NUFFIELD DEPARTMENT OF PRIMARY CARE HEALTH SCIENCES

ALABAMA
ALlergy AntiBiotics And Microbial resistAnce

The Leeds Teaching Hospitals NHS
NHS Trust

UNIVERSITY OF LEEDS

We would like to invite you to take part in the ALABAMA trial, ALlergy AntiBiotics And Microbial resistAnce:

- Antibiotics are important medicines for fighting infections caused by bacteria.
- Penicillins are an important group of antibiotics and the best treatment for many infections.
- Doctors will avoid prescribing penicillin for their patients who have a "penicillin allergy label" in their health records. These patients are usually prescribed different types of antibiotics for their infections, which may not work as well as penicillins.
- When people are formally tested, about 9 out of 10 people who have a record of penicillin-allergy are found to be not truly allergic to penicillin.
- We are going to find out if people with penicillin-allergy record in their GP health records really do have an allergy by carrying out specialist testing, to see if we can reduce the number of patients wrongly labelled as penicillin allergic.
- The trial is important during the COVID pandemic as people become ill with the virus may require antibiotics and your penicillin allergy label may affect what antibiotics you are prescribed.

Why am I invited?

- Because your medical records state that you are allergic to penicillin antibiotics
- You are over 18 years old
- You have taken an antibiotic in the previous 24 months

What will happen to me if I take part?

- If you are willing to take part, the trial team will arrange a call for you to talk to a Doctor or a trained and qualified member of staff.
- If you are eligible and would like to proceed you will be asked to give your consent to participate in the trial. Following this, a member of the trial team (a Research Nurse) will call you at a time that is convenient to you to ask a series of questions reviewing your medical history, penicillin allergy history and your personal understanding of your penicillin allergy and a quality of life questionnaire (this will take up to 25 minutes).

You will then be **randomly allocated to one of two groups**:

- **Penicillin Allergy Assessment Pathway (PAAP) trial group**: you will be asked to attend one clinic appointment at a hospital immunology clinic which will take half a day to complete. During the clinic appointment, you will go through the penicillin allergy testing which will happen in **three stages**:
  - At the first stage, the clinical research team will ask you about your penicillin allergy history.
  - Depending on your history you may need to complete the second stage - a skin test. The skin test involves a tiny amount of penicillin being injected into your arm. If there is no reaction, you will be moved on to the third stage, the oral challenge test.
  - The oral challenge involves taking a syrup solution containing penicillin. The clinical research team will ask you to take three increasing doses of penicillin in an hour and you will be monitored closely throughout this time and a further dose one hour after the last dose. If you have no reaction at this time, you will then be asked to take penicillin at home for 3 days to check there is no delayed reaction. A research nurse will tell you what to do if you experience any symptoms and will call you a few days after to check for delayed reactions.

You will receive test results via letter shortly after your appointment.

- **Usual care trial group**: you will not be required to attend any hospital visits.

*__Patients in both trial groups__: If you are prescribed antibiotics for a list of pre-defined infections during the follow

How do I get involved?

If you are interested in taking part, please complete the reply slip attached and post it to us in the envelope provided. Alternatively, please call on 07586 530 341 oremail alabama@phc.ox.ac.uk to notify us.

Need more information?

Thank you for taking the time to read this leaflet. If you would like to speak to a member of the trial team, Please feel free to get in touch.

Kelsey Armitage, Trial Manager, 07586 530 341
kelsey.armitage1@nhs.net

ALABAMA: ALlergy AntiBiotics And Microbial resistAnce

Penicillin allergy status and its effect on antimicrobial prescribing, patient outcomes, and antimicrobial resistance.

PARTICIPANT INFORMATION SHEET

You are being invited to take part in a research trial. Before you decide if you would like to take part, it is important that you understand why we are doing this research and what it would involve for you.

Please take time to read the following information carefully and decide whether or not you wish to take part.

