UNIVERSITY OF CAMBRIDGE

Cambridge University Hospitals NHS
NHS Foundation Trust

PARTICIPANT INFORMATION SHEET (SUMMARY)
ACQUIVAS: Acquired immunodeficiency in ANCA associated vasculitis

Background to the trial

- Infection is a common problem in patients with ANCA associated vasculitis (AAV), due to the medications used to treat the disease.
- Vaccines are recommended for patients with AAV to reduce the risk of common infections such as flu or pneumonia.
- The medications used to treat vasculitis, particularly rituximab, may reduce the effectiveness of these vaccines.
- This trial will measure responses to vaccines after rituximab, and look at possible ways to improve responses, by using different forms of the vaccine and boosting strategies.

Participant involvement

- Patients with AAV who have received rituximab previously will receive one form of vaccine against pneumococcus. Blood tests will be taken prior to the vaccine and 28 days later to measure responses.
- Other patients with AAV who have never received rituximab will be recruited as disease controls. Blood tests will be taken prior to the vaccine and 28 days later to measure responses.
- In addition, 20 healthy volunteers will receive the vaccine, as little is known about response rates to pneumococcal vaccines in the general adult population.
- In total, 124 subjects will participate in this trial.
- A booster dose of another form of pneumococcal vaccine will be administered at 6 months and responses again measured 28 days later, to see if this approach can improve response rates.
- You will be asked to attend for 4 visits over 7 months. For AAV patients, we will aim to co-ordinate at least 2 of these visits with standard clinic appointments.

Potential participant benefits

- We hope that individuals will benefit from the protection offered against pneumococcal infections using this combination of vaccines.
- Responses to vaccines also give us much more information about the immune system. In the future, it may be possible to adjust individuals' immunosuppression depending on how suppressed their immune system already is (measured by vaccine responses), and so reduce infection risk, but still control disease effectively.

If you would like to know more about this trial, then please read the full participant information sheet and consent form attached.

Many thanks for your time and interest.

PARTICIPANT INFORMATION SHEET & INFORMED CONSENT FORM
(for patients with AAV recruited at Cambridge University Hospitals NHS Foundation Trust)

ACQUIVAS: Acquired immunodeficiency in ANCA associated vasculitis

You are being invited to take part in a research trial. Before deciding whether to take part, you need to understand why this trial is being done and what it involves. Please take time to read the following information carefully and talk to others about the trial if you wish. Please ask us if anything is not clear or if you would like more information. Please take time to decide whether or not you wish to take part.

Section 1 tells you the purpose of this trial and what will happen to you if you take part. Section 2 gives you more detailed information about the conduct of the trial.

Section 1: Purpose of the trial and what will happen

1. What is the purpose of the trial?

You have a condition called ANCA associated vasculitis (AAV). This is an autoimmune disease, when the immune system, which normally protects the body from infection, becomes over active, causing damage to any part of the body, but particularly to the lungs and kidneys. Vasculitis can be very serious if left untreated. Usual treatment involves suppressing the immune system which can put patients at increased risk of infections. Consequently, it is recommended that patients with AAV receive vaccinations against influenza (flu) and pneumococcus (a bacterium which causes pneumonia and meningitis).

However, medications used to treat vasculitis, particularly rituximab, may reduce the effectiveness of these vaccines, meaning that patients are not protected against these infections. This trial will measure responses to vaccines after patients with AAV have received rituximab therapy, and look at possible ways to improve these, by using different forms of the vaccine and boosting strategies and comparing data with AAV patients who have never received rituximab and healthy controls.

