University Hospitals Birmingham NHS Foundation Trust

Development of a vaccine against *Salmonella* Paratyphi A (VASP)

PARTICIPANT INFORMATION SHEET

You are invited to take part in a study to investigate whether

CVD 1902, an oral live-attenuated vaccine, protects against infection

with *Salmonella* Paratyphi A in a human model of infection.

The Oxford Vaccine Group, which is part of the University of Oxford, is running the study in conjunction with University Hospitals Birmingham NHS Foundation Trust.

Before you decide whether to take part, it is important for you to understand what the study is about and what participation would involve. Please take time to read the information carefully and discuss with others if you wish. If anything is unclear or you would like further information, please contact the study team (details below). Participation in this study is entirely voluntary.

Thank you for taking the time to consider taking part in the study.

Contact Details can be found at the end of this booklet

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Where is this study taking place?

If Oxford is your local study site then all your visits will take place at the CCVTM building at the Churchill Hospital in Oxford.

If a non-Oxford site is your local study site then the majority of your visits will take place at your local study site. However, the vaccination and challenge appointments (3 visits in total) will take place at the CCVTM building in Oxford. Travel to Oxford for these visits will be arranged by the study team and time expenses will be reimbursed. If your study site is more than 4 hours away from the Oxford site, we may also arrange for you to stay overnight nearby to the Oxford site for a maximum of one night.

Why have I been invited?

We are looking to recruit healthy male and female volunteers who are between 18 - 55 years of age. We use various ways to contact anyone who may be interested in this study, including via the Electoral Roll, by requesting a data extract from NHS patient databases, or using a relevant mailing list or registry that individuals may have independently signed up to. In the case of NHS databases, we will only request identification of persons based on postcode and appropriate age range. This information is shared with CFH Docmail (who have been assessed under the NHS Data Security and Protection Toolkit) solely for the purpose of arranging for the invitations to be sent. Please note that we do not have your contact details unless you have been contacted using the open version of the electoral register or you have previously provided us with this information. For more information about how we approach and invite individuals to take part in our research please visit: https://www.ovg.ox.ac.uk/

What is *Salmonella* Paratyphi A?

Typhoid and Paratyphoid fever are both forms of an illness called Enteric fever. Their names come from the bacteria that cause them: *Salmonella* Typhi (typhoid) and *Salmonella* Paratyphi A (paratyphoid). Although they are from the same family as the Salmonella bacteria that cause gastroenteritis in the UK, they are quite different.

Typhoid and paratyphoid both cause high fevers, headache, muscle and joint aches, abdominal pain, constipation, and cause individuals to feel generally unwell. If severe or left untreated, it can result in complications, long-term carriage of the bacteria or death.

There are approximately 14.3 million cases of Enteric fever every year, approximately three quarters are due to Typhoid for which there are vaccines available. A quarter of cases, approximately 3.3 million per year are due to Paratyphoid for which there is no vaccine. Both Typhoid and Paratyphoid are spread by the faeces of an infected person, typically via contaminated water or food. They are found in parts of the world where people don't have access to clean water and sanitation.

Are there vaccines against Salmonella Paratyphi A?

No. There are currently no licensed vaccines against *Salmonella* Paratyphi A. There are effective vaccines to protect against *Salmonella* Typhi, but as yet there are no vaccines against *Salmonella* Paratyphi A. Vaccines are being developed, however designing a vaccine is difficult as it is not yet understood exactly what immune responses may protect individuals from disease.

What is the vaccine being tested in this study?

A live vaccine called CVD 1902 has been developed by the University of Maryland in Baltimore, USA. It is taken as a drink in a solution of bicarbonate of soda.

CVD 1902 is a weakened (attenuated) form of *Salmonella* Paratyphi A bacteria designed to stimulate the immune system without causing disease. In this case a wild-type (ordinary) bacteria has had two sequences of genetic material deleted. No new active DNA has been inserted in their place. For this reason, CVD 1902 is classified as a genetically modified organism (GMO).

This vaccine has already been tested in humans. In a Phase 1 trial in the USA 30 healthy participants received CVD 1902 once, in 5 different doses. This trial showed that the vaccine was safe and well-tolerated. In those who received the highest doses, many participants showed an immune response to the vaccine. There were no serious adverse events related to the vaccine.

In this study we will be giving participants two doses of this vaccine (or the placebo) as data from other live bacterial vaccines suggest that more than one dose may give a better immune response. Following vaccination, all participants will be 'challenged'.

What is a human infection ('challenge') study?

Human infection or challenge studies involve deliberately exposing participants to an infectious agent (such as a bacteria) by asking them to drink a solution that contains bacteria. 'Challenge' using bacteria that cause enteric fever (*Salmonella* Typhi and Paratyphi A) has been performed at the Oxford Vaccine Group since 2011. Over 400 participants have been involved in these studies.

This is done in a very controlled way using a specific dose. Participants are then closely monitored for signs of infection. **All** participants are treated with antibiotics at the end of the observation period, regardless of whether they develop signs of infection, to make sure that the challenge bacteria are eradicated. This type of study is very powerful as they can be used to study diseases that are hard to study when they occur naturally.

For this challenge study the Oxford Vaccine Group will use *Salmonella* Paratyphi A. We know that by giving a specific dose of *Salmonella* Paratyphi A approximately 60% of people exposed to the bacteria will develop paratyphoid infection. This is the third challenge study undertaken using this strain of *Salmonella* Paratyphi A.

By using this very controlled setting to expose people to *Salmonella* Paratyphi A we can test vaccines to determine how well they protect against infection.

What is the purpose of this study?

In this study we will be assessing if a new vaccine, CVD 1902, can protect against *Salmonella* Paratyphi A infection.

We will also collect data looking at:

- The safety and tolerability of CVD 1902
- How the immune system responds to challenge in those participants who have received CVD 1902 vaccination compared to placebo
- If there is an immune response that correlates with protection from disease

What does this study involve?