You may like to talk to others, friends or family members, about the trial. Please ask if there is anything that is not clear or if you would like more information.

Why have I been invited to take part?

This trial is all about trying to improve the care of patients with a record of penicillin allergy.

You have been invited to take part because your medical records state that you are allergic to penicillin antibiotics; you are over 18 years old, and; you have taken an antibiotic in the previous 24 months.

What is the purpose of the trial?

Antibiotics are important medicines for fighting infections caused by bacteria. Their widespread use has caused a worrying rise in antibiotic resistant bacteria, which cause infections that are difficult to treat. We can slow the spread of resistant bacteria by using antibiotics more carefully. Penicillins are an important group of antibiotics that are recommended as the best treatment for many infections. Doctors will avoid prescribing penicillin for their patients who have a "penicillin allergy label" in their health records. These patients are usually prescribed different types of antibiotics for their infections. There is concern that these non-penicillin antibiotics may not work as well as penicillins, may cause more side-effects or long-term harm.

About 9 out of 10 people who have a record of penicillin-allergy are found to not have a true allergy when thoroughly tested. This means they could safely take penicillins. The aim of ALABAMA is to find out if people with a penicillin-allergy record in their GP health records really do have an allergy by carrying out specialist testing. This will allow us to reduce the number of patients wrongly labelled as penicillin allergic. We will also test if we can better use antibiotics to resolve infections quicker.

We are asking GPs to help us with this research, and we are planning to recruit 2090 people to our trial.

What will happen to me if I take part?

You have been contacted by us as your surgery is participating in the trial and you have been reviewed as potentially eligible by a GP. If you are willing to take part, or wish to find out more information, the trial team will arrange either a face to face or telephone appointment for you to talk to a Doctor or a delegated member of staff at a time that is convenient to you. You will receive a reminder text message one week before your appointment and another text message 48 hours before your appointment. At this appointment, a Doctor or delegated member of staff will check that you are eligible to take part in the trial (including a review of your penicillin allergy history), and that you understand what being in the trial involves. If you are eligible and would like to proceed you will be asked to give your consent to participate in the trial. You will receive a copy of the consent form and another copy will be retained in your GP practice. We estimate that this first face to face or telephone appointment will take about 30 minutes. You may receive a txt message reminder to contact the study team if we are unable to contact you to book this appointment,

Following this, a member of the trial team (a Research Nurse) will call you at a time that is convenient to you to ask you a series of questions reviewing your medical history, penicillin

allergy history and your personal understanding of your penicillin allergy and a quality of life questionnaire. This phone call will take about 20-25 minutes. You will then be randomly allocated to either usual care or the Penicillin Allergy Assessment Pathway (PAAP) trial group. You may receive a txt message reminder to contact the study team if we are unable to contact you to book this appointment,

If you are randomised to the usual care group, you will not be required to attend any further visits for the purpose of the trial. However, if you are prescribed antibiotics for a list of pre-defined infections during your participation in the trial, you will be asked to complete a symptom diary for up to 28 days (this takes no longer than 5 minutes per day). You will receive a text message on day 7, 14 and 21 to remind you about completing your daily diary. You will also receive daily email reminders if you decide to complete your symptom diary online. You can stop completing the diary before 28 days if you feel better and you have completed your antibiotic course. You will be contacted by the trial team to support you in the completion of this diary 2-4 days and 28-30 days after your antibiotic prescription (each call will take up to 10 minutes).

