study you will have 3 clinic visits.

*Please bring **all** of your current tablets, medicines, inhalers and/or topical treatments with you to the first appointment regardless of whether they are being used for acne.*

First clinic visit

At this clinic visit, you will be asked to give informed consent and you will have the tests described in Section 3. If the trial is suitable for you, the research nurse will measure your height, weight, waist circumference and blood pressure.

The research nurse will also take a photograph of your acne (using an instant picture camera) and you will be given this photograph to take home with you. Please note, if you are wearing make-up, you will be asked to remove it before having your photograph taken. You will have the opportunity to reapply make-up if you would like to.

At a later date, you will be asked to refer to the photograph to see how well you think the treatment has or has not worked for you. If you give permission, another photograph will be taken and stored securely at the hospital (in a restricted, locked environment that only the study team have access to) for you to use at later clinic visits.

You will be asked to fill in some questionnaires about your acne, any treatments you use for it, and any costs to do with your health and care needs relating to your acne.

You will be given a bottle of tablets - either spironolactone or placebo - to take home with you. You will be asked to take 1 tablet a day every morning for 6 weeks.

You will also be given a trial card with emergency contact details for your study team at the hospital.

Please contact the study team immediately if you experience any side effects (contact details are also on the front page of this leaflet).

If you cannot reach the study team please contact your own doctor or go to A&E, depending on how bad the side effect(s) are, and take your trial card with you. Section 5 has more information about potential side effects.

6 week clinic visit

After 6 weeks you will come back to the clinic to see how your acne has responded to the treatment. Please bring your bottle of tablets back with you.

If you are tolerating the tablets well and you and your doctor feel there has been little improvement and/or things are slow to improve your dose will be increased to 2 tablets a day taken in the morning, otherwise it will be kept at 1 tablet a day, for another 6 weeks. You will be given a new bottle of tablets to take home.

You will also be asked to fill in some questionnaires at this appointment. Using the photograph that was taken 6 weeks before, you will be asked to rate the overall change in your acne.

If 2 tablets cause side effects at any time, please contact the study team straight away and the dose will be reduced back to 1 tablet.

12 week clinic visit

At 12 weeks you will come back to the clinic again to see how your acne has responded to the treatment. Please bring your bottle(s) of tablets back with you. If you are not already taking 2 tablets a day, your dose may be increased to this, otherwise it will be kept at 1 tablet a day taken in the morning, for another 12 weeks.

If the treatment has not helped your acne as much as expected, your doctor may decide to try different topical treatments (cream, lotions or gels), or may prescribe you oral antibiotics to take as well.

Using the photograph that was taken 12 weeks before, you will be asked to rate the overall change in your acne. If a photograph was stored at the hospital, you will be given it to take home with you.

24 week postal questionnaire

12 weeks after the 12 week clinic appointment (at 24 weeks) you will finish taking the study tablets you have been given. You will be sent questionnaires to fill in and asked if you are satisfied with your treatment. Between 24 and 52 weeks, you can ask your usual doctor for different topical treatments, or treatments taken by mouth such as oral antibiotics and Roaccutane (isotretinoin).

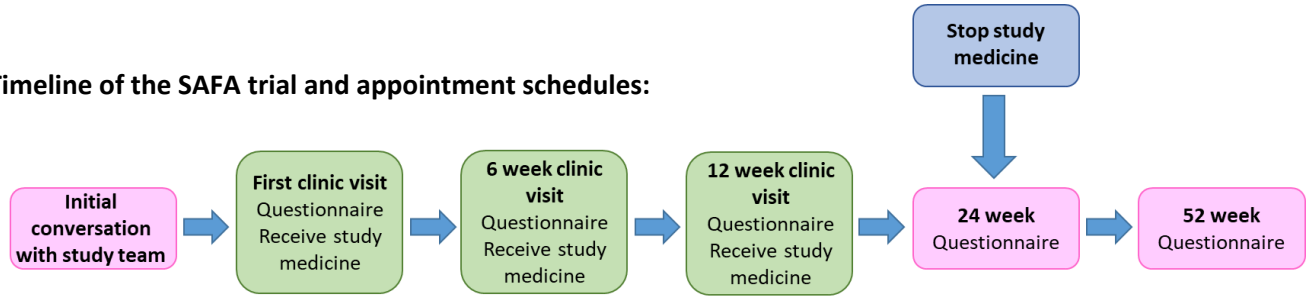
After 24 weeks, we will send you a letter to tell you which study tablets you were taking (spironolactone or placebo). If you would like to continue or try taking spironolactone for your acne, please speak to your GP about this. We will also write to your GP to let them know which tablets you were taking.

