

Prof Adrian Hill
Chief Investigator
The Jenner Institute
University of Oxford



National Research Ethics Service
Committee: South Central - Oxford A
Number: 16/SC/0545

Centre for Clinical Vaccinology &
Tropical Medicine (CCVTM)
Churchill Hospital
Oxford OX3 7LE

Recruitment Co-ordinator
Tel: 01865 611424
Fax: 01865 857471
Email: vaccinetrials@ndm.ox.ac.uk

PARTICIPANT INFORMATION SHEET: HAV001

A study to assess the new candidate vaccine for Crohn's disease in healthy adults

"A phase I clinical trial to determine the safety and immunogenicity of the candidate *Mycobacterium avium* subspecies *paratuberculosis* (MAP) vaccine ChAdOx2 HAV and MVA HAV in healthy adult volunteers".
(HAV001)

We would like to invite you to take part in a research study. Before you make a decision, it is important you take the time to understand why the research is being done and what it would involve. Please read the following information carefully and discuss it with friends, relatives and your General Practitioner (GP) if you wish.

- Part 1 tells you the purpose of the study and what will happen to you if you take part.
- Part 2 tells you more information about the conduct of the study.

Please ask us if there is anything that is not clear, or if you would like more information. Take time to decide whether or not to take part.

PART 1

What is the purpose of this trial?

Crohn's disease is a long-term condition that causes inflammation of the lining of the digestive system. There are currently at least 115,000 people living with the condition in the UK. Inflammation can affect any part of the digestive system, from the mouth to the back passage, but most commonly occurs in the last section of the small intestine (ileum) or the large intestine (colon). Common symptoms can include: diarrhoea, abdominal pain, fatigue (extreme tiredness), unintended weight loss, blood and mucus in your faeces (stools). Over time, inflammation can damage sections of the digestive system, resulting in complications such as narrowing of the intestine (stricture), or a channel developing between the end of the bowel and the skin near the anus or vagina (fistula). These problems usually require surgical treatment and health care costs are substantial. There's currently no cure for Crohn's disease, so the aim of treatment is to stop the inflammatory process and relieve symptoms (induce and maintain remission). Once symptoms are under control, further medication may be needed to help maintain this.

The exact cause of Crohn's disease is unknown. However, research suggests a combination of factors may be responsible. These include: genetics, the immune system, smoking, environmental factors and previous infection.

Mycobacterium avium subspecies *paratuberculosis* (MAP) belongs to a class of microbes called mycobacteria which cause diseases such as tuberculosis and leprosy. The microbe can be found in the environment and is known to cause a very similar chronic bowel disease in cattle. The scientific evidence suggests it can also play an important role in the development of Crohn's disease in humans. A vaccine against MAP could potentially lead to significant clinical improvement of Crohn's disease.

The purpose of this study is to assess the new MAP vaccines, ChAdOx2 HAV and MVA HAV, at different doses. The study will enable us to assess the safety of the vaccines and the extent of the immune response in healthy volunteers. We will do this by giving participants one or two vaccines in addition to doing blood tests and

collecting information about any symptoms that occur after vaccination. This is the first trial to use these vaccines in humans and we plan to recruit a maximum of 18 participants to be vaccinated.

What are the vaccines being tested?

ChAdOx2 HAV is based on a virus (ChAdOx2) that has been genetically altered so that it is impossible for it to grow in humans. To this virus we have added 4 genes that make proteins from the MAP mycobacteria, which were called HAV. The MAP mycobacterium needs these proteins in order to survive inside the human and animal bodies. We are hoping to make the body develop an immune response to these proteins, in order to stop the MAP mycobacteria from developing inside the human body.

The ChAdOx2 HAV vaccine has now been given to 12 healthy adult volunteers as part of this trial and there were no safety concerns reported to date. ..