We will be giving participants either two doses of the vaccine or two doses of placebo to drink. The group receiving the placebo will receive bicarbonate solution without the vaccine. The placebo group act as the comparison group so that we can see if there is any difference between those who received the vaccine and those who received the placebo when challenged. Participants are randomly assigned to each group by a computer programme and will not know which group they are in. The researchers running the trial will also be unaware of which group participants are in. This is known as a participant-blind observer-blind trial. This method gives greater confidence to the results of the study as it reduces the impact of bias.

One month after the second dose, we will be deliberately exposing ('challenging') **all** participants to live *Salmonella* Paratyphi A bacteria. We do this by asking them to swallow a solution containing the bacteria. Blood and stool (faeces) samples will be collected daily to find out how participants respond to the bacteria, and the protective effect of the vaccine (or placebo) they received. Saliva samples will be taken at some visits to see if we can see an immune response in the saliva. The doctors and nurses will then monitor participants very closely for the next two weeks to find out if they develop any symptoms. We do not expect everyone to develop paratyphoid infection and some participants may not feel unwell at all. Regardless of this, **everyone will receive a course of antibiotics**, either when they develop paratyphoid infection or 14 days after drinking *Salmonella* Paratyphi A (if they do not develop symptoms).

If fewer people are infected with paratyphoid after receiving the investigational vaccine (less than 60 to 70%) compared with those in the placebo group, then we can show that the vaccine protects against paratyphoid infection.

In addition, we will be able to study how the immune system responds to this paratyphoid vaccine and how this helps to prevent paratyphoid infection. This will add to our general understanding of paratyphoid disease and vaccine development.

All participants will be informed of whether they received the vaccine or the placebo once the *last* participant in the study has completed the 'challenge' stage of the study (after the Day 28 visit).

How does the COVID-19 pandemic affect this study?

The safety of our participants is paramount and before any participants are vaccinated or challenged the current COVID-19 situation in the UK will be assessed to decide if the trial can proceed. There are limited data on the risk of coincident COVID-19 infection and *Salmonella* Paratyphi A, and it is unknown if being infected with both at the same time would make the outcome of either infection more severe.

For this reason, we will test you for COVID-19 by taking a nose and throat swab two days before challenge, and again if you develop a fever, are diagnosed with paratyphoid fever, or start on antibiotics 14 days after challenge. We will also ask you to keep in close contact with the study team during the study especially if you develop any symptoms of COVID-19 and they can advise you about what to do next. To reduce the risk of becoming infected with COVID-19, participants must have had at least one COVID-19 vaccine to take part in the study.

Your visits to study clinics will adhere to current local and government social distancing guidelines. We will ask you to follow government guidelines regarding self-isolation, but it may be necessary for us to review you, for your safety even if you are self-isolating.

If you develop COVID-19 infection during the challenge period of the study, you will automatically be withdrawn from the study and treated for paratyphoid if this occurs in the 14 days after you have been challenged. We will continue to monitor you for safety.

Do I have to take part?

No. **Taking part is entirely voluntary**. We are looking for volunteers. Should you volunteer and later change your mind (for whatever reason) it is your right to do so, and you would not need to provide an explanation to the study team or anyone else but because of the nature of this study you may need follow up and treatment even if you chose to withdraw, depending on the stage of the trial you were at when you chose to withdraw.

Whatever you choose it is important that you are happy with your decision, and it is not the role of the study team to decide for you. We would help present the details of the study and answer all your questions so you could make an informed decision.

Who can take part in the study?

We are looking to recruit volunteers who are willing be available for all necessary visits and are healthy, aged 18 to 55 years of age, have not been exposed to *Salmonella* Paratyphi A before, and have not lived in overseas areas where enteric fever is endemic for more than 6 months.

Certain things may mean you are not able to take part in the study:

- If you work in food handling
- If you live or work with vulnerable people (e.g., people with poor immune systems, young children)
- If you have surgical implants
- If you are pregnant, planning on becoming pregnant, or breastfeeding
- If you had any significant medical conditions (including significant psychiatric illness)
- If you have had gallstones or have had your gallbladder removed
- If you have an allergy to the antibiotics used in this study
- If you had a history of alcohol or drug abuse
- If you have not had at least one dose of a COVID-19 vaccine

We would also like to know if you are expecting to receive any vaccines during the study period as this may affect whether you are able to participate in the study.

If you have already been in one of our enteric fever challenge studies unfortunately you would **not** be able to participate in this study.

This is an outpatient model but requires regular visits to the study site. You would need to be available for two vaccination visits in Oxford (if travelling from a non-Oxford site these visits may take an entire day with travel times), and three other visits to your local study site during the first six weeks (vaccination period). You would also need to be available for the challenge visit in Oxford.

Transport to Oxford will be provided for participants travelling from a non-Oxford site.
Following challenge, you would need to attend your local study site for **daily morning visits for approximately 2 weeks**.

Everyone will need to complete a course of antibiotics (first line will be Ciprofloxacin antibiotics for 14 days). You would also need to remain in contact with the study team during this period (contactable by mobile telephone and have access to the internet at home).

Follow up visits would then be at 1, 3, 6 and 12 months after 'challenge' day. These would take place at your local study site. The total study duration would be approximately 14 months.

Why might I be excluded from taking part?

Pregnancy

Paratyphoid infection can potentially be dangerous during pregnancy both to the mother and to the unborn child. Women will therefore be asked to use an effective method of contraception until tests show that the *Salmonella* Paratyphi A bacteria had been fully treated. A pregnancy test would be carried out at the screening visit, before vaccinations, before challenge and prior to starting antibiotics.

Contact with young children and other vulnerable people (including household contact)

You would be advised not to have close contact with young children (those in pre-school care/nursery or under 2 years of age) or with anyone who may be especially vulnerable to infection until we have confirmed that you have cleared the *Salmonella* Paratyphi A from your stool after challenge.