However, although it is a well-established treatment for other medical conditions, spironolactone is currently unlicensed for acne. Until we have the results of the SAFA study, we do not have evidence to prove if it works for acne or not. Therefore, your GP does not have to prescribe spironolactone for you after 24 weeks, but most are happy to do so.

52 week postal questionnaire

After 52 weeks you will be sent the final questionnaire to fill in.

Timeline of the SAFA trial and appointment schedules:



4. What will happen to the samples I give?

A member of the hospital study team (Research Nurse or Clinical Research Fellow) will take the blood sample needed to check your blood potassium level and check how well your kidneys work. This sample will be sent to the hospital lab for testing. Once the results are known, the sample will be disposed of locally at the hospital. Samples will not be kept for future tests.

After the urine pregnancy test, the Research Nurse or Clinical Research Fellow will dispose of the used kit.

5. More about the trial medicine

If you decide to take part in the SAFA trial, you will be asked to take spironolactone or a placebo tablets.

Each tablet contains 40 mg of lactose. Therefore, you cannot take part in this trial if you are lactose intolerant (i.e. react badly to lactose or milk).

What exactly is the medicine that is being tested?

Spironolactone is part of a group of medicines called 'potassium sparing diuretics' or water tablets. It is usually given to people who have excess fluid in their body and helps to get rid of this extra fluid. Spironolactone also lowers some of the hormones that cause grease production. Grease production is raised in acne, so some dermatologists think that spironolactone can help treat acne.

Has spironolactone been given to people before?

Yes, spironolactone is currently widely used to help with high blood pressure, heart failure, nephrotic syndrome (a kidney disorder), liver cirrhosis with fluid retention (oedema) and swelling of the abdomen. Spironolactone has been used by many dermatologists for acne, particularly in the US, but only small trials have been carried out to test its effectiveness, so spironolactone is not currently licenced for use in acne.

6. What are the possible side effects?

As with most medicines, spironolactone may cause unwanted side effects. This information sheet does not list all of the known side effects, only the most common ones. The study clinician will discuss all other potential side effects not listed here.

Side effect	How common is it?	
Headache	Uncommon	Affects between 1 in 1,000 and 1 in 100 people
Dizziness	Uncommon	Affects between 1 in 1,000 and 1 in 100 people
Tingling	Not known	Cannot be estimated from the available data
Indigestion/heartburn	Uncommon	Affects between 1 in 1,000 and 1 in 100 people
Diarrhoea	Uncommon	Affects between 1 in 1,000 and 1 in 100 people
Passing much more urine than normal	Not known	Cannot be estimated from the available data
Nausea (feeling sick)	Uncommon	Affects between 1 in 1,000 and 1 in 100 people
Vomiting (being sick)	Uncommon	Affects between 1 in 1,000 and 1 in 100 people
Tenderness of the breasts	Common	Affects between 1 in 100 and 1 in 10 people
Breast enlargement	Common	Affects between 1 in 100 and 1 in 10 people
Irregular menstrual periods	Rare	Affects between 1 in 10,000 and 1 in 1,000 people
Abdominal pain	Uncommon	Affects between 1 in 1,000 and 1 in 100 people
Weight gain	Uncommon	Affects between 1 in 1,000 and 1 in 100 people
Reduced libido (reduced interest in sex)	Not known	Cannot be estimated from the available data
Fatigue/tiredness	Not known	Cannot be estimated from the available data
Drowsiness/sleepiness	Uncommon	Affects between 1 in 1,000 and 1 in 100 people