2. What is the drug being tested?

In this trial you will receive one dose of two different forms of the pneumococcal vaccine which act via different parts of the immune system. You will receive a single injection of one form of pneumococcal vaccine at month 0 and then 6 months later you will receive a single injection of another form of pneumococcal vaccine which works in a different way. Both vaccines are licensed for use in the UK. The approach of using the two vaccines has been used successfully in individuals immunosuppressed for other reasons, such as patients who have received an organ transplant, patients with HIV infection, and patients with other autoimmune diseases such as rheumatoid arthritis. The Centre for Disease Control and Prevention, based in the USA, have also published guidance recommending combination pneumococcal vaccinations in several situations, including in patients receiving immunosuppressive drugs.

3. Why have I been invited?

You have been invited to participate in this trial because you have been diagnosed with ANCA vasculitis (which may also be called granulomatosis with polyangiitis (Wegner's granulomatosis), or microscopic polyangiitis or eosinophilic granulomatosis with polyangiitis (Churg Strauss Syndrome)) and your disease is presently well controlled.

We plan to include 104 participants with ANCA vasculitis, and 20 healthy controls from two UK vasculitis centres.

4. Do I have to take part?

Participating in this trial is completely voluntary. If you decide to participate you will be asked to sign an Informed Consent Form, however you are still free to change your mind and leave the trial at any time without giving a reason. If you choose not to participate or to leave the trial, your future medical treatment and normal standard of care will not be affected in any way.

5. What will happen to me if I take part?

If you agree to participate in the trial, you will be asked to sign the Informed Consent Form at the end of this document. You will be given a copy of this to take away and refer to later.

Once you have agreed to participate in the trial you will have your first visit. During this visit your trial doctor will discuss the trial with you and check whether you are eligible to participate. Your trial doctor will also ask you about your medical history and any medications you are taking, and will assess the activity of your vasculitis and its effects on the body. A blood sample (approximately 60ml, equivalent to ~4 tablespoons) will be taken for laboratory tests, including a pregnancy test for women of childbearing potential. You will then receive the first pneumococcal vaccine, which will be administered into a muscle in your buttock, thigh or upper arm.

You will return to clinic 28 days (+/- 7 days) later. Your doctor will ask you about any symptoms you may have experienced after the vaccination, any medications that you are currently taking, and will again assess the activity of your vasculitis. A blood sample (approximately 40ml) will also be taken to measure your response to the vaccine.

Your next trial visit will be 6 months after enrolment, unless you have already received the Pneumococcal Polysaccharide Vaccine within 5 years of the screening visit when your participation in the study will stop after your month 1 visit, as administration of a further dose of Pneumococcal Polysaccharide Vaccine is not advised. Your trial doctor will ask you about any medications that you are currently taking, episodes of infection and will assess the activity of your vasculitis. A blood sample (approximately 60ml, equivalent to ~4 tablespoons) will be taken for laboratory tests, including a pregnancy test for women of childbearing potential. You will then receive the second form of pneumococcal vaccine, which will be administered into a muscle in your buttock, thigh or upper arm.

You will return to clinic 28 days (+/- 7 days) later (month 7). Your doctor will ask you about any symptoms or episodes of infection you may have experienced since your last visit, any medications that you are currently taking, and will again assess the

activity of your vasculitis. A blood sample (approximately 40ml) will also be taken to measure your response to the vaccination. At this point your participation in the trial ends.

Each clinic visit will take approximately 30 minutes. If a serum pregnancy test is required, the visit duration will be longer (~ 4 hours), in order to obtain the result of this test prior to each vaccine administration.

In total, approximately 200mls, equivalent to ~14 tablespoons of blood will be taken during the trial for trial purposes. In total you will be in the trial for approximately 7 months.

In the unlikely event that blood tests show any unexpected findings, we will take the responsibility of informing your General Practitioner (GP) and referring you to the appropriate specialists for further investigation and management. We will arrange any further follow-up as necessary.

Subjects recruited in Cambridge may be invited to attend for two additional visits, one week after each vaccination for an additional blood draw (approximately 30ml taken at each visit). These extra samples will look in detail at the effect of the vaccine on specific immune cells, and whether it is possible to predict whether people will respond well to the vaccine, or even predict their subsequently vasculitis disease course. These are OPTIONAL visits, and if you do not wish to take part you will still be able to participate in the main trial. If you would like to take part in these additional visits, you can select the relevant section on the Informed Consent Form at the end of this document.