Clinical and social care occupations (including healthcare students)

If you work in these areas, you will have to agree to stay away from your work or studies for the entire vaccination and challenge period (or to be redeployed to alternative work which does not involve direct contact with individuals). We would need to inform your employer (or occupational health department) of your participation in the study. If you have direct contact with people or vulnerable individuals (including those under 2 years of age) then you would not be allowed to return to work until we have confirmed that you have cleared the *Salmonella* Paratyphi A from your stool after challenge.

Food handlers

Salmonella Paratyphi A can be transmitted in food handled by people who are infected with *Salmonella* Paratyphi A. If your work or voluntary activities involves handling or preparing unwrapped food that is not subject to further heating, then you would not be able to participate in this study unless you were willing and able to confirm that you are not working in this role from vaccination until we have confirmed that you have cleared the *Salmonella* Paratyphi A from your stool after challenge.

What will happen to me if I decide to take part?

Between 74-76 participants will be enrolled into this study. If you choose to take part, you would be involved in the study for approximately 14 months in total. The different stages of the study will now be considered in detail.

Study Procedures

Recruitment

Online and Telephone screening

Online questionnaire – 5-20 minutes

If you decide you would like to participate in this trial, there is a two-part online questionnaire to check initial eligibility.

Part-One: The first part broadly checks whether you can or cannot take part in the trial. The information you provide will not be stored unless you progress to part two.

Part-Two: If you are found to be eligible on completing the first part, you will be asked to provide us with information about yourself such as your date of birth, address and contact information.

If the questionnaire does not identify any obvious reason why you should not participate, we will review the information you provide, and a trial doctor or nurse may telephone you to go through this in more detail. If, after this process, you are eligible to join the trial, you will be invited to an in-person screening visit.

Following this, if you were interested and appeared to meet the criteria for the study, we would arrange for you to come to clinic for a screening visit.

Face to Face Screening Visit (Up to 2 hours)

The purpose of screening is to assess whether you can participate in the study.

At the screening visit we will outline the nature of the trial either through a video or slide presentation or in person, and this will explain what to expect by taking part, the risks involved and what side-effects you might expect to experience. This visit would provide an opportunity for you to ask any further questions you might have to a member of the study team and what is involved. You would be allowed as much time as you needed before making any decision on whether or not to take part.

If you wished to proceed, we would ask you to complete a short quiz to ensure you had understood the study and sign an **informed consent form**. Only once this was signed would we then start any study procedures.

We would ask you questions about your health, undertake a physical examination including an ECG ('heart tracing') and take a urine and blood sample to ensure you are healthy.

Blood would be screened for general health (to check your blood count, kidney, and liver function), HIV, hepatitis B and C and coeliac disease as well as for a congenital immune deficiency that some people have without knowing (called IgA deficiency).

To confirm your eligibility, your blood would also be tested for the presence of the HLA-B27 gene. HLA-B27 has been shown to be associated with some autoimmune diseases. There is a theoretical risk of developing autoimmune side effects to a *Salmonella* Paratyphi A infection, which can affect the

joints. Autoimmune diseases are caused by the immune system targeting cells in the body. Being positive for the HLA-B27 gene does not mean that you have or that you will develop an autoimmune disease. It is estimated that 8 in every 100 people in the UK general population are HLA-B27 positive, but the vast majority don't have autoimmune diseases. The safety of our participants is the most important aspect of the study so we would exclude anyone who tests positive for HLA-B27.

All participants are asked to complete a questionnaire to assess anxiety and depression. In addition, you would be asked to attend an appointment for a gallbladder ultrasound to check for gallstones, which can cause you to carry *Salmonella* Paratyphi A.

For all females, we would perform a pregnancy test on your urine sample.

Following the screening tests if an abnormal result was found on one of the tests, we would discuss this with you. We may provide you with the information and ask you to attend your GP, alternatively with your permission we would share this information with your GP or other relevant healthcare provider.

We would ask your permission to access your medical and vaccination records (also known as history) so that we can assess if you are eligible to take part. After the screening visit, we would access your NHS health records and ask your GP if they knew of any reason why you should not take part.

During your screening, you would be asked to provide your National Insurance number (or passport number if you do not have a National Insurance number). This would be entered on to a national database which helps prevent volunteers from taking part in too many clinical trials. The Over-volunteering Prevention Service (TOPS) database is to ensure safety of all our participants in this study and therefore if you are unwilling to have your information submitted on TOPS you would not be able to take part in our study. If you withdraw from the study before you receive a vaccine, the database will show that you never received a dose. Only the study staff and other medicines research units can use the database. We may call other units, or they may call us, to check your details. Data entered by us in TOPS is determined based on whether you receive a vaccine or not. If you receive a vaccine, this data will be retained in TOPS. If we need to contact you about the study after you've finished it, but we can't because you've moved or lost contact with your GP, we might be able to trace you through the information in the database. Further information can be found at:

https://www.hra.nhs.uk/about-us/committees-and-services/the-over-volunteering-prevention-system/

If the study team at your local site found any reason why you could not take part in the study this would be discussed with you.

Once the study team have confirmed your suitability for the study, we would inform you and arrange a date for your first visit. If more than 120 days have elapsed from your screening visit to enrolment, we would repeat your face to face screening visit including some of the procedures.

