Patient Information Sheet

Short Study Title: Treating Acute Exacerbation of COPD with Chinese Herbal Medicine to aid Antibiotic Use Reduction

Full Study Title: Study of Shufeng Jiedu® (SFJD) capsules to aid antibiotic use reduction in acute exacerbations of chronic obstructive pulmonary disease: a mixed-methods, double blind, randomised placebo-controlled feasibility trial

This study is also known as EXCALIBUR

We would like to invite you to take part in a research trial about Chinese herbal treatment for flare-ups ("acute exacerbations") of COPD.

Your doctor or nurse have suggested that you read this information sheet because they would like you to think about taking part in the EXCALIBUR trial.

You are being invited to take part in the EXCALIBUR trial because you are presently experiencing a flare-up of your COPD, which started in the last 21 days.

Before you decide whether or not to take part, it is important that you understand as much as possible about what is being done and what is involved, so:

- Please take the time to read this information sheet carefully.
- Please also read the Patient Medication Information Leaflet.
- Please feel free to ask your doctor or nurse any questions you may still have after reading these information documents.

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, the care you receive from your own doctor or nurse 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—the standard of 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 your recruiting practice, or the Southampton Clinical Trial Unit at excalibur@soton.ac.uk

Important things you need to know about EXCALIBUR:

1) You will need to sign a consent form before taking part in the trial to confirm that you understand it and agree to take part.
2) The trial medication is a combination of 8 different herbs contained within a gelatine capsule.
3) You will be put into one of two treatment groups. Your treatment will be decided by chance: this process is called "Randomisation".
4) One of the treatment groups is a placebo group. The placebo is a capsule that contains an inactive substance that has no medical properties. You will have a 50% chance of receiving the herbal treatment.
5) Neither you nor your GP will know whether you are receiving the real herbal treatment or the placebo.
6) You will be asked to take the medication for 14 days.
7) Your GP may prescribe antibiotics to you as well as the herbal treatment or placebo and will advise you on when to start taking the antibiotics.
8) You will be asked to complete a treatment and symptom diary for up to 28 days.
9) You will receive texts/calls from the research team to prompt and discuss diary/questionnaire completion.
10) We have no evidence that the trial medication would cause any harm if taken by women who are pregnant or breastfeeding, but to be on the safe side these women are not allowed to take part in the study. Also, women who are able to become pregnant will not be allowed to participate unless they are using effective contraception.
11) You can stop taking part in the trial at any time, without giving a reason and without affecting the care that you receive.

1. Why we are doing the EXCALIBUR trial?

Patients with COPD commonly experience flare-ups ("acute exacerbations") and antibiotics are often prescribed. However, only one in three flare-ups are caused by bacterial infections and are helped by antibiotics. The remaining two out of three flare-ups are caused by viruses or environmental factors and in these cases, antibiotics will not help. If you take antibiotics, you are more likely to suffer from an infection from drug-resistant bacteria in the future, so it is important to find a safe and effective way to control the symptoms of COPD flare-ups without using antibiotics. There is evidence, based on studies conducted in China, that a herbal combination treatment called Shufeng Jiedu could help control symptoms of COPD flare-ups.

We would like to know whether the herbal combination, Shufeng Jiedu, could be an alternative to antibiotics. This study will not answer this question but will help us to plan a large, full-scale trial.

2. Who is this trial for?

This trial is for men and women aged 40 years and over; who have a diagnosis of COPD; and are experiencing a flare-up of their COPD, which started in the last 21 days. There are different things, including your current symptoms and medical history, that your doctor will take into account to make sure that you are suitable to take part in the EXCALIBUR trial.

In this trial we aim to recruit 80 patients from 8 GP practices in the Wessex region.

3. More about the trial medicine

The trial medication on the EXCALIBUR trial is a patented traditional Chinese medicine called "Shufeng Jiedu" (SFJD). SFJD is a standardised combination of eight herbs, all of which have been used in traditional Chinese Medicine for centuries and are individually available through consultation with a medical herbalist in the UK. These herbs are:

English names and plant parts	Botanical species	Chinese name
Japanese Knotweed, *rhizome*	*Fallopia japonica*	Hu Zhang
Weeping Forsythia, *fruit*	*Forsythia suspensa*	Liao Qiao
Indigo Woad; *root*	*Isatis indigotica*	Ban Lan Gen
Chinese thoroughwax; *root*	*Bupleurum chinense*	Chai Hu
Yellow Flowered Valerian; *herb*	*Patrinia scabiosaefolia*	Bai Jiang Cao
Vervain; *herb*	*Verbena officinalis*	Ma Bian Cao
Reed; *rhizome*	*Phragmites communis*	Lu Gen
Liquorice; *root*	*Glycyrrhiza uralensis*	Gan Cao

SFJD is already widely used in China for the treatment of coughs and colds. Preliminary research conducted in China indicates that SFJD may also help the symptoms of flare-ups of COPD, though further research is needed to confirm this. The trial medication and matching placebo will be prepared by the company in China (Anhui Jiren Pharmaceutical Co. Ltd) which has been manufacturing and marketing the product in China since 2009. Its quality will be controlled and tested by a quality assurance company in Germany (Phytochem Ltd) before importing into the UK.