Please see details of what will happen at each visit in the table below:

Trial Date W=Week M=Month *optional visit for some Cambridge recruits	Screening visit (screening and M0 visits will be conducted on the same day if possible)	Baseline visit (Month 0)	Month 0 + 1 Week* *optional	Month 1	Month 6*	Month 6 + 1 Week* *optional	M7
Eligibility Review	X						
Informed Consent	X						
Demographics	X	X					
Medical review and prior vaccination history	X	X					
Physical examination	X	X					
Medication check	X	X		X	X		X
Disease activity assessment		X		X	X		X
Vasculitis damage assessment		X			X		
Safety review	X	X		X	X		X
Routine Blood tests	X	X			X		
Serum pregnancy test for WOCBP		X			X		
Trial blood test		X	X	X	X	X	X
Administration of vaccine		X			X		

*Subjects who received the Pneumococcal Polysaccharide vaccine within 5 years of screening will cease participation in the trial at Month 1.

6. What will I have to do?

If you are enrolled on to the trial, you should continue with your normal activities (e.g. driving and exercise) if you feel well enough. You should continue your other regular medications. You should not donate blood or participate in other drug studies during the phase when you are actually receiving any medication whilst you are participating in this trial. In the event of hospitalisation, please ensure that either you, or your admitting doctors inform the trial team of your admission, as soon as possible.

Trial medicines could harm an unborn baby or nursing infant. You will not be able to take part in this trial if you are pregnant or breastfeeding. Women of child bearing potential will have a pregnancy test performed prior to each vaccine administration.

Women who are able to have a baby must use one of the following, reliable forms of contraception for the duration of the trial:

- Oral contraceptive (either combined or progestogen alone)
- Contraceptive implant, injections or patches
- Vaginal ring
- Intrauterine device (IUD, coil or intrauterine system)
- Condom **and** cap or diaphragm **plus** spermicide (chemical that kills sperm)
- True abstinence where this reflects your usual and preferred lifestyle

You do not need to use contraception if:

- you have only one partner, and the man has had an operation to cut the tubes that carry sperm (vasectomy)
- you (or your partner) are a woman who cannot become pregnant
- You practice true abstinence as part of your usual and preferred lifestyle (no sexual activity from screening until the end of the trial. If you become sexually active, you must use one of the methods listed above.

If you become pregnant during the trial you should inform your trial doctor immediately. Your trial doctor will discuss all the options available to you. The outcome and progress of any pregnancy would be followed and you would be asked questions about the pregnancy and baby, if appropriate.

Immediately on completion of the trial, you may cease to use contraception if you wish to do so, as there are no concerns about long lasting adverse effects of the vaccines on an unborn child.

You should tell the trial team if you feel unwell or different in anyway. If you have any major concerns or are feeling very unwell please contact your trial doctor immediately using the contact numbers at the end of this information sheet.

You should discuss your participation in this trial with any private medical, protection or life insurance provider you use, as failure to notify them may affect or invalidate your cover.

7. What are the side effects of the drug being tested?

The commonest side effects of both pneumococcal vaccines are local site injection reactions which can include pain, swelling, redness, warmth and possible limitation of limb movement. Rarely, cellulitis (skin infection) at the injection site or some swelling elsewhere in the body can occur. Other commonly experienced effects of both vaccines include fatigue, muscular pain and headaches.

Following administration of the first pneumococcal vaccine at month 0, you may develop joint aches, a temperature, rash and poor appetite. Nausea, vomiting and diarrhoea have also been reported. Very rarely, individuals may have a hypersensitivity reaction to the vaccine and develop facial swelling, wheeze and shortness of breath.