MVA HAV is based on a different virus (MVA) but contains the same MAP genes as the ChAdOx2 HAV vaccine. This virus has also been weakened so that it is impossible for it to grow in humans. We have given MVA carrying genes for other proteins including Malaria, Flu, Tuberculosis and Ebola to over 4000 people with no serious side effects. It appears safe and well tolerated but can cause short-lived side-effects, also explained below. Until now this vaccine has only been tested on laboratory mice and this is the first time that the vaccine will be given to humans. Therefore, the main focus of this study is to determine a safe dose that won't cause unacceptable side effects. For this reason the doses given to the first participants will initially be very low. The dose will then be increased in a step-wise fashion.

Do I have to take part?

No. It is up to you to decide whether or not to take part. Your decision will not result in any penalty, or loss of benefits to which you are otherwise entitled. If you do decide to take part, you will be given this information sheet to keep (or be sent it electronically) and be asked to sign a consent form. You are free to withdraw at any time and without giving a reason, but you may be asked to return to the clinic for follow up for safety reasons.

Can I take part?

In order to be involved in the study you must:

- Be a healthy adult aged between 18 and 50 years.
- Be able and willing (in the Investigator's opinion) to comply with all study requirements.
- Allow the Investigators to discuss your medical history with your GP.
- Practice continuous effective contraception for the duration of the study (women only).
- Refrain from blood donation during the course of the study.

You cannot participate in this study if:

- You have participated in another research study in the last 30 days.
- You are planning to participate in another study at the same time as this study.
- You have previously received an investigational vaccine likely to impact on interpretation of the trial data or any adenovirus vectored vaccine in the past 12 months
- You have an allergy to any of the vaccine's components (e.g. Egg products)
- You have had immunoglobulins and/or any blood products (such as a blood transfusion) in the 3 months preceding your involvement in this trial.
- You have any bleeding disorders
- You have problems with your immune system.
- You are pregnant, breast feeding or intend to become pregnant during the study.
- You have a history of a severe allergic reaction to a vaccination.
- You have a history of cancer.
- You have a history of a serious psychiatric condition that may affect participation in the study.
- You have any other serious long-term illnesses requiring hospital follow-up.
- You drink on average more than 42 units of alcohol a week (a pint of beer is 2 - 3 units, a small glass of wine (125mL) one unit and a shot of spirits (25mL) one unit).

- You have injected drugs at any time in the last 5 years.
- You have hepatitis B, hepatitis C or HIV infection.

Mild conditions which are well-controlled, would not automatically exclude you from participating. If you are unclear whether you are eligible to be involved in the study you can contact the study team who will be able to advise you.

You must be able to comply with all of the trial requirements and be able to attend all of the follow up visits.

What will happen if I decide to take part?

If you decide you would like to take part in this trial, you will need to attend a screening visit up to 3 months before the vaccination day and it should last for about two hours. The screening visit, the vaccination and all of the post-vaccination follow-up visits will take place at the Centre for Clinical Vaccinology and Tropical Medicine (CCVTM).

At the screening visit you will be met by one of the Investigators who will go through this information sheet with you to ensure you understand what to expect by taking part, the risks involved and what side-effects you might expect to experience. You can of course expect to receive full and comprehensive answers to any questions you may have.

Once you are happy that you understand what the trial involves, and the Investigator is happy that you have understood everything, you will be asked to sign two copies of a consent form; one for you to take away and keep, and one for the Investigator which will be kept at the trial site. You will be asked to agree to allow the Investigators to contact your own Doctor (GP) to make sure there are no medical reasons why you should not participate. You will also be asked to agree to being registered on the confidential TOPS (The Over-Volunteering Prevention System) database which is set up to prevent people entering into multiple studies or trials at the same time.

Having signed the appropriate forms, the Investigator will go through a few questions for administrative purposes and detailed questions related to your health. This will be followed by a brief medical examination. Your blood pressure, pulse and temperature will also be recorded.