4. What will I have to do if I decide to take part?

Screening

After reading this information sheet and asking your nurse or doctor any questions, you will be asked to sign a consent form (either on paper or electronically) with your GP or nurse, to confirm that you wish to take part in this research. The nurse or doctor will then consult your medical notes and ask you questions about your medical history to see if you are suitable to take part. If you are recruited at your GP practice, your GP or nurse may also carry out a routine clinical examination. If you are recruited by telephone or video call, the clinical assessments may take place over telephone / video call after you are provided with your trial medicine.

Tests

Once you have been screened and found eligible for the trial, your GP may decide, as part of your standard care, to undertake some tests so that they can understand better how to treat your COPD flare-up. For instance, you may be asked to cough up some phlegm for a colour chart test. If any tests are undertaken, we will ask your GP to record the results which will help us identify what may have caused your flare-up.

Allocation to a treatment group

Sometimes we do not know which way of treating people is best. To find out, we need to put people into groups and give each group a different treatment. To try and make sure the groups are the same to start with, each participant is put into a group by chance (randomly). The results are then compared to see if one treatment is better.

In this trial you will be allocated to receive:

- EITHER: four Shufeng Jiedu capsules, three times a day
- OR: four Placebo (dummy) capsules, three times a day

This means that you have a 1 in 2 chance of receiving the herbal treatment.

You will not know whether you have been given the real Shufeng Jiedu treatment or the dummy, and neither will your nurse or doctor. However, you will be provided with a trial card which details the medication involved in the trial and contact numbers so that, in the unlikely event that you feel unwell from taking the medication, it is possible to find out whether you have been taking the real herb or the dummy capsules.

Antibiotic prescription

Along with your trial medication, you may be given an antibiotic prescription by your GP or nurse practitioner. Your GP or nurse may instruct you to take the antibiotic immediately; give you a prescription for antibiotics but ask you to delay using it; or prescribe no antibiotics. The doctor or nurse will tell you when to start taking any prescribed antibiotics.

There are no known drug interactions between the trial medication or the placebo and COPD medication so you can take the antibiotics or other medicines at the same time as taking the trial medication or placebo. However, we ask that all medication you take by mouth (tablets, capsules, liquid medication, etc) to treat your COPD flare-up are recorded in your participant diary.

Participant Diary

You will be given a 28-day paper diary to complete. The diary is divided into three sections.

The first section will be completed on the day that you start taking your trial medicine. This section contains questions about your gender, employment, ethnicity and smoking history, which allows us to understand our patient population.

The second section should be completed daily over the next 28 days, and contains:

1) The Treatment Diary in order to record:
    - Trial Treatment use (14 days)
    - Antibiotics use (up to 28 days)
    - Steroid Tablet Use (up to 28 days)
    - Other medication use for your flare-up (up to 28 days)
2) A daily questionnaire to record symptoms of your COPD flare-up called the “EXACT-PRO”, and to tell us when you feel that you have gotten better (up to 28 days).
3) A questionnaire to answer more general questions about your COPD called the “CAT” questionnaire (on day 14 only).

You can stop completing the second section of the diary if you have completed at least 14 days of the participant diary and the symptoms of your COPD have returned to their usual level for 7 days.

The third section, completed on day 28, contains:

1) Questions about the trial treatment and completing the diary.

2) A further general COPD (CAT) questionnaire.
3) General questions about your views on herbal treatment.

Please answer this section even if you stopped completing the treatment/symptom diary section before day 28. We will give you a Freepost envelope so that you can return your completed diary to the Southampton Clinical Trials Unit.

Final Questionnaire

A final CAT questionnaire to capture information about your COPD will be mailed out to you 12 weeks after you started the trial. This will also come with a Freepost envelope and be sent by the Southampton Clinical Trials Unit.

Follow Up Phone Calls

A member of the research team may phone you shortly after the second day of the study to answer any questions you may have about completing the diary.