8. What are the possible disadvantages and risks of taking part?

Additional blood samples will be required as part of this trial and it is possible that you may experience bruising or soreness at the needle site.

Wherever possible we will try to arrange your trial visits at the same time as your normal routine hospital visits; however you may be asked to attend the hospital more frequently than normal if this is not possible.

Please talk to your trial doctor before considering having any vaccinations whilst participating in this trial as they may interact with the trial vaccines.

9. What are the possible benefits of taking part?

There is no guarantee that you will benefit from taking part in this trial, although it is hoped that you should gain some protection from the vaccines administered. As part of your involvement in this trial you will receive closer monitoring of your vasculitis which may result in detection and treatment of other medical problems earlier than normal. In the event that anything of this nature is found, we will make your results available to your GP, and arrange appropriate follow-up, with your permission.

The information collected from your participation in this trial may help doctors to make decisions about treating patients with vasculitis in the future.

10. What are the alternatives for treatment?

Pneumococcal vaccination is recommended for all vasculitis patients receiving immunosuppressant treatment to protect against infection from pneumococcal bacteria. Preventative antibiotics can help protect against infection, however, they are only beneficial whilst actually being taken, and do not give longer lasting protection, whereas vaccines are able to in certain circumstances. However, if you do not wish to receive vaccines against pneumococcus, you will not be able to participate in this trial.

11. What happens when the trial stops?

When the trial stops standard vasculitis treatment will be continued as required, according to your local hospital practice. You will still need to come to clinic to see the doctor as usual. Your doctor will provide you with further details about the frequency of your clinic visits.

12. Expenses & Payment?

You will not receive any payment for participating in this trial and we are unable to reimburse any expenses incurred by your participation in this trial.

Section 2: Trial Conduct

13. What if new information becomes available?

Sometimes during the course of a trial, new information becomes available which might affect your decision to continue participating in this trial. Your trial doctor will contact you to discuss the new information and whether you wish to continue participating in the trial. If you still wish to continue on the trial, you will be asked to sign a new Informed Consent Form.

The trial sponsor, the regulatory authority or the trial doctor may decide to stop the trial at any time. If that happens we will tell you why the trial has been stopped and arrange for appropriate care and treatment for you.

14. What if I decide I no longer wish to participate in the trial?

You are free to withdraw from this trial at any time without giving a reason and without affecting your future care or medical treatment. If you decide not to participate any further, no more tests will be performed and you will no longer receive the treatment for this trial. Any information already provided or results from tests already performed on you or your samples will continue to be used in the trial, however no further information or samples will be collected. Analyses may be performed on samples already provided for the trial unless you request that they be destroyed.

The trial doctor may also choose to withdraw you from the trial if they feel it is in your best interests or if you have been unable to comply with the requirements of the trial. Reasons for trial withdrawal could include:

- You have experienced a serious side effect
- You have experienced a relapse of vasculitis necessitating a major change in your therapy
- You are unable to complete the visits, treatment or trial documentation as required
- You become pregnant or plan to become pregnant

If you have experienced any serious side effects during the course of the trial which require you to withdraw from the trial, your trial doctor will follow-up with you regarding your progress until the side effect has stabilised or resolved.

15. What if there is a problem?

Any complaint about the way you have been dealt with during the trial or any possible harm you might suffer will be addressed. If you have any concerns about any aspect of this trial you should speak to your trial doctor who will do their best to answer your questions. Contact information is given at the end of this form.

In the event that something does go wrong and you are harmed by taking part in the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against Cambridge University Hospitals NHS Foundation Trust or the University of Cambridge. The normal National Health Service complaints

mechanisms will still be available to you (if appropriate).The University has obtained insurance which provides no-fault compensation i.e. for non-negligent harm, you may be entitled to make a claim for this.

If you wish to make a complaint or have any concerns about any aspect of the way you have been approached or treated during this trial, you can do this through the NHS complaints procedure. In the first instance it may be helpful to contact the Patient Advice and Liaison Service (PALS) at your hospital (see point 21 below).