If you are randomised to the PAAP trial group, you will be asked to attend one clinic appointment at the immunology clinic at your local immunology clinic which will take half a day to complete. You may receive a txt message reminder to contact the study team if we are unable to contact you to book this appointment. Prior to this appointment you will be sent an appointment letter and information booklet on penicillin allergy testing. You will also receive a text message one week and 48 hours before the appointment to remind you to attend. During the clinic appointment, you will go through the penicillin allergy testing which will happen in three stages. At the first stage, the doctor or nurse will ask you about your penicillin allergy history. Depending on your history you will either have a skin test or go straight to the 'oral challenge' test. The oral challenge involves taking a syrup solution containing penicillin. The skin test involves a tiny amount of penicillin being injected into your arm, just under the surface of the skin which takes about 5 minutes. After 15 minutes, your skin is examined to see if the test is positive. Sometimes a second skin test is needed which takes about 45 minutes. If there is no reaction, you will be moved on to the third stage, the oral challenge test. A doctor will ask you to take three increasing doses of penicillin in an hour and you will be monitored closely throughout this time and also one hour after the last dose. If you have no reaction at this time, you will then be asked to take penicillin at home for 3 days to check there is no delayed reaction. A research nurse will tell you what to do if you experience any symptoms and she will call you a few days after to check for delayed reactions.

You will then receive the results of the PAAP test via letter.In addition, if you have tested negative for penicillin allergy you will receive a leaflet explaining the result. Your GP surgery will be informed of the test result and will update your health records if needed.

Each time you are prescribed an antibiotic for a list of pre-defined infections by your GP during the trial period, you will be asked to complete a daily symptom diary. Filling out the diary takes up to 5 minutes per day. We ask you to complete your diary for up to 28 days when you start taking your antibiotic. You will receive two text messages to remind you about completing your daily diary at day 7, 14 and 21. You will also receive daily email reminders if you decide to complete your symptom diary online. You can stop completing the diary before 28 days if you feel better and you have completed your antibiotic course. You will be

contacted by the trial team to support you in the completion of this diary 2-4 days and 28-30 days after your GP appointment (each call will take up to 10 minutes).

Some of the participants will be invited to take part in a telephone interview after receiving their results to ask about their experiences of taking part in the trial. This will take about 30-45 minutes (only participants that have consented to take part in the interviews will be contacted).

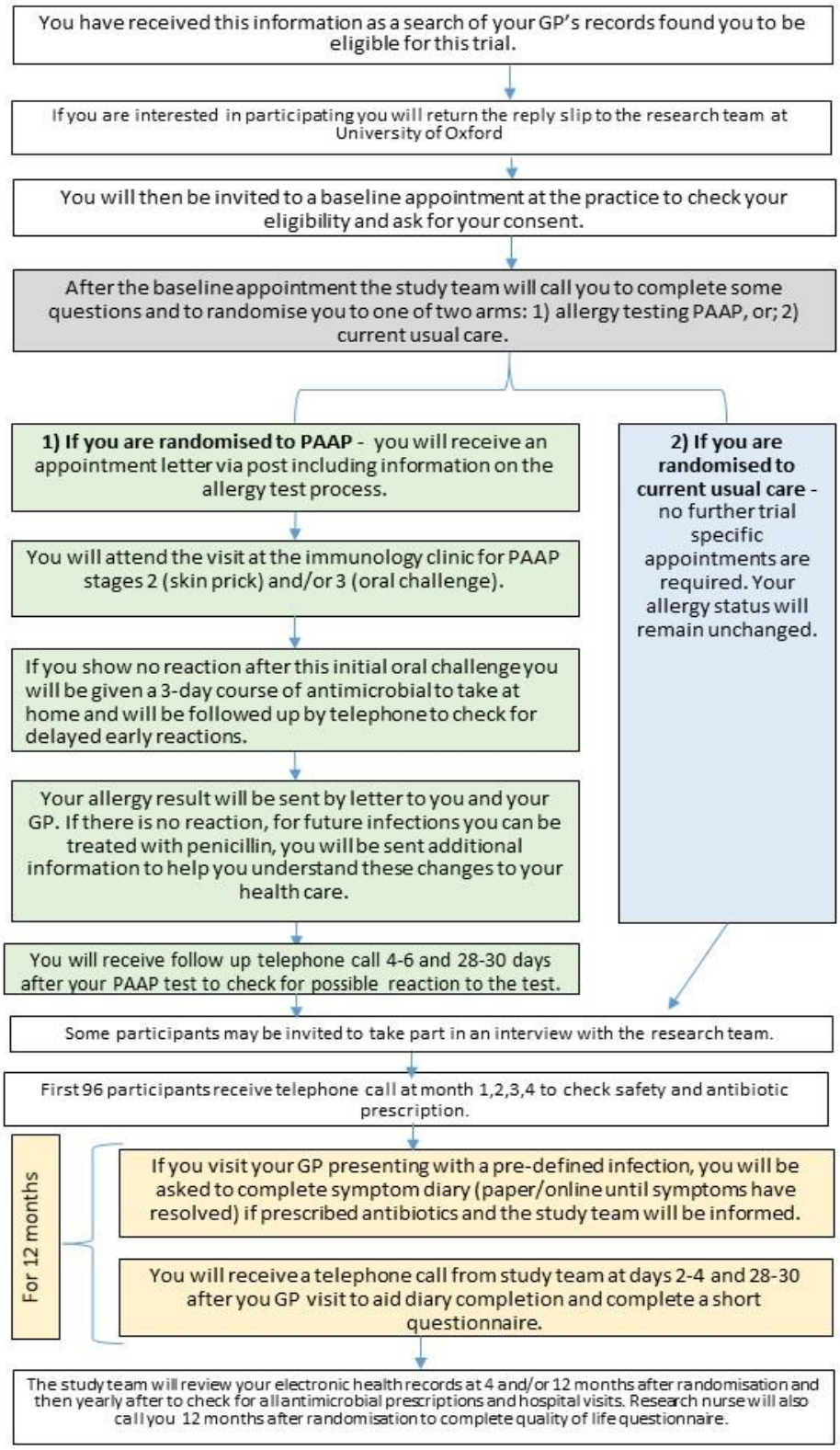
If you are randomised to the PAAP trial group and do not wish to proceed with the testing, you will still be followed up as per the PAAP arm and your data will be analysed the same way.