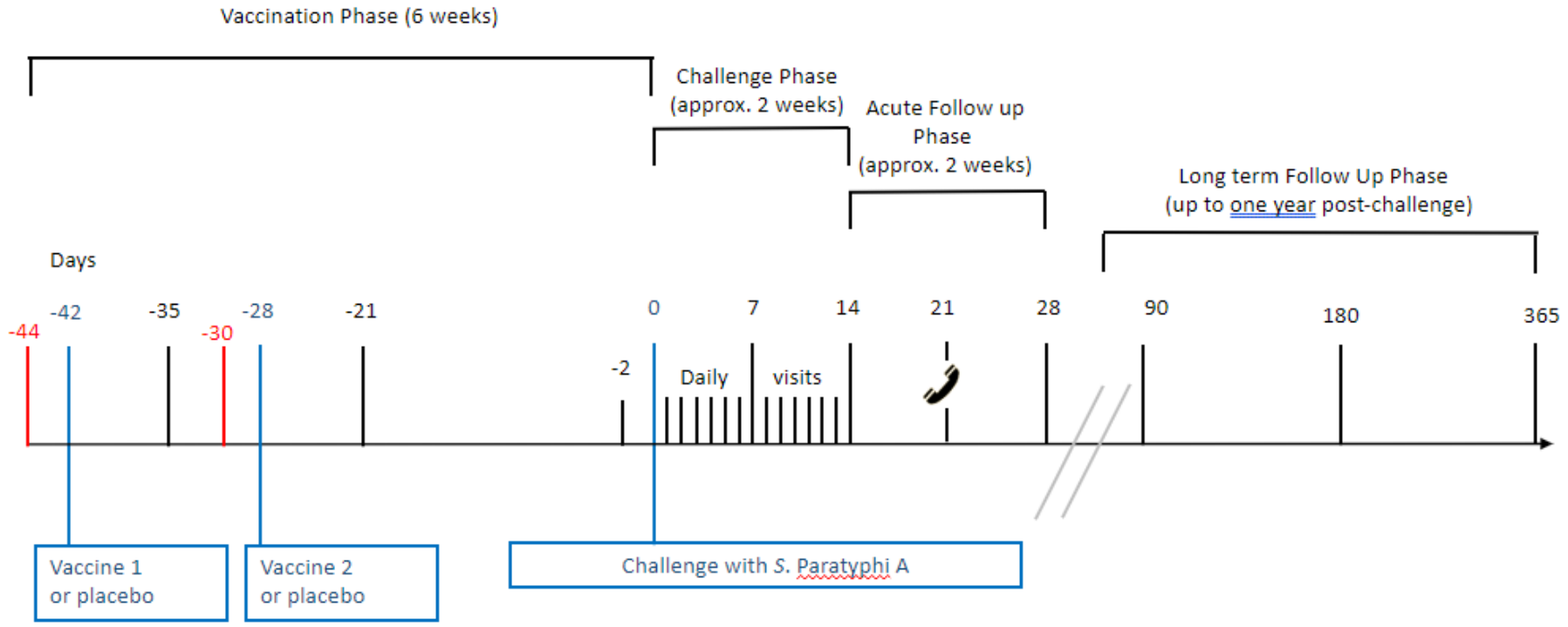
Your participation in this study is at the researchers' discretion.

Is coming to screening a commitment to taking part?

No. It is an opportunity to meet with the study staff and ask questions. You do not need to make a decision there and then.

Overview of the Study

This diagram shows an overview of the whole study. This information booklet will now go through each part of the study in detail.



Vaccination days (Up to 2 hours)

Vaccinations would take place in Oxford, at the Churchill Hospital. Before the vaccination is given, samples of blood, saliva and stool will be collected and a mood assessment performed. For participants from a non-Oxford site, these activities will take place at your local site up to 3 days before the vaccination day.

Travel to Oxford for participants from a non-Oxford site will be arranged and you would be accompanied by a member of your local study team.

On the day of vaccinations you would be asked to fast (i.e. not eat or drink anything) for 90 minutes before the visit. Women would have a urinary pregnancy test performed.

We would give you a drink to counteract the acid in your stomach (as stomach acid can kill the *Salmonella* Paratyphi A in the vaccine) then we would give you the vaccine (or placebo) to drink. You will need to be monitored for 60 minutes (+/-30 minutes) after receiving each vaccine to make sure you have no unexpected reactions. We would also ask you to fast for 90 minutes after having each vaccine.

We would ask you to record your temperature in the morning and evening and any symptoms or additional fevers you experience every day for one week after each vaccination. We would ask that you let us know if you have a high temperature (greater than or equal to 38°C). **You can take paracetamol and ibuprofen during the vaccination part of the study.**

We would give you access to a web-based electronic diary (e-diary) via a daily email link sent to your email address, and a thermometer to take your temperature with and make sure that you knew how to use these. We would give you a 24-hour contact sheet to complete prior to vaccination with the details of someone close to you that we can contact them if we can't reach you for any reason.

A second vaccination will be given 14 days after the first vaccine.

Post vaccination visits (Up to 1 hour)

These will take place at your local study site. After receiving the vaccine, we would ask you to attend follow up visits. During these post-vaccination visits we would review your e-diary for symptoms, ask if you have taken any medications, and obtain further blood (47.5 mL) and stool samples to assess your body's response to the vaccine and to make sure you have cleared the bacteria. At some visits, saliva samples will also be taken.

Pre-challenge visit (Up to 30 minutes)

This visit is to take a nose and throat swab to ensure that you do not have COVID-19 before undergoing challenge.

Challenge day (day 0) - Start of the intense monitoring period (Up to 2 hours)

As with the vaccination days, the challenge would take place in Oxford, at the Churchill Hospital. Before the challenge is given, samples of blood, saliva and stool will be collected and a mood assessment performed. For participants from a non-Oxford site, these activities will take place at your local site up to 3 days before the challenge day and can be done at the same time as the COVID-19 swab (see above).

Travel to Oxford for participants from a non-Oxford site will be arranged and you would be accompanied by a member of your local study team.

On the day of challenge you would be asked to fast (i.e. not eat or drink anything) for 90 minutes before the visit. Women would have a urinary pregnancy test performed.

We would give you a drink to counteract the acid in your stomach (as stomach acid can kill *Salmonella* Paratyphi A) followed by a drink containing *Salmonella* Paratyphi A bacteria. You would then be asked to fast for a further 90 minutes.

We would check that you still had access to your e-diary and your thermometer. We would ask you to record your temperature in the e-diary twice a day, plus record any additional fevers you may have, and your symptoms once a day for the following three weeks. **During this time, it is very important that you do not take paracetamol, ibuprofen or any other medication that may lower your temperature unless instructed to do so by the study team, as this will interfere with the diagnosis of paratyphoid infection.**

What happens at the follow up visits?