16. Will my taking part in this trial be kept confidential?

Cambridge University Hospitals NHS Foundation Trust (CUHFT) and the University of Cambridge are the sponsors for this trial based in England. They 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 they are responsible for looking after your information and using it properly.

Your rights to access, change or move your information are limited, as the Sponsor organisations need to manage your information in specific ways in order for the research to be reliable and accurate. 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.

You can find out more about how we use your information by visiting the links below:
- For Cambridge University Hospitals NHS Foundation Trust, please visit: https://www.cuh.nhs.uk/corporate-information/about-us/our-responsibilities/looking-after-your-information, or email the Data Protection Officer at: gdpr.enquiries@addenbrookes.nhs.uk

- For University of Cambridge, please visit: https://www.medschl.cam.ac.uk/research/information-governance/, or email the Information Governance team at: researchgovernance@medschl.cam.ac.uk

Addenbrooke's Hospital will use your name, NHS number and contact details to contact you about this 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 the Sponsors and regulatory organisations may look at your medical and research records to check the accuracy of the research. Addenbrooke's Hospital will pass these details to the Sponsors along with the information collected from you and your medical records. The only people in the Sponsor organisations who will have access to information that identifies you will be people who need to contact you in relation to this trial and to 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, NHS number or contact details.

When you agree to take part in a clinical trial, 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 and 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.

Once the trial has come to an end, we will be required to archive trial documentation, which may contain some personal data (e.g. your name will be recorded as part of completing the consent form). Trial documentation will be kept for a minimum of 5 years on completion of the trial.

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. 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 need to inform your GP or medical practitioner of your participation in this trial so that any medical decisions made by your GP account for any treatment you are receiving as part of this trial.

17. What will happen to my samples?

Four blood samples (six if you are invited and agree to undertake the two additional OPTIONAL visits) will be taken just for the purposes of the trial. These samples will either be processed at Addenbrooke's Hospital, Cambridge, or University of Birmingham.

Part of the research blood samples that we will be collecting are optional and involve collecting a sample of blood for the storage of your genetic material (which is called DNA and RNA). These blood samples are optional and you will have the opportunity to provide separate consent for these samples later in this document. The purpose of obtaining such samples is to try to identify genes that may affect immune cell function and responses to the vaccines. Results may inform future treatment of patients with vasculitis, but any results obtained will have no impact on your current medical treatment and you will not be identified from any of the results. We will not perform full genome analysis, any animal experiments, or create immortal cell lines using your samples.

If you provide consent, some of your samples will be stored at an approved Research Tissue Bank and may be used in studies in the future, including genetic studies. Your samples will only ever be used for research that is approved and deemed appropriate by a Research Ethics Committee. We will not contact you about these future studies. If you do not consent to your samples being stored in a Research Tissue Bank, the samples will be analysed or destroyed within 2 years of completion of the study.

All samples collected as part of this trial will be labelled with your unique trial number to maintain your confidentiality. You will not be able to be identified from your samples during any future studies.

Samples for routine laboratory tests will be destroyed after they have been analysed.

18. What will happen to the results of the trial?

The results of the trial will be anonymous and you will not be able to be identified from any of the data produced. Anonymised data may be submitted to the Regulatory Authorities, responsible for drug licencing. When the results of this trial are available they may be published in peer reviewed medical journals and used for medical presentations and conferences. They will also be published on the EU Clinical Trials Register website, a central registry for all clinical trials conducted in the EU.

During the trial, a trial steering committee will receive anonymised data from the trial, specifically to assess the safety of the participants in this trial and to ensure that the trial is progressing satisfactorily. Anonymised results will also be sent to the funders to update them on trial progress as required.

If you would like to obtain a copy of the published results please contact your trial doctor directly who will be able to arrange this for you.

19. Who is organising (sponsoring) and funding the trial?

This trial is sponsored by Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge. The trial is being funded by Arthritis Research UK.