In order for us to contact you and provide the final questionnaire, we will need, with your permission, to collect and store your contact details for the duration of the trial. This information includes your name; telephone number; email address; home address; and GP practice. Your GP or nurse will ask you to enter your contact details on a secure online consent and contacts database; or to complete a paper contact details form, which will be entered onto the database on your behalf. This personal data will only be used for the purpose of performing the trial and will be kept separate from any other data collected from you on the trial.

The information that you record in the diary is very important to the success of the trial. You will receive text message or email reminders from the research team about diary and questionnaire completion. If after five weeks we have not received your diary; or after 14 weeks we have not received the 12 week questionnaire; or if there is information missing, a member of the research team will call you to collect this key information.

Once you have returned your 28-day symptom/treatment diary, and your final 12 week follow-up questionnaire, your participation in the trial is complete.

Qualitative Interviews

As part of the EXCALIBUR trial, we would like to talk to both people who entered the trial and those who chose not to enter. We would be interested in your views about herbal medicine and delayed (i.e. ”just in case”) prescriptions of antibiotics in the treatment of flare-ups of COPD. Additionally, we would like to learn about your experience of taking part in the EXCALIBUR trial or your reasons for not doing so. We may use your completed Participant Diary to help guide this interview.

We will be looking to interview up to 40 patients in this part of the trial. Please note that all interviews will be audio recorded and transcribed.

Please let your GP or nurse know if you would be interested in taking part in these interviews.

5. What is the treatment schedule?

You will be given 168 capsules of trial medication and will be asked to take 4 capsules, 3 times a day, preferably after meals. This treatment should be taken for 14 days.

It is best to take the trial medication after food, but no harm will be caused if you take it at other times.

If you forget to take your trial medication, do not take twice the dose but continue to take your usual dose at the usual time.

When you have finished your 14-day course of trial medication, you will be asked to return any unused trial

medication or the empty packaging to the research team using the Freepost envelope provided.

If you stop taking the trial medication prior to completing the 14-day course, we would like you to remain in the study and continue to complete the patient diary as explained above. It's important to us that all trial information is captured even if you do not take a complete medication course.

Please note that when the trial has finished you will not receive any more trial medication.

6. What are the possible side effects?

Like all medicines, this product can have side-effects, although not everybody gets them.

We have produced a scientific summary on safety of the SFJD formula and 8 individual herbs involved, through gathering information from laboratory and clinical research, and remedy safety data from the Chinese national safety monitoring database.

Millions of patients take Shufeng Jiedu every year in China. Based on randomised controlled trials performed in China with Chinese population, side effects of Shufeng Jiedu are uncommon and are no more frequent than in patients taking antibiotics. Where possible side effects have been reported, the most common are an upset stomach (nausea/vomiting 1%, diarrhoea 1%, abdominal discomfort 0.3%), a rash 0.2% and dizziness 0.1%.

Tell your doctor or qualified healthcare professional if you notice a side-effect not listed (e.g. general weakness; easy bruising; or bleeding).

In the very unlikely event of a serious reaction to the trial medication, please stop taking the trial medication and seek medical advice immediately following the instructions on the trial card that you will be given.

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

Possible benefits:

- It is not known whether you will have any additional benefit from taking part in this trial. However, your participation will give important information about how best to treat people with flare-ups of their COPD.

Possible risks/disadvantages:

- You may experience mild side effects from taking the trial medication.

8. More about contraception and pregnancy during the trial

Women

If you are pregnant or breast feeding, you will not be able to enter the EXCALIBUR trial. Women who are of child-bearing potential must be using effective contraception to enter the trial.

If you become pregnant during the trial, you must stop taking the study medication and tell your doctor immediately. We will need to follow the pregnancy, with your permission, to check that the trial drug has not caused any problems.

9. Other questions you may have about the trial

Do I have to take part?

No, it is entirely up to you to decide whether or not to take part. If you decide you want to take part, you will need to sign a consent form to show you have agreed to take part.

What does informed consent mean?

No-one can enter you into the trial without your permission. To help you decide if taking part in a trial is right for you, the trial doctor/nurse should discuss the trial with you in depth. The most important thing is that you should feel satisfied that you know enough about the trial to make an informed decision. You should feel free to ask as many questions as you need to.

If you decide to take part in the trial, you will be asked to sign a consent form which confirms that you agree to take part. This will either be on a paper form; or completed electronically on the trial website.

If you lose capacity to consent whilst taking part in the study, you will be withdrawn, and any data already collected with consent will be retained. No further data will be collected and no further procedures will be carried out.

What if I change my mind?

You can withdraw from the EXCALIBUR trial at any time and you do not have to give a reason. The standard of your care will not be affected. Information collected up to the time you withdraw may still be used. Please let your doctor know if you wish to withdraw and he/she will carry on your care in the normal way.