Follow up visits during the challenge period would typically take place at your local study site (Birmingham CRF). At the visit we would review your symptoms as recorded in your e-diary, measure your vital signs, and take a blood and stool sample. These samples would be examined for the paratyphoid bacteria and also to study your body's immune response to paratyphoid infection.

It is essential that you are available to attend for the study visits after challenge, potentially at short notice until you have completed antibiotic treatment. We would ask each participant to attend every visit, complete the e-diary, and keep in contact with the team, who are there for your safety.

We would then see you for visits at 1, 3, 6 and 12 months after challenge.

What happens if I get paratyphoid infection?

The main symptom of paratyphoid infection is fever (a high temperature). Some people will also feel very tired, have a headache, have muscle or joint aches, go off their food, have stomach pain, and/or feel sick. If you develop a temperature (≥38°C) you need to let one of the study team know immediately. If your temperature remains high for 12 hours or if we found bacteria in your blood tests, then you would be diagnosed with paratyphoid infection. You would then be treated with a course of antibiotics to clear the paratyphoid infection.

Once you have started the course of antibiotics, paracetamol can be taken to lower your temperature, which we will provide. If you develop paratyphoid infection, you could feel unwell for several days. With early antibiotic treatment people usually do not develop severe symptoms. We do not expect you to become severely unwell during this time. However, if this did occur then we would arrange for you to be admitted to a hospital ward until you had recovered.

For safety reasons, we would need to see you when you are first diagnosed and then at 12, 24, 48, 72 and 96 hours later. Attending both the 12-hour or 24-hour visit may not always be required (you will need to attend at least one) – this will be up to the clinical team. These visits are to ensure that you are responding well to the antibiotic treatment. As at other times in the study, additional visits may be required for your safety and the study team would talk to you about these.

What happens if I do not get paratyphoid infection?

If you are not diagnosed as having paratyphoid infection, at day 14 after challenge we would give you a course of antibiotics. This is to ensure *Salmonella* Paratyphi A bacteria is eliminated from your body.

What antibiotics will I be taking and what are the potential side effects?

We would use an antibiotic called ciprofloxacin which comes as a tablet and is taken twice a day for 14 days. This is recognised as being one of the best treatments for paratyphoid infection and is widely used for treatment of many different types of infections. The strain of the *Salmonella* Paratyphi A that is being used in this study is known to be sensitive to ciprofloxacin. In order to monitor your response to antibiotics and any potential side effects, we would ask you to continue completing the e-diary after starting treatment. If you were to develop any symptoms after starting antibiotics, we would ask you to contact us. We would be able to advise you on the most appropriate course of action, which might include switching you to an alternative antibiotic.

Most people do not have any side effects from these antibiotics. General side effects of antibiotics can sometimes occur. These might include nausea, vomiting, diarrhoea, headache, or thrush.

Occasionally ciprofloxacin gives people an upset stomach, rash, dizziness or itching. Very rarely ciprofloxacin causes sensitivity to sunlight, kidney problems, seizures, problems with the blood, tendon inflammation or makes people feel confused, depressed or experience hallucinations or other strange sensations. We will discuss these with you at your screening visit. If after starting ciprofloxacin it was found that you were unable to continue taking it, there are several other effective antibiotics we can use, including azithromycin, trimethoprim/sulfamethoxazole, or amoxicillin. If you needed an alternative antibiotic, we would discuss any potential side effects with you.

Female participants using oral hormonal contraceptives ('the pill') should use additional barrier contraception (such as condoms) during the vaccination and challenge period until shown to have cleared the bacteria (approximately 3 months in total), in case absorption through the gut lining has been affected by the bacteria from the vaccine or the challenge.

The amount of antibiotic that is absorbed can be affected by antacids and iron supplements. We would therefore ask you not to take these whilst you were taking the antibiotics.

It is possible that the vaccine, paratyphoid exposure and the antibiotics used to treat the infection have a transient effect on your gut and the balance of bacteria that naturally live in your body. One aspect of this study will be to look at the effect of an antibiotic course on the bacteria in the stool.

Will I need to take any other medicines?

Some people may experience symptoms after being 'challenged' and, if required, the study doctor can prescribe medication to help with these (e.g., laxative for constipation). Any such medicine, including its benefits and side effects, will be discussed with you beforehand.

In certain circumstances it is acceptable to continue to take long term medications (e.g., the 'pill') – one of the study doctors would discuss this with you during screening. If during the study any other treatment became necessary, it would be important to inform us immediately so that we could ensure that the antibiotics and treatment you had been given were safe. We would ask you to keep a record of all the medications (including vaccines) that you took during the study.

What samples will be collected?

We would take blood and urine samples as part of the screening visit, to help us assess your general health. Blood and stool samples would also be collected at most of your study visits, in order for us to monitor your immune response and for safety reasons. Saliva samples will be taken at some visits. Some of the samples are for research tests, and we would not be able to provide these results, but we can give you the results of your other tests, if you would like them.

The total volume of blood taken will not be the same for everyone. This is because we intend to take different samples depending on whether people develop paratyphoid infection or not. A maximum of 1122 mL of blood will be taken over the study period. As a comparison, if you were to give blood to the National Transfusion Service a woman would be able to give a maximum of 1410 mL per year over three visits, and men 1880 mL per year over four visits. For this reason, participants will be asked not to donate any blood while participating in the study.

What will happen to the samples I give?

The blood, saliva and stool samples collected during this study would be transported to either the University of Oxford research laboratories or locally to Study Centres or to local study site laboratories for analysis. Those analysed in local study site laboratories will either be discarded once analysed, or where bacteria have been grown, the bacteria will be transferred to University of Oxford research laboratories for storage and further analysis for this study. We would also send some samples to other researchers working with us on this research project, including researchers outside the European Union. These samples would be anonymised.

Would any genetic tests be done?

