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PARTICIPANT INFORMATION SHEET v4

Varying Keyhole Limpet Haemocyanin-adjuvant dose combinations to explore the immune response: a human challenge study

We'd like to invite you to take part in our research study. Before you decide, it is important that you understand why the research is being done and what it would involve for you. Please take time to read this information, and discuss it with others if you wish. If there is anything that is not clear, or if you would like more information, please ask us.

First, we want to introduce you to the study and key facts. Then we will go through the study in more detail. There will be time for you to ask us any questions, and to discuss your participation with friends, relatives, and your General Practitioner (GP), if you wish. **Taking part in this study is entirely your choice.**

You will be compensated £400-800 for your time, travel, and inconvenience.

Could I be eligible to take part?	
✓ You must	✗ You must not
Be aged 18-45 years old	Have any significant medical conditions
Be in good health	Be a current smoker, including vaping
Be willing to travel to our research facility in Oxford for a screening visit, and six study visits over up to 49 days	

If you decide to join our study:

1. You will be given injections of keyhole limpet haemocyanin (KLH; trade name: Immucothel) into the muscle or skin, on up to three occasions, with or without a medicine ('adjuvant') which helps the immune response (either aluminium hydroxide or Montanide ISA-51). All these products are used clinically and are manufactured to the standard of medicines.

2. You will have to attend a screening visit, where we will ask questions about your health, perform a physical examination, and take a blood sample. If you are eligible based on the screening assessment and decide to take part, you will have to attend the research facility on up to 6 further occasions over up to 49 days, for about an hour per visit (about 2 hours for the final visit).

3. You will be closely monitored by the study team with a range of tests and procedures, including questionnaires, physical examinations, blood tests, skin imaging using Laser Doppler Imagers, and ultrasound of the lymph nodes in your armpit.

4. We will take a tiny sample of skin (punch skin biopsy) from up to three areas on your forearm, using local anaesthetic. The timing of these biopsies depends on which phase of the study you are enrolled into.

5. Depending on which phase of the study you take part in (explained below), you may be asked if you are willing to undergo a procedure called fine needle aspiration of the lymph nodes in your armpits, on two of the study visits. This is an optional extra, and you will receive additional payment for undertaking these procedures.

6. You will be free to withdraw from the study at any time you wish.

Contents

1. Introduction

Faulty regulation of the immune system contributes to multiple diseases including inflammatory arthritis, cardiovascular disease and cancer, and therefore represents a leading cause of disability and death worldwide. Whilst there have been revolutionary advances in our understanding of how to use drugs to treat abnormal immune responses, there remains huge unmet need for new, better medicines. Unfortunately, as many as 9 in every 10 promising drugs studied in humans ultimately do not succeed in becoming clinical treatments. A significant cause of failure is when information gained in the laboratory or in animal studies does not hold true when the drug is given to humans.

2. Why are we doing this study?

One approach to improve the efficiency of the drug development process is the use of human 'immune challenge' studies. In these studies, healthy volunteers are given small amounts of substances which are foreign to their immune system to provoke a temporary response: the 'challenge'. Depending on the nature and dose of the challenge, the body's immune system will react in a different but predictable way, elements of which mimic those seen in disease, thereby 'modelling' them. These models can help safely bridge the gap between animal experiments and people with disease, allowing us to test the effect of new drugs safely without exposing patients to risk. Sadly, whilst immune challenge models have been used in drug development for many years, this has been done in an *ad hoc* manner, which greatly limits the usefulness of the approach.

The purpose of this research is to better understand, improve, and standardise a common method of immune challenge which uses a protein called 'Keyhole Limpet Haemocyanin' (KLH). KLH is available as a highly-purified formulation, and because it is not usually encountered by the human immune system (it is derived from an inedible shellfish), it allows us to study the development of immune responses right from the time it is administered. We plan to give different groups of healthy volunteers different doses of KLH with or without an 'immune-boosting' agent (Alhydrogel™ or Montanide ISA™51, commonly referred to as adjuvants), before measuring and comparing their response. We will then re-challenge all the volunteers a month later with different doses of KLH in the skin on their forearms, similar to an allergy test, taking images, blood samples, skin biopsies, and in some cases lymph node biopsies to understand the nature, time course, and variability of the immune response in each individual. The results will help us to select the best doses of KLH to model different diseases and test drugs with. In turn, this will allow earlier and better evaluation of new therapeutics.