20. Who has reviewed this trial?

All research within the NHS is reviewed by an independent group of people called a Research Ethics Committee, to protect your interests. This trial has been reviewed and given favourable opinion by NRES Committee East of England – Cambridge East and The Medicines and Healthcare Products Regulatory Agency (MHRA) who are responsible for regulating medicines in the UK.

21. Further information and contact details

Information on vasculitis can be found on the Vasculitis UK website at:
http://www.vasculitis.org.uk/

Patient Advice and Liaison Service (PALS) at Addenbrooke's Hospital can be contacted as follows:
Tel: 01223 216 756
Fax: 01223 256 170
Email: pals@addenbrookes.nhs.uk

Name	*Role*	*Phone Number*
Dr Rona Smith	*Trial Doctor (PI)*	*01223 349350*
Valentina Rufollo	*Research Nurse*	*01223 217259*

In the event of an emergency please contact:

If you require advice out of normal office hours, please call Addenbrooke's switchboard on 01223 245151 and ask to speak to the on call renal registrar.

UNIVERSITY OF CAMBRIDGE

Cambridge University Hospitals NHS
NHS Foundation Trust

INFORMED CONSENT FORM
(for patients with AAV from CUH)

Trial Title: ACQUIVAS: Acquired immunodeficiency in ANCA associated vasculitis

Principal Investigator:

Participant Number:

If you agree with each sentence below, please initial the box

		INITIALS
1	I have read and understood the Participant Information Sheet version 3.0, dated 21st June 2019 for the above trial and I confirm that the trial procedures and information have been explained to me. I have had the opportunity to ask questions and I am satisfied with the answers and explanations provided.	
2	I understand that my participation in this trial is voluntary and that I am free to withdraw at any time, without giving a reason and without my medical care or legal rights being affected.	
3	I understand that my date of birth (personal information) will be collected on the trial documentation and stored in the trial database, but that this information will be kept in the strictest confidence and none of my personal data will be published.	
4	I understand that sections of my medical notes or information related directly to my participation in this trial may be looked at by responsible individuals working for or with the sponsor, regulatory authorities, the NHS Trust or trial personnel where it is relevant to my taking part in the trial. I give permission for these individuals to have access to my records.	
5	I have read and understood my responsibilities for the trial as listed in section 6.	
6	I give permission for my GP to be informed of my participation in this trial, to be sent details of the ACQUIVAS trial and to provide information on my vaccination history to the trial team if requested.	
7	I understand that I will not receive any payment for participating in this trial and that my treating hospital is unable to reimburse any expenses incurred by my participation in this trial.	
8	I have read and understood the compensation arrangements for this trial as specified in the Participant Information Sheet.	
9	I understand that the doctors in charge of this trial may close the trial, or stop my participation in it at any time without my consent.	
10	I understand that samples and data relating to procedures performed as part of my standard clinical care will be used as part of this trial. I understand that samples and results will be sent securely within the trial team and that I will not be identifiable from the information sent.	
11	I agree to participate in this trial.	

OPTIONAL

		YES	NO
12	I agree to attend for 2 additional visits approximately one week after the administration of each vaccine at month 0 and month 6 and for the collection of blood for obtaining RNA information for research purposes as described in section 17.		
13	I agree for the collection of blood for obtaining DNA information for research purposes as described in section 17		
14	I give permission for my anonymised samples to be stored in an approved Research Tissue Bank for future, ethically approved studies, including genetic studies.		
15	I give permission for my anonymised data, which I have donated, to be used in future ethically-approved studies.		
16	Should I become pregnant during the trial, I consent to follow up of the pregnancy.		

_____	_____	_____
Name of participant	Signature	Date

_____	_____	_____
Name of person taking consent	Signature	Date

Time of Consent (24hr clock) _____:_____

1 copy for the participant, 1 copy for the trial team, 1 copy to be retained in the hospital notes.