Some blood would be used to look at the pattern of genes being actively used by your body in response to the vaccine and during *Salmonella* Paratyphi A infection. The response to infection and to vaccines is in part genetically controlled, so knowing the pattern of genes that are being used may help us to understand how individuals respond to vaccination and paratyphoid infection.

What else do I need to know?

If you chose to take part in this study, we will be asking for your separate permission to store blood (including DNA) and stool samples, in a collection of samples called 'BioBank'. Details of this will be provided in a separate booklet provided to you after you are enrolled into this paratyphoid study, and you are free to say no to the Biobank and continue to take part in this study if you wish.

What if we find something unexpected?

If abnormal results or undiagnosed conditions are found during the course of the study these would be discussed with you and, if you agreed, your GP would be informed of these results (we would not report them to anyone else without your permission). For example, a new diagnosis of high blood pressure might be made. Any newly diagnosed conditions would be looked after by your GP.

What are the advantages of taking part in the study?

There is no direct benefit from taking part in the study. As part of the screening investigations, you will receive information about your general health, but this is not a health check. We hope that the knowledge gained from this study will contribute to the understanding of paratyphoid disease and

vaccine development. You may receive an experimental paratyphoid vaccine that could prevent you becoming unwell with the infection, either as part of the study or at some future date. We cannot guarantee that you will be protected from paratyphoid infection however, either in taking part in this study or from future infection.

Are there any disadvantages or risks from taking part?

Risks of vaccination

The vaccination may cause side effects. These might include: fever, headache, abdominal cramps, nausea, vomiting, diarrhoea, reduced appetite and feeling generally unwell. The placebo (bicarbonate solution) may cause abdominal cramps and flatulence. We will observe everyone in the study for any side effects, particularly in the first seven days after receiving a vaccine by asking you to complete an electronic diary. Side effects may be mild or severe. Most effects will stop shortly after receiving the vaccine. In the Phase 1 study of this vaccine, it was found to be safe and well tolerated. However, it is important to notify the study team if you are at all worried about your symptoms.

You may take medicines after you've received a vaccination to help lessen side effects; for example, if you have a fever after vaccination, you could take paracetamol to help treat it. Any medication you have taken during the study should be recorded in your e-diary. If you have a severe reaction to the vaccine, we may need to give you a course of antibiotics.

With any vaccination there is a very small risk of an allergic reaction. This is very unlikely with this vaccine as the vaccine is made up of water, sodium bicarbonate and bacteria. We will monitor you after receiving the vaccine for 60 minutes.

As this vaccine contains live bacteria, we ask you to maintain good hand hygiene and food preparation habits throughout the study to prevent transmission. The bacteria has been weakened and is unlikely to cause illness in people with normal immune systems. It is very unlikely that anyone could contract the vaccine strain of bacteria from you if you maintain good hand washing and food preparation habits. However, to offer peace of mind to your close contacts we would offer them a screening test to check that they are not infected with the vaccine strain of bacteria. We would give you information for your close contacts about the vaccine and offer them screening once you had received both doses of the vaccine.

Risks of undergoing challenge

The risks of taking part in this study are very low provided that you comply with study visits and maintain close contact with the study team as outlined in this booklet. If untreated, paratyphoid infection can result in serious illness or even death. However, over 400 people have been successfully challenged with *Salmonella* Typhi and Paratyphi bacteria that cause enteric fever at the Oxford Vaccine Group since 2011 and all have made a complete recovery from infection.

Paratyphoid Infection

While some individuals in the study would remain well and experience no symptoms, we would expect most people to experience symptoms of paratyphoid infection. Whilst symptoms differ from person-to-person, common symptoms include:

- fever
- chills
- headache
- feeling tired and generally unwell
- muscle or joint aches
- abdominal discomfort
- loss of appetite

You may need to take time away from work/study if you develop symptoms of paratyphoid infection.

Severe problems are unlikely as we would treat participants very early on in the course of illness (within 12 hours of onset of fever or if a participant has bacteria in their blood tests). Severe complications are rare and mainly occur when paratyphoid fever is not treated properly or immediately. If paratyphoid fever is left untreated, possible complications include bleeding from the gut, a hole developing in the gut, becoming a carrier of paratyphoid, altered consciousness, coma, or death. It is for these reasons that it would be crucial that you take the full course of antibiotics, stay in contact with the study team and let a study doctor know as soon as you developed a temperature or felt unwell.

Excretion of bacteria in the stools

A small percentage (up to 10%) of people who contract paratyphoid infection can go on to carry the bacteria and excrete the bacteria in their stools for 3 months or even longer periods. These people are known as 'carriers' and we know that people with gallstones are especially vulnerable to becoming carriers. For this reason, we would do an ultrasound scan of your gallbladder at screening and if we found that you had evidence of gallstones, you would not be able to take part in the study.

We also collect 3 stool samples after you have completed your antibiotics to prove that the paratyphoid bacteria have been fully cleared from your body (called clearance samples). Very rarely, stool cultures can remain positive even after you have completed a course of antibiotics. In the unlikely event that this were to occur, you would receive further antibiotics to significantly reduce the risk of you becoming a carrier. If you became a carrier, you would be referred to an Infectious Diseases specialist for further antibiotic treatment.

Antibiotics

A small number of people may have side effects to the antibiotics used to treat the paratyphoid infection. We will discuss these with you when you come to screening. There is further information in the section above called '**What antibiotics will I be taking and what are the potential side effects?'**

General risks

This study involves blood tests at all visits. Taking blood samples may sometimes result in bruising to the area and some people can feel faint. If you were feeling faint, our staff would ask you to stay at the clinic until you felt well again. It is also possible that due to the volume of blood taken in the study you may become anaemic, your blood tests are closely monitored for this.

Can I give paratyphoid infection to anyone else?

Paratyphoid infection is transmitted to other people through them coming into contact with the faeces of infected individuals. This would only occur following poor hygiene practices such as not thoroughly washing hands after using the toilet and before preparing food. Most cases occur within a household and other close contact situations (e.g. sexual contact) but transmission is extremely unlikely if good hygiene practices are followed. We will discuss this with you at screening.