A number of blood tests will also be carried out which include tests for anaemia, any blood clotting problems, tests to see how your liver and kidneys are functioning and tests to see if you have been exposed to HIV (the virus that leads to AIDS), Hepatitis B or Hepatitis C (viruses which affect the liver). In the event of you testing positive to any of these infections, we would inform you of the result and, with your permission, offer referral for medical review, confirmation of the result, and treatment if necessary. You will also be asked to provide a urine sample to check for glucose (to exclude diabetes), protein and blood (which can indicate kidney disease). Women will also have a urine pregnancy test performed.

Sometimes minor abnormalities can be found with the blood tests. In this situation you may be asked to return for a repeat blood test so that it can be checked again. If the test results are still abnormal you may not be able to participate and we will ask your permission to contact your GP or a specialist doctor, whichever is the most appropriate, to ensure the abnormality will be followed up.

Once all your test results have been checked and there are no problems, you will be contacted to arrange a date to start the trial.

Length of research

If you decide to take part in this study, you will be involved in the trial for approximately 3-5 months, depending on which group you are allocated to.

Considerations before taking part in this study

Blood Donation: Under current UK regulations, participants will not be able to donate blood during the course of the study.

Private Medical Insurance: If you have private medical insurance you are advised to contact your insurance company before participating in this trial, as involvement may affect the cover provided

Contraception: It is currently unknown whether the vaccine being tested is safe during pregnancy. For this reason, it is important that all women use adequate contraception throughout the trial period, i.e. approximately 12 months. This will be discussed with you at the screening visit. If you were to become pregnant during the trial you must tell us immediately and you will be withdrawn from the study, although we will ask to follow you up for safety reasons. Male participants with female partners are not required to use barrier contraception, as the risks of vaccine excretion are negligible.

How is the trial going to work?

For this part of the trial we plan to recruit a maximum of 16 people. Volunteers will be allocated into 3 different groups of 3-10 participants. Groups 1-3 are now completed and you will be allocated to groups 4, 5 or 6. Volunteers will be firstly recruited into group 4 and secondly into group 5. Group 6 volunteers will be recruited following a review of the data from previous groups vaccinated.

Group 1: Volunteers will receive a very low dose of ChAdOx2 HAV.

Group 2: Volunteers will receive a higher (but still low) ChAdOx2 HAV.

Group 3: Volunteers will receive a higher (standard) dose of ChAdOx2 HAV.

Group 4: Volunteers will receive a low dose of MVA HAV (n=3)

Group 5: Volunteers will receive a standard dose of MVA HAV (n=3)

Group 6: Volunteers will receive a standard dose of ChAdOx2 HAV followed by a standard dose of MVA HAV, 8 weeks apart (n=10).

If you qualify to be in the trial, you will be asked to attend in the morning on the vaccination day (Day 0). You will be asked a few questions to check there have been no new problems since screening. Your blood pressure, pulse and temperature (observations) will be checked and blood samples taken. All women will have a urinary pregnancy test before vaccination.

The vaccine will then be given by injection into your arm and the vaccine site will be covered with a dressing. We will need to keep an eye on you in the waiting room of the department for 1 hour after the vaccine. After this period, observations will be checked again and the injection site inspected. You will then be given a thermometer, tape measure and an E-diary account to record all your symptoms and your temperature every day for 7 days after vaccination. After these 7 days we will ask you to record if you feel unwell or take any medications over the next 3 weeks. Overall the vaccination visit will take about one and a half hours.

You will be asked to attend for a series of follow-up visits (lasting 15-30 minutes) at 2, 7, 14, 28 and 56 days after your vaccination appointment. You will also receive a telephone call 1 month after your last visit. If you are allocated to group 6 you will receive your second vaccination at your day 56 visit and the same pattern of follow-up procedures will apply after your second vaccination.