After 12 months a member of the trial team will call you to ask you to complete a quality of life questionnaire

The trial period is from the time you are randomised until the expected trial end date of April 2024. During the trial period the trial team will review your health records annually for any information on infections, antibiotic prescriptions and hospital admissions.

Once the trial has finished we would like to continue to collect data on any infections, antibiotic prescriptions for a list of pre-defined infections and hospital admissions you may have for an additional 10 years. To do this we will need to access your medical records and collect routine health data using NHS Digital. We will not require any further contact with you and we will ask for your consent to do this follow up.

Trial Participation Flowchart



Do I have to take part?

No. You are free to decide whether or not to take part. If you decide to take part, you are still free to withdraw at any time, without giving a reason. A decision not to take part or to withdraw will not affect the standard of care you receive from your healthcare team.

What are the possible benefits of taking part?

If your penicillin allergy status is changed, first-line penicillin treatment for many infections can resume. That means you can access a wider range of antibiotics including the recommended antibiotic for the condition you are suffering from when you need them. We also hope the outcomes of this trial will improve access to penicillin-allergy testing; improve patient outcomes related to infection e.g. fewer days of symptoms; reduce antibiotic prescriptions and reduce resistant bacteria; and benefit the NHS by saving GP time and improving value for money.

As a result of COVID-19 pandemic, we are aware that you can be affected by secondary infections, therefore having penicillin allergy assessment could enable you to have your penicillin allergy status changed if you are truly not allergic to penicillin and clinicians to prescribe a wider choice of antibiotic medications for you.

What we will expect from you?