Please tell your study doctor or nurse straight away if you notice any side effects, whether they are listed here or not. Please also let your study doctor or nurse know if any side affects you may experience get worse. In the very unlikely event of a serious reaction to the trial medicine, please stop taking the trial medicine and seek medical advice immediately following the instructions on the trial card that you will be given.

Stop taking the trial medicine and contact your study team immediately if you experience any of the following:

- Suspected high blood levels of potassium
  - Symptoms include muscle twitching or weakness, irregular heartbeat, unusual tiredness or weakness, paralysis with or without loss of muscle tone, circulatory failure
- An allergic reaction (hypersensitivity)
  - Symptoms such as swelling of the face, lips, tongue or throat, difficulty breathing or swallowing, shock, collapse, skin rash or itching
- Severe skin rashes
  - Severe form of skin rash with flushing, fever, blisters or ulcers. A severe rash involving reddening, peeling and swelling of the skin that resembles severe burns or a severe skin rash involving fever and swelling

7. What will happen at the end of the trial?

52 weeks after you started the study you will have a final questionnaire to fill in. Once this has been completed, you will have finished the trial.

At the end of the study, the results will be analysed, but this can take a further 6 months. The results will then be published in a medical journal. No directly identifiable personal data will be used in any reports or publications that come from the SAFA study. We will send you a summary of the study results, unless you have told us that you would prefer not to receive this. The summary will also be available to members of the public on the Southampton Clinical Trials website: www.southampton.ac.uk/ctu/index.page

8. What are the possible benefits, risks and disadvantages of taking part in the trial?

Clinical trials are designed to reduce the risks and increase the benefits to the people who take part, regardless of which treatment they get. However, we cannot guarantee any specific treatment benefits or that there are no risks involved when taking part in a clinical trial.

Possible benefits:

- You may see an improvement in your acne and avoid needing to use antibiotics or Roaccutane (isotretinoin)
- You will be helping to further our knowledge of how to treat adult female acne and this will benefit other women with the same condition in the future

Possible risks/disadvantages:

- The trial treatment may not control your acne
- There may be some side effects (please see the side effects section [section 5] for more information)
- There could be risks to your child if you become pregnant (please see the pregnancy and contraception section [section 8] for more information)
- You will need to attend 3 clinic visits, provide blood samples and answer some questionnaires, which you would not do if you were not taking part in the trial.

9. More about contraception and pregnancy during the trial

If you are pregnant you will not be able to enter the SAFA trial. Women who could become pregnant will need to have a negative urine pregnancy test before starting treatment. If you become pregnant during the trial, you will not be able to continue taking part in it.

If you become pregnant during the trial, you must tell your study team immediately because we will need to follow the pregnancy, with your permission, to check that the trial drug has not caused any problems

Risk of harm to a developing foetus when taking spironolactone is not thought to be high. It is likely to be lower than for other oral treatments for acne, such as tetracycline antibiotics, co-cyprindiol or oral isotretinoin, which can lead to birth defects or miscarriage.

If you could become pregnant and you decide to take part in the trial, it is important that you agree to use your usual hormonal or barrier method of contraception from the start of your trial treatment and for the first 6 months of the study and for 4 weeks (about one menstrual cycle) afterwards.

10. What are the alternative treatments?

If you prefer not to take part in the SAFA trial, your doctor will be able to discuss all treatment options with you. Please be reassured that it is entirely up to you whether or not you take part in the SAFA trial. If you decide not to take part, the standard of your care will not be affected in any way.

11. Other questions you may have about the trial

What does informed consent mean?