At each of your follow-up visits we will check your observations, take a blood sample and review your completed E-diary. During the course of the trial you may be asked to attend for an extra visit, for example, if a blood test needs to be repeated. You will be compensated for the time and inconvenience of any extra visits. After the last visit, trial participation is complete

We may ask to photograph your vaccination site(s) and you can choose whether or not to agree to this when you sign the consent form. You will not be identifiable in these photographs, as only the vaccination site and your unique trial number will be visible. These photographs may be shown to other professional staff, used for educational purposes, or included in a scientific publication.

What should I avoid during the trial?

You should not donate blood during the trial or take part in other studies that involve blood sampling or the administration of drugs or vaccines. If during the trial you require any vaccinations for health, travel, or

occupational reasons, you should inform the Investigators beforehand. We will discuss with you the most appropriate time to receive them.

Are there any risks from taking part in the trial?

The risks and side effects of the proposed vaccinations and trial procedures are detailed here:

1. Blood samples

Drawing blood may cause slight pain and occasionally bruising at the site where the needle enters. Rarely, people feel light-headed or even faint. During the course of the trial we will need to take up to 60 mL of blood (approximately 4 tablespoons) at a single visit. The total amount we will take over the period of the trial is approximately 200mL for groups 4 & 5 and 410mL for group 6 volunteers, which is less than the amount taken if you donate blood.

The following blood tests will be performed;

- Tests for Hepatitis B, Hepatitis C and HIV are done at the screening visit.
- HLA typing, a test of a component of the body's immune system may be done at the first vaccination visit.
- Tests of red and white blood cells, liver and kidney function are done at the screening visit and most of the other visits (including the vaccination day), in order to check the vaccines are safe.
- Tests of the immune responses to vaccines are done at most of the visits.
- The volume of blood taken at each visit ranges from 5 to 60 mL.

The blood samples we collect will be stored after testing, and may be used in future research. Samples will be anonymised and you can request that your samples are destroyed at any time. You will be asked to consent specifically for blood to be stored.

If abnormal results or undiagnosed conditions are found in the course of the study these will be discussed with you and, if you agree, your GP (or a hospital specialist, if more appropriate) will be informed. Any newly diagnosed conditions will be looked after within the NHS.

2. Vaccination Side Effects

It is likely that you will experience some symptoms at the vaccination site as well as general symptoms due to vaccination. It is important to remember these are vaccines in the early stage of development and the amount of safety data available is limited. For this reason, there is a chance you could experience a side effect that is more severe than what is described below, or that has not been seen before.

Although the vaccine is being tested for the first time, a closely related viral vector vaccine has previously been administered in other clinical trials. We can predict from past experience what the symptoms should be like with this new vaccine. We expect that symptoms will be mild in strength most of the time, although symptoms may also be moderate or severe. All symptoms should resolve completely within a few days.

a) Local Reactions

You may experience some discomfort at the injection site as the vaccination is given. This usually gets better in 5 minutes. Later, you might experience pain resulting in some difficulty moving your arm, but this should resolve within a few days. In addition to pain, you may experience redness, swelling, or warmth at the injection site.

b) General reactions

During the first 24 - 48 hours after vaccination you may experience flu-like symptoms such as muscle aches, joint aches, feverishness, chills, headache, nausea, tiredness and/or feeling generally unwell. Some volunteers might experience moderate abdominal pain. These symptoms should usually resolve within a few days.

c) Serious Reactions

With any vaccination there is a risk of rare serious adverse events, such as an allergic reaction. These may be related to the immune system or to the nervous system. Severe allergic reactions to vaccines (anaphylaxis) are rare, but can be fatal. In case of this unlikely event, medication for treating allergic reactions is kept in the clinic room and the investigators are appropriately trained. Reactions in the nervous system are also extremely rare, but can cause an illness called Guillain-Barré syndrome. This is a condition in which people can

develop severe weakness and can be fatal. These adverse events have not previously been seen following administration of the ChAdOx1, ChAdOx2 or MVA based vaccines. ChAdOx1 is a viral vector closely related with ChAdOx2.