By taking part in the trial we would expect you to:

- ✓ Attend a face to face or a telephone call appointment to confirm eligibility and give consent.
- ✓ Answer a short phone call from the research team to answer a baseline questionnaire and be given the result of the random selection which will decide which trial group you are in.
- ✓ If you are randomised to the PAAP allergy testing, you are required to attend a hospital clinic for skin testing and/or oral challenge.
- ✓ 4 – 6 and 28 – 30 days after completing the PAAP testing answer short phone calls from the research team to check for any delayed reactions and complete a short questionnaire.
- ✓ During the follow up period, each time your GP prescribe you an antibiotic for a list of pre-defined infections, you will complete a diary about your symptoms for 28 days. You can stop completing the diary when you feel better.
- ✓ You will also be required to answer 2 phone calls by the research team, 2-4 and 28-30 days after your antibiotic prescription and one phone call after 12 months of your participation, each phone call will require you to answer a short questionnaire.

Will my taking part in the trial be kept confidential?

Yes. You will be given a trial participant identification number. Any information you provide will be recorded against that number, not your name. Therefore all information is anonymous, as is any data we collect from your medical records.
The University of Leeds is the sponsor for this trial based in the United Kingdom. We will be using information from you and your medical records in order to undertake this trial and will act as the data controller for this trial. This means that we are responsible for looking after

your information and using it properly. The University of Leeds will keep identifiable information about you for 10 years after the trial has ended.
Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. To safeguard your rights, we will use the minimum personally-identifiable information possible.
You can find out more about how we use your information by contacting Data Protection Officer at the University of Leeds using the dpo@leeds.ac.uk email address. Your GP will use your name, NHS number and contact details (address, telephone number, email) to contact you about the research trial, and make sure that relevant information about the trial is recorded for your care, and to oversee the quality of the trial. Individuals from University of Leeds, University of Oxford and regulatory organisations may look at your medical and research records to check the accuracy of the research trial. Your GP will pass these details to the University of Leeds and University of Oxford along with the information collected from you and your medical records. The only people who will have access to information that identifies you will be people who need to contact you to ask you the follow up questionnaires, collect information from your medical records or audit the data collection process. 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.
Your GP will keep identifiable information about you from this trial for 15 years after the trial has finished.
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.

We will also share identifiable data (name, date of birth and NHS number) in a secure manner (including encryption during data transfer) with NHS Digital. As soon as the required information has been gathered your contact details will be destroyed. NHS digital provide us with some additional health data from databases including Hospital Episode Statistics data and Mortality data for up to 10 years after the trial has finished. The data will be returned to us in an encrypted format and we will use a trial ID before access is granted to the researcher. The data supplied by NHS Digital will be linked using the participant ID assigned to you at the time of enrolment into the ALABAMA trial.

The trial identifiers will be kept separately in a password protected file and only the trial team will have access to these. We will use the data we collect from NHS Digital only for this trial and not for any other purposes.

You are free to withdraw your consent for data linkage with NHS Digital at any time and it will not affect your ongoing care.

What are the possible disadvantages or side effects of taking part?

If you take part in this trial there is a small risk of reaction from skin testing and oral challenge testing and a risk from any antibiotics that are prescribed as part of your usual clinical care during the time of the trial.

- Skin testing is generally safe and severe reactions following testing are rare. For example, in a previous trial five patients (0.5%) had severe reactions in one eight year trial including 998 skin tests.
- Severe reactions to an oral challenge test in patients with negative skin-tests are uncommon but do occur. Among 580 orally challenged patients with a history of non-serious skin reactions to penicillin, 14 had reactions, 11 of which were early and 3 delayed. A reaction was more likely if the allergy report was within 15 years.

We will use a series of increasing drug doses during the oral challenge, and it will take place in a specialist unit with facilities to deal with any potential severe allergic reactions. You will be called 4– 6 days after the PAAP appointment by a trial research nurse to check how you are feeling and if you have had any delayed adverse reactions.

Penicillin allergy testing is routinely carried out in the NHS but it carries a very small risk of anaphylaxis and death. This risk will be minimised by excluding any patient with a prior history suggestive of anaphylaxis or a previous serious reaction.

Will the GP be informed of participation?