No one can enter you into the SAFA trial without your permission. To help you decide if taking part is right for you, the trial doctor/nurse should discuss the trial with you in depth. The most important thing is that you are satisfied you know enough about the trial to make an informed decision. You are free to ask as many questions as you like. In addition, you will be given as much time as you need to make your decision – you should not feel rushed.

If you decide to take part in the SAFA trial, you will be asked to sign an Informed Consent form, which confirms that you agree to take part. You will be given a copy, a copy will be kept in your medical notes, a copy will be kept in the hospital study records, and a copy, with your permission, will be sent to the Southampton Clinical Trial Unit via secure e-mail and held securely.

Will my details be kept confidential?

Yes. Your participation and the information we collect about you during the course of the research will be kept strictly confidential.

Only members of the research team and responsible members of the University of Southampton may be given access to data about you for monitoring purposes and/or to carry out an audit of the study to ensure that the research is complying with applicable regulations. Individuals from regulatory authorities (people who check that we are carrying out the study correctly) may require access to your data. All of these people have a duty to keep your information, as a research participant, strictly confidential.

Non-identifiable data, managed by the Southampton Clinical Trials Unit, will be held on servers located within and outside of the EU. Access will be strictly controlled and all current Data Protection Regulations will be abided by. This data is described as 'pseudonymised' because your initials will be stored on the server.

You can find out more about how we use your information by contacting the Southampton Clinical Trials Unit: https://www.southampton.ac.uk/ctu/contact.page; telephone: 02381 205154; email: ctu@soton.ac.uk

Your Hospital will collect information from you for this research study in accordance with our instructions. Your Hospital will keep your name and contact details confidential and will not pass this information to the University of Southampton, without your informed consent. Your Hospital will use this information as needed, to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study.

Certain individuals from the University of Southampton and regulatory organisations may look at your medical and research records to check the accuracy of the research study. The University of Southampton will only receive information without any identifying information. The people who analyse the information will not be able to identify you and will not be able to find out your name, or contact details.

With your permission, a copy of your consent will be sent to the Southampton Clinical Trials Unit (where it will be kept securely), to allow confirmation of your consent.

With your permission, we will tell your General Practitioner (GP) that you are taking part in the SAFA Trial. We may also need to talk to your GP about adverse events linked to your trial acne treatment. Your medical records will be available to those involved in your clinical care and authorised individuals from the Sponsor or the Sponsor's delegates from the Southampton Clinical Trials Unit, Funder and Regulatory Authorities.

Data Protection Privacy Notice

The University of Southampton conducts research to the highest standards of research integrity. As a publicly-funded organisation, the University has to ensure that it is in the public interest when we use personally-identifiable information about people who have agreed to take part in research. This means that when you agree to take part in a research study, we will use information about you in the ways needed, and for the purposes specified, to conduct and complete the research project. Under data protection law, 'Personal data' means any information that relates to and is capable of identifying a living individual. The University's data protection policy governing the use of personal data by the University can be found on its website (https://www.southampton.ac.uk/legalservices/what-we-do/data-protection-and-foi.page).

This Participant Information Sheet tells you what data will be collected for this project and whether this includes any personal data. Please ask the research team if you have any questions or are unclear what data is being collected about you.

Our privacy notice for research participants provides more information on how the University of Southampton collects and uses your personal data when you take part in one of our research projects and can be found at http://www.southampton.ac.uk/assets/sharepoint/intranet/ls/Public/Research%20and%20Integrity%20Privacy%20Notice/Privacy%20Notice%20for%20Research%20Participants.pdf

Any personal data we collect in this study will be used only for the purposes of carrying out our research and will be handled according to the University's policies in line with data protection law. If any personal data is used from which you can be identified directly, it will not be disclosed to anyone else without your consent unless the University of Southampton is required by law to disclose it.

Data protection law requires us to have a valid legal reason ('lawful basis') to process and use your Personal data. The lawful basis for processing personal information in this research study is for the performance of a task carried out in the public interest. Personal data collected for research will not be used for any other purpose.