We would give you detailed advice on how to make sure you do not give paratyphoid infection to other people and provide you with liquid soap and disposable towels. It is very unlikely that anyone could contract paratyphoid infection from you if you maintain good hand washing and food preparation habits. However, to offer peace of mind to your close contacts we would offer them a screening test to check that they are not infected with *Salmonella* Paratyphi A. This would occur after you have started antibiotics, but we would provide you with information to give to your close contacts to explain the risks before this.

In summary:

This study involves being given two doses of an oral vaccine against *Salmonella* Paratyphi A or a placebo drink, and then one month later drinking a solution containing a strain of *Salmonella* Paratyphi A which causes paratyphoid fever. The aim of the study is to see if the vaccine can protect volunteers from developing infection when exposed to it. This study involves a number of study visits including an intensive period of at least two weeks after challenge where you would need to be seen **every day.** It involves having blood, saliva and stool samples taken at a number of visits over the course of the study (approximately 14 months).

What is expected of me during the study?

- You need to attend all study visits (including daily visits for 14 days post challenge).
- If Oxford is not your local study site you will need to travel to Oxford for three visits (both vaccinations and challenge visit).
- You must remain in mobile telephone contact throughout the study.
- You must have access to the internet.
- You must stay in close contact with the study team throughout the study.
- You must stay/ live within a (~) two-hour commute to your local study site during the challenge period until you are shown to be clear of infection.
- You must nominate someone who lives near to you and who would know where you were for the duration of the study as an alternative contact for the study team. You would give this person the study information and ask them to return a signed reply slip with their details and a 24-hour phone number. If for any reason we could not get hold of you, or your 24-hour contact during the study and were concerned about your welfare we may visit your home and/or call the Police.
- You must provide all household and sexual contacts with study information given to you by the study team which will offer them screening for the vaccine strain and for *Salmonella* Paratyphi A infection.
- You should record in the study e-diary all of your symptoms once a day and your temperature twice a day for the first 7 days after each vaccination and the first 21 days after challenge.

- After *Salmonella* Paratyphi A **challenge**, you must **not** take paracetamol, ibuprofen or any other medication that may lower your temperature unless instructed to do so by a study doctor.
- You must take a full course of antibiotics when given to you.
- Female participants should use an effective method of contraception from one month prior to vaccination until they are shown to be cleared of *Salmonella* Paratyphi A bacteria.
- Female participants using oral hormonal contraceptives should use additional barrier contraception (such as condoms) during the vaccination and challenge period, until shown to have cleared the bacteria (approximately 3 months in total).
- You must provide at least 3 stool samples after the completion of antibiotics so we can ensure you are clear of paratyphoid. These would be obtained 1 week after you completed antibiotics and would be collected at least 48 hours apart.

Who will be informed of my participation?

Your General Practitioner: In order to enrol into this study, you would be required to consent for us to contact your GP.

This is to ensure there are no medical reasons that would prevent you from taking part in this study. If you subsequently took part, we would let them know of your participation and demonstrated stool clearance.

As outlined earlier, we would only notify your GP of the results from any other medical tests we performed with your permission.

United Kingdom Health Security Agency (UKHSA, previously known as Public Health, England): We would inform the local UKHSA Health Protection Team of the names, addresses and dates of birth of all participants that were challenged with *Salmonella* Paratyphi A. This is to ensure that there is independent oversight of the public health aspects of this trial. We will also tell them when you have demonstrated stool clearance.

Your close contacts: We would provide you with information about the study to distribute to anyone who is identified as a close contact (for example, members of your household) to invite them to be screened for the vaccine strain or *Salmonella* Paratyphi A following challenge.

Your employer: In certain circumstances (see Why might I be excluded?) it may be necessary to tell your Employer about your participation in the study.

Will my taking part be kept confidential?

Yes. All information that is collected about you during the course of the research would be coded with a study number and kept strictly confidential. Any information about you that leaves the clinic would have your name and address removed so that you could not be recognised (with the exception of letters sent to UKHSA, your own GP and employer – see above).

Responsible members of the University of Oxford team, local study team, local study site laboratories, authorised representatives appointed by the Sponsor and regulatory authorities may be given access

to data, to ensure your safety as well as for monitoring and/or audit of the study to ensure that the research is complying with applicable regulations. The following groups may inspect the study records without violating your confidentiality:

- Monitors who check that the study is being conducted to a high standard, including the Data and Safety Monitoring Committee (DSMC), an independent panel of experts responsible for trial safety.

- The Research Governance, Ethics and Assurance (RGEA), University of Oxford, who are responsible for ensuring the appropriate conduct of the study on behalf of the research Sponsor (the University of Oxford).

Pseudo-anonymised data and samples would be sent to other researchers working with us on this research project, including researchers, within and outside of the European Union and the study funders.

Will I be reimbursed for taking part?

All participants will be reimbursed for their time, travel and for inconvenience based on the following figures:

- Travel expenses: £15 per visit (maximum total for 32 visits = £480)*
- Inconvenience of blood tests: £10 per blood donation (maximum total for 30 blood tests = £300)
- Inconvenience of delivering clearance stool samples: £15 per stool sample (total for 3 samples = £45)
- Time required for visit: £20 per visit (maximum total for 34 visits = £680)
- Time off work compensation (for challenged participants only): £150 per day for 10 days (total = £1500).
- Time off work compensation (for participants travelling from sites to Oxford only): £150 per day (maximum total for 6 days) = £900

*Travel and, if applicable, overnight stays (only if your travel time is longer than 4 hours) from local sites to Oxford for the vaccination and challenge days will be arranged for participants and therefore are not included in the reimbursement costs.

Participants will receive a maximum of £3340 if they remain in the study for the entire period and attend all study visits (including screening). Payments will be made via internet bank transfer. Participants will be asked to provide banking details including account name, sort code and account number. All details will be stored confidentially and retained by University Hospitals Birmingham NHS Foundation Trust while the participant is actively involved in the study. These details will be retained for 7 years as per local site policy.