Your GP is aware that you have been invited to take part in this trial. Any changes to your medical records will be made by your GP and your GP is aware we will need to access your medical records for prescribing and hospital attendance information.

Will I be reimbursed for taking part?

We will cover the cost of your travel to the immunology clinic up to the sum of £30.00. Any travel expenses above £30.00 will need to be pre-approved by the trial team.

Who is organising and funding the research?

The researchers are from the University of Leeds and the University of Oxford. The programme lead and the Chief Investigator is Dr Jonathan Sandoe, Associate Clinical Professor of Medical Microbiology, University of Leeds, joint lead co-applicant Prof Sue Pavitt, Professor in Translational and Applied Health Research, University of Leeds, and Co-Investigator Professor Christopher Butler, Professor of Primary Care, University of Oxford. The funding for this research comes from the National Institute for Health Research (NIHR). Your GP surgery is being paid for including you in this trial.

What happens if I don't want to carry on with the trial?

You can withdraw from the trial at any time without giving a reason. Withdrawing from the trial will not affect your future medical care.
If you withdraw from the trial, 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.

If you wish to withdraw from the trial or you want to find out more about how we use your information, please contact the trial team using the contact details on the back page.

What happens once the trial has stopped?

Once you have finished the trial you will be looked after as usual by your GP. Any changes to your penicillin allergy status will remain in your health records beyond the end of the trial.

What if new information becomes available?

Sometimes we get new information about the intervention being studied. If this happens, the research team will contact you and ask if you wish to continue in the trial. If you decide to continue we may ask you to sign an updated consent form. It may be that the new information means that we think it's best to withdraw you from the trial, or stop the trial altogether, in which case we will let you know and explain the reasons.

What will happen to my test results and samples?

Your GP will receive your PAAP allergy results via letter or electronically and if your status has changed your GP will be asked to update your medical records with your new allergy status. You will also be sent the PAAP test results via letter or electronically as you prefer.

What will happen to the results of the research trial?

We will publish the results in scientific journals and present them at scientific meetings. The results will also be available to all GP practices that participate in the trial and also be published on the ALABAMA trial website page (at **https://www.phc.ox.ac.uk/phctrials/trial-portfolio/ALABAMA-trial**). Your details will remain strictly confidential, with no personal information being included in any results or publications.

Who has reviewed the trial?

All research in the NHS is looked at by an independent group of people called a Research Ethics Committee, who protect your safety, rights, wellbeing and dignity. This trial has been reviewed and given a favourable opinion by London Bridge NRES Committee.

What if there is a problem?

If you have any queries about this trial, then please contact the trial team who will do their best to answer your questions. You can either call them on 01865 289336 or email: **alabama@phc.ox.ac.uk.**

If you wish to complain about any aspect of the way in which you have been approached or treated during the course of this trial, you should firstly contact the trial co-ordinator on the details above or you may contact the University of Leeds, Faculty of Medicine and Health Research Office, on 0113 343 4897 (email: **governance-ethics@leeds.ac.uk**).

The University of Leeds has arrangements in place to provide compensation for non-negligent harm arising from participation in the trial for which the University of Leeds is the Research Sponsor. NHS indemnity operates in respect of the clinical treatment with which you are provided.

Thank you for taking the time to read this information sheet

Further information and contact details:

Kelsey Armitage
Clinical Trial Manager
Primary Care Clinical Trials Unit
Nuffield Department of Primary Care
Health Sciences
Radcliffe Primary Care Building, Radcliffe
Observatory Quarter
Woodstock Road
Oxford, OX2 6GG
Work mobile: 07586 530 341
Fax: +44 (0)1865 289412
Email: kelsey.armitage1@nhs.net

Catherine Porter
Research Programme Manager
DenTCRU (Dental Translational and
Clinical Research Unit)
School of Dentistry
Worsley Building
Clarendon Way
University of Leeds
LS2 9LU
Tel: 0113 343 9685
Work mobile: 07596 886 490
Email: catherine.porter1@nhs.net