For the purposes of data protection law, the University of Southampton is the 'Data Controller' for this study, which means that we are responsible for looking after your information and using it properly. The University of

Southampton will keep identifiable information about you for 25 years after the study has finished after which time any link between you and your information will be removed.

Your Hospital will keep identifiable information about you from this study for 25 years after the study has finished.

To safeguard your rights, we will use the minimum personal data necessary to achieve our research study objectives. Your data protection rights – such as to access, change, or transfer such information - may be limited, however, in order for the research output to be reliable and accurate. The University will not do anything with your personal data that you would not reasonably expect.

If you have any questions about how your personal data is used, or wish to exercise any of your rights, please consult the University's data protection webpage (https://www.southampton.ac.uk/legalservices/what-we-do/data-protection-and-foi.page) where you can make a request using our online form. If you need further assistance, please contact the University's Data Protection Officer (data.protection@soton.ac.uk).

Expenses and Payment

You will not receive any monetary payment for taking part in this trial nor will travelling expenses be reimbursed. However, you will be given a £20 shopping voucher at your first clinic visit, a £10 voucher at the 6 week clinic visit, and a £10 voucher at the 12 week clinic visit.

What happens if something goes wrong?

If you decide to take part in the SAFA trial and feel concerned about any part of the trial at any point, you should contact study team as soon as possible. The study team will do their best to help you and answer your questions.

If you wish to complain, or have any concerns about the way you have been approached or treated during the SAFA trial, please contact the Research Integrity and Governance Manager at the University of Southampton on 023 8059 5058 or by email to rgoinfo@soton.ac.uk. If you remain unhappy and wish to complain formally, you can do this through the normal NHS complaints procedure. Details can be obtained through the following NHS web site:

http://www.nhs.uk/choiceintheNHS/Rightsandpledges/complaints/Pages/AboutNHScomplaints.aspx

Please be aware that if you are harmed as a result of taking part in the SAFA trial, there are no special compensation arrangements. The University of Southampton provides clinical trials indemnity insurance for negligence in its management or design of the trial. NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the study. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. If you are harmed because of someone's negligence, you may be able to take legal action but you may have to pay your own legal costs.

If you have private medical insurance you may wish to check with your provider before agreeing to take part in this trial to make sure that your participation will not affect your cover.

Who is organising and funding the trial?

This trial is being coordinated by the Southampton Clinical Trials Unit. The trial is funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme.

https://www.nihr.ac.uk/funding-and-support/funding-for-research-studies/funding-programmes/health-technology-assessment/

The Sponsor is the University of Southampton.

What will happen to the results of the trial?

At the end of the trial, any results will be analysed and presented at national or international meetings, and will also be published in a medical journal. Your personal details will remain strictly confidential. No directly identifiable

personal data will be used in any reports or publications that come from the SAFA trial. A lay version of the trial results will be prepared and made available for patients and members of the public.

When you agree to take part in a research study, the information about your health and care may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Your information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research.

Your information could be used for research in any aspect of health or care, and could be combined with information about you from other sources held by researchers, the NHS or government.

Where this information could identify you, the information will be held securely with strict arrangements about who can access the information. The information will only be used for the purpose of health and care research, or to contact you about future opportunities to participate in research. It will not be used to make decisions about future services available to you, such as insurance.

Where there is a risk that you can be identified your data will only be used in research that has been independently reviewed by an ethics committee.

12. Contact information

If at any stage you have questions about the SAFA trial, or would like to discuss your participation in more detail, please contact:

Doctor's name: *(Insert)*

Name of treatment centre: *(Insert)*

Telephone number: *(Insert)*

Further information about acne, treatments and other clinical trials can be found at:
http://www.nhs.uk/Conditions/Acne/Pages/Introduction.aspx

The British Skin Foundation can also provide support and information:
http://www.britishskinfoundation.org.uk/Community.aspx

Thank you for taking time to read this information sheet.