Participant payments will be requested after you have attended the following visits: Screening, Day 0, Day 14, Day 90, Day 180 and Day 365. Payments usually take 4-6 weeks to be processed. Participants have a different number of visits depending on if they are diagnosed with paratyphoid infection and

at what stage; the figures above are a maximum figure. Due to the generous reimbursement for scheduled visits, you will not be given extra reimbursement for unscheduled visits or unscheduled blood tests.

Note that "time off work" reimbursement is limited to the 10 days after challenge. If you were to take time off work after this period, we would not be able to reimburse you for this.

If you chose to leave the study early or were withdrawn from the study, you would be reimbursed according to the length of your participation based on these figures.

Is there anything else I should know?

If you have private medical insurance, you are advised to contact your insurance company before participating in this trial.

Where can I get advice on whether to take part?

We are happy to answer any questions you might have and contacting us does not commit you to taking part in the study. For independent advice you can contact **INVOLVE** (www.invo.org.uk) which is a government funded national advisory group supporting those considering involvement in NHS, public health and social care research. Please feel free to discuss this study before deciding whether or not to participate.

What will happen to my data?

Data protection regulation requires that we state the legal basis for processing information about you. In the case of research, this is 'a task in the public interest.' The University of Oxford is the data controller and is responsible for looking after your information and using it properly.

We will be using information from you and your medical records in order to undertake this trial and will use the minimum personally-identifiable information possible. We will keep identifiable information about you such as contact details for 5 years. This includes a copy of your consent form. The need to store this information for longer in relation to licensing of the vaccine will be subject to ongoing review. De-identified research data will be stored indefinitely.

Paper notes will be held by University Hospitals Birmingham NHS Foundation Trust in locked cabinets. Once the trial has been completed, all documents, including personally identifiable data, would be archived in a secure facility, for a minimum of 5 years. Storage of this data will be reviewed every 5 years and files will be confidentially destroyed if storage is no longer required.

If you supplied your medical history online or underwent telephone screening but were not enrolled on the trial either because you were not eligible after screening or decided not to take part, then any data collected will be kept until the end of the trial.

If you have agreed that samples can be retained for future research, then your personally identifiable information will be kept with restricted access solely for the purposes of sample management for a minimum of five years and a maximum of 15 years after the study has been finished. Samples will be provided for future research only in a form that does not identify you.

If you agree to your details being held to be contacted regarding future research, we will retain a record of this consent until such time as your details are removed from our database but will keep this separate from your research data.

The trial team will use your name and contact details, to contact you about the research trial, and make sure that relevant information about the trial is recorded for your care, in relation to your health during the trial and to oversee the quality of the trial.

At the completion of the trial, unless you consent otherwise (e.g., if you request to be informed of other trials), your personal details will not be used to contact you other than exceptional circumstances concerning your safety. If you consent to take part in another trial carried out by University Hospitals Birmingham NHS Foundation, personal information and medical information including blood test results may be accessed to avoid unnecessary repetition.

Your bank details will be stored for a minimum of 7 years in line with University Hospitals Birmingham NHS Foundation Trust financial policy.

Data protection regulation provides you with control over your personal data and how it is used. When you agree to your information being used in research, however, some of those rights may be limited in order for the research to be reliable and accurate. Further information about your rights with respect to your personal data is available at: https://www.uhb.nhs.uk/legal-and-regulatory/privacy/privacy-notice-for-patients.htm

Note that in order to check that we are conducting the trial to high standards we will be engaging trial monitors, who will have access to your data (including personal identifying information). They will not be retaining data beyond the end of the study.

What will happen if I do not want to carry on with the study?

If at any time after agreeing to participate, you change your mind about being involved in this study, you would be free to withdraw without giving a reason. If you wish to leave after drinking the challenge (*Salmonella* Paratyphi A) bacteria then you would need to take the course of antibiotics and provide stool samples after this, as very serious consequences can occur in individuals with untreated paratyphoid infection. We would also need to ensure that you had been treated appropriately and so would refer you for follow up with either your own GP or UKHSA. This follow up would include you providing stool samples, ensuring you are clear of paratyphoid.

If you withdraw from the study after we have collected samples from you, unless you state otherwise, any biological samples, which have been collected whilst you have been in the study, will be used for research as detailed in this participant information sheet.

What if there is a problem?

The University of Oxford, as Sponsor, has appropriate insurance in place in the unlikely event that you suffer any harm as a direct consequence of your participation in this study.

If you wish to complain about any aspect of the way in which you have been approached or treated, or how your information is handled during the course of this study, you should contact either Dr Chris

Green/Site Research Nurses on 0121 371 3178 or PALS on 0121 371 3280 or you may contact the University of Oxford, RGEA office on 01865 616480, or the head of RGEA, email rgea.sponsor@admin.ox.ac.uk.

Who is organising the funding?

This study is funded by a grant from the Medical Research Council to Oxford Vaccine Group.

Who has reviewed the study?

The study has been reviewed by the study sponsor (the University of Oxford). It has been approved by an independent research ethics committee (21/SC/0330) and has also been approved by the other regulatory authorities.

What will happen to the results of the study?

The results of the research will be published in a scientific medical journal, which can potentially take a few years. All OVG publications will appear on the OVG website, and you will receive a letter containing these results. Your individual results would not be identifiable, nor would you be identified in any report or publication.

The results of the research and the data generated by the research will also potentially be used for future academic research.

What do I do now?

Thank you for considering taking part in this study.

If you do not wish to participate in the study, you do not need to contact us. If we do not hear from you, we will assume that you do not want to take part in the study. However, you are welcome to contact us using the contact details below and provide feedback if you wish.

If you are interested in participating in the study, you do not need to make a final decision straight away. If you wish to discuss any element of the study further, please consider:

- Checking our website: https://trials.ovg.ox.ac.uk/trials/vasp
- Contact us using the contact details below

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Yours sincerely,

Dr Christopher Green

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