With any new medicine or vaccine there is always a possibility of an unexpected side effect. You will be provided with the 24h study mobile number. If you experience unexpected events or become in any way concerned you can use this to contact one of the study doctors at any time. We will ask you to record these symptoms too.

What are the advantages of taking part?

You will not necessarily gain any direct benefit from the trial, but the information gained from the study might help to develop an effective vaccine against Crohn's disease.

Will I be paid for taking part in this trial?

You will be compensated for your time, the inconvenience of having blood tests and procedures, and your travel expenses. The total amount compensated will be approximately **££300-£530** depending on the exact number of visits and whether any repeat or additional visits are necessary.

Trial reimbursement will be made by bank transfer within six weeks of your completion of the trial, so please bring your bank details with you to your screening visit (no cash payments can be made). Should you decide to withdraw from the trial before it is completed, payment will be *pro rata* (you will receive a proportion of the total amount).

PART 2

What if new information becomes available?

Sometimes during the course of a trial, new information relevant to the trial becomes available. If this happens, we will tell you about it and discuss whether you want to, or should, continue in the study. If you decide to continue to take part, you will be asked to sign an updated consent form. On receiving new information, we may consider it to be in your best interests to withdraw you from the study. Your participation in this study may also be stopped at any time by the study doctor or the Sponsor for other reasons.

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

If, at any time after agreeing to participate, you change your mind about being involved with this study you are free to withdraw without giving a reason. If you withdraw we would not usually perform any more research procedures, although occasionally we might need to offer you a follow up visit, for example, to check the injection site or a blood result. Your decision will not result in any penalty. Unless you state otherwise, any blood taken whilst you have been in the study will continue to be stored and used for research as detailed above. You are free to request that your blood samples are destroyed at any time during or after the study. If you choose to withdraw from the trial, your standard medical care will not be affected.

What if something goes wrong?

The investigators recognise the important contribution that volunteers make to medical research, and make every effort to ensure your safety and well-being. The University of Oxford, as the research Sponsor, has arrangements in place in the unlikely event that you suffer any harm as a direct consequence of your participation in this trial.

In the event of harm being suffered, while the University will cooperate with any claim, you may wish to seek independent legal advice to ensure that you are properly represented in pursuing any complaint. The study doctor can advise you of further action and refer you to a doctor within the NHS for treatment, if necessary. NHS indemnity operates in respect of the clinical treatment which may be provided if you needed to be admitted to hospital.

Complaints statement

If you wish to complain about any aspect of the way in which you have been approached or treated during the course of this study, you should contact the research investigators who will do their best to address your concerns. Alternatively you may contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 616480 or the head of CTRG, email ctrg@admin.ox.ac.uk.

Would my taking part in this trial be kept confidential?

All information that is collected about you during the course of the research will be coded with a study number and kept confidential. The information is available to the trial team, authorised collaborators, ethical review committees, government regulatory agencies and the Sponsor (The University of Oxford), who can ask to assess the trial. Responsible members of the University of Oxford may be given access to data for monitoring and/or audit of the trial to ensure we are complying with regulations. They are bound by the same confidentiality rules. Any information about you that leaves the hospital/clinic will have your name and address removed so that you cannot be recognised from it.

Every effort will be taken to maintain confidentiality. Information about you may be stored electronically on a secure server, and paper notes will be kept in a key-locked filing cabinet at the CCVTM – Churchill Hospital, University of Oxford. Records are stored for at least 15 years, and in accordance with the applicable regulations. Trial results will be published in a scientific journal but nothing that could identify you will be included in any report or publication.