If you withdraw from the study, we will keep the information that you have already given us, unless you specifically tell us that you don't agree to this.

Will my taking part in this trial be kept confidential?

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

Research Data

We will be using information from you and your medical records in order to undertake this study. We are responsible for looking after your information and using it properly. The Southampton Clinical Trials Unit will keep your non-identifiable research data for 10 years after the study has finished.

Non-identifiable data, managed by the Southampton Clinical Trials Unit, will be held on the online clinical trial database software Medidata Rave. This software is hosted on secure servers in the EU and the US. Access to this data will be strictly controlled by the Southampton Clinical Trials Unit and no third parties will be granted access to the Medidata servers holding your research data. All applicable Data Protection legislation will be obeyed by the University of Southampton.

In order to properly manage your data and ensure the research is reliable and accurate, your rights to view, change or move the research information we collect about you are limited. You can find out more about how we use your information on the Southampton Clinical Trials Unit website at https://www.southampton.ac.uk/ctu/about/index.page or you can contact the Southampton Clinical Trials Unit on 023 8120 5154 and ask to speak to the EXCALIBUR team.

Your GP Practice will collect information from you and your medical records for this research study in accordance with our instructions. Only members of the research team at your GP practice 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 look at your medical and research records to check the accuracy of the research study. All of these people have a duty to keep your information strictly confidential.

Your GP practice will keep identifiable information about you from this study for 10 years after the study has finished.

Contact Details

As mentioned in Section 4, your contact details will be accessed by the Southampton Clinical Trials Unit so that we can contact you about your diary completion and send you the final trial questionnaire. Your details will be stored securely at the Southampton Clinical Trials Unit in a locked filing cabinet and/or electronically on the EXCALIBUR consent and contacts database. This database is hosted on secure servers in the UK and access to this information will be strictly controlled by the Southampton Clinical Trials Unit.

Only authorised members of staff involved in the delivery of the trial will be able to see and use your details, following strict guidelines. The people who analyse the research data information will not be able to identify you and will not be able to find out your name or contact details. Access to registration data may be granted to delegated third-party website design staff working on the trial to provide tech support. Strict GDPR guidelines and confidentiality agreements will be adhered to in these cases.

Following completion of the trial, the EXCALIBUR consent and contacts database will be securely archived for 10 years.

We will also, with your permission, share your contact details with members of our research team who will be conducting interviews about the EXCALIBUR trial to find out your views on taking part in the trial.

Consent Forms

A copy of your consent form, containing your name and initials, will be accessed by the Southampton Clinical Trials Unit for confirmation of your consent. This form will be kept securely, as detailed above, and archived for 10 years following completion of the trial.

Audio Recordings and Transcripts

Audio recordings of qualitative interviews will be transferred to a secure restricted folder on the University of Southampton server, and will be deleted from the digital audio recorder. Transcripts will be anonymised and will also be stored on the secure folder on the University server and/or on password-protected encrypted computers.

Data Protection Privacy Notice

See *Addendum 1* for information regarding the University of Southampton's Data Protection Privacy Notice.

Expenses and Payment

You will receive a £10 shopping voucher as a thank you for taking part in the trial, and a £20 shopping voucher if you take part in the Qualitative Interviews.

What happens if something goes wrong?

If you decide to take part in the EXCALIBUR trial and feel concerned about any part of the trial at any point, you should contact your research doctor/nurse as soon as possible. Your clinical research 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 EXCALIBUR 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 National Health Service Complaints Procedure. Details can be obtained through the following NHS website:

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

Please be aware that in the unlikely event that you are harmed as a result of taking part in the EXCALIBUR 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 and your GP provides professional indemnity for any clinical negligence. 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.

Who is organising and funding the trial?

This is a clinical trial coordinated by the Southampton Clinical Trials Unit. The trial is funded by the **UK Government, Department of Health and Social Care** via Innovate-UK**.** 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 published in a medical journal. You will not be personally identified in any way in any reports or publications that come from the EXCALIBUR trial. A public version of the trial results will be prepared and made available for patients and members of the public; please ask your doctor.

When you agree to take part in a research study, de-identified 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.

10. Contact information

If you have any further questions about your illness or available treatments please discuss them with your doctor. If at any stage you have questions about EXCALIBUR trial, or would like to discuss your participation in more detail, please contact:

Doctor's name: [Not available on online version – please ask your recruiting centre]

Name of GP surgery: [Not available on online version – please ask your recruiting centre]

Telephone number: [Not available on online version – please ask your recruiting centre]

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

ADDENDUM 1

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 in the unlikely event that 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 unidentifiable information about you for 10 years after the study has finished, when it will be destroyed.

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).