Involvement of the General Practitioner/Family doctor (GP)

In order to enrol into this study, you will be required to sign a form documenting that you consent for us to contact your GP. This is to inform them that you are interested in being involved in the study, and to check there are no medical reasons that they are aware of that would make your participation inadvisable. Your GP may be asked to share information about your medical history and give access to any other medical records as required. The researchers will not enrol you in the trial if your GP has relevant concerns about your eligibility or safety. We will write to your GP to let them know whether or not you are finally enrolled in the study, and whether or not you completed the study, so they can update your medical records accordingly.

Prevention of ‘Over Volunteering’

Volunteers participating in this study must not be concurrently receiving investigational medications or vaccines in another study at the same time. In order to check this, you will be asked to provide your National Insurance or Passport number. This will be entered on to a national database which helps prevent volunteers from taking part in too many clinical trials. More information can be found at www.tops.org.uk. Your national insurance or passport number is also required to allow processing of compensation payments.

What will happen to any samples I give?

If you consent, some of your leftover blood samples will be stored and may be used for further studies of the human body’s immune response and/or the vaccines used in this study, and/or your safety. Any such tests will have an appropriate ethical review. Upon your request at any time, your remaining blood samples will be destroyed. Your participation in this study will not be affected by your decision whether to allow storage and future use of your leftover samples.

To avoid repeat testing, if you are not enrolled into this study and you apply to enter another study conducted by the Jenner Clinical Vaccine Trials Group based at the CCVTM, the results from your screening visit blood tests may be used to determine whether you are eligible for the trial you applied for.

Your study visit blood tests will be analysed in the hospital laboratories and Oxford University research laboratories. Other blood tests to look at the response of your body to the vaccine will be done with

collaborating laboratories in the UK and in other countries. Any samples or data sent to them would be anonymous.

Will any genetic tests be done?

We will do genetic tests on your blood samples to look at the patterns of genes that regulate your own individual immune response (these are called Human Leukocyte Antigen genes). Doing this helps us to work out which aspects of the immune response to vaccines are due to genetic differences between individuals. We may also look at the expression of certain genes which relate specifically to the immune response to MAP infection, but no genetic tests concerning diseases or conditions other than Crohn's disease will be done. You can opt out of 'genetic tests' if you wish, without any effect on your participation in the trial.

What will happen to the results of the research study?

The results of this research study may be presented at scientific meetings or conferences and published in a scientific medical journal. This may not happen until 1 or 2 years after the study is completed. If you contact the researchers in the future, you can obtain a copy of the results. You will not be identified in any report or publication.

The anonymised data from this study will be shared with the collaborating partners who are organising and funding this research work, including the vaccine company HAV Vaccines Limited. Data from this study may be used to file patents, licence vaccines in the future or make profits in other ways. You will not be paid for any part of this. Data from this study may be used as part of a student post-graduate degree, for example a MD or PhD.

Who is sponsoring, organising and funding the research?

The study is organised and sponsored by the University of Oxford. The study is funded through financial support to Oxford University from HAV Vaccines Limited. Neither your GP nor the researchers are paid for recruiting you into this study.

Who has reviewed the study?

This study has been reviewed by the National Research Ethics Service (NRES) – South Central Oxford A and has been given a favourable ethical opinion. The Medicines and Healthcare products Regulatory Agency (MHRA), which regulates the use of all medicines in the UK, has reviewed the study design and has granted permission to use this unlicensed vaccine in this clinical study.

Further information and contact details

We hope this information sheet has answered all of your questions. If you would like further information about participating in research please visit the following website: <http://www.nhs.uk/conditions/clinical-trials/pages/introduction.aspx>. For independent advice about participating in this trial you may wish to contact your GP. If you would like to speak to one of our team members to discuss any aspect of this trial or **if you are interested in taking part in the study, please contact us:**

Recruitment Coordinator
Centre for Clinical Vaccinology & Tropical Medicine
Churchill Hospital, Old Road, Headington, Oxford, OX3 7LE
Telephone: **01865 611424**
Email: **vaccinetrials@ndm.ox.ac.uk**