3. Why have I been invited?

You have been invited because you are aged 18-45 years, are healthy, take no regular medications affecting the immune system, and have mark-free forearms (no skin damage, tattoos or scars on the hairless part of either arm). If you tell us

you are healthy, don't take any regular medications and don't smoke, then you can participate.

4. Are there any advantages to taking part?

You will not gain any direct benefit from the study. We hope that the information we gather from this and future studies will help us to develop new treatments for diseases caused by, or affecting the immune system.

5. Do I have to take part?

- No, taking part is entirely your choice.
- You can withdraw at any time without giving a reason.

6. Can I take part?

To take part in the study, ALL of the following must apply to you:

- Be willing and able to give informed consent for participation in the study and able to comply with the study protocol.
- Be aged between 18 and 45 years of age inclusive, at the time of signing the informed consent.
- Be healthy, based on a detailed medical history and a complete physical examination including vital signs and laboratory measurements.
- Have a body mass index (BMI) within the range 18 to 35 kilogram/meter squared (inclusive).
- If female, be of non-child bearing potential or if female and of child bearing potential not be pregnant (negative pregnancy test on the day of both screening and vaccination) and willing to use effective methods of contraception to prevent pregnancy from the time of first dose to 60 days afterwards. This should include two methods of contraception simultaneously (e.g. condoms and the oral contraceptive pill).
- If male and with a female partner of child-bearing potential, agree to use effective methods of contraception from the time of the first dose of challenge agent to 60 days afterwards.
- Have sufficient English language ability to enable appropriate informed consent procedures to be conducted in English

You CANNOT participate if any of the below exclusion criteria apply to you:

- Have had antibiotics or antiviral therapy after a serious illness within 30 days of study entry.
- SARS-CoV2 (COVID-19) infection within the previous 30 days, diagnosed using PCR test or lateral flow device
- Have any use of immunosuppressant or immunomodulatory agents (systemic or topical) in 3 months prior to study entry.

- Have chronic medical conditions with potential effect on immune responses including diabetes, significant history of atopy, or any condition that, in the opinion of the investigator, would interfere with the study
- Have any tattoos, naevi or other skin abnormalities such as keloids (or history of keloids) that may, in the opinion of the investigator, interfere with study assessments.
- Are pregnant or breastfeeding
- Have an allergy to KLH, aluminium hydroxide, Montanide ISA-51, related vaccine adjuvants, or components of the study challenge agents
- Have an allergy to shellfish
- Have a history of a tropical infection called schistosomiasis, either formally diagnosed, or suspected based on clinical assessment at the screening visit. (due to potential cross-reactive immune responses to KLH)
- Have previous exposure to Keyhole Limpet Haemocyanin, e.g. in the context of a previous study
- Participate, within 7 days of screening, in recreational sun-bathing, or use of sun-bed, on the area of the skin from wrist to shoulder inclusive.
- Have a phobia of needles or minor surgical procedures.
- Are a current smoker (including vaping) or using nicotine replacement therapy
- Have received any vaccinations within 2 months prior to screening visit, or will require vaccination prior to the end of study follow-up
- Have any other significant disease, disorder, or finding, which, in the opinion of the investigator, may either put you at risk, affect your ability to participate in the study or impair interpretation of the study data

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

7.1. Pre-screening

You may have already completed pre-screening if you are reading this information sheet. Pre-screening involves a brief (~15 minute) meeting, phone call, or video call to give some preliminary information and to register your details. Additionally, there will be a few brief questions to check you are eligible for the study, which will include questions about your medical history.

If you decide that you might like to take part, a member of the study team will ensure you have a copy of this document to keep (the ‘Participant Information Sheet’)—we can give you a paper copy, or send it to you via email. We will go through this document in detail, to ensure you understand what to expect if you decide to take part, the risks involved, and what side-effects you might experience. You will receive full and comprehensive answers to any questions you might have. After this appointment you will have time to think about this study, and

we encourage you to discuss with friends, family, and GP if you wish. If you have any additional questions at this stage you will be encouraged to contact us by phone or email to discuss them.

7.2. Screening phase

If you are eligible, and if you decide that you would like to proceed, a member of the study team will arrange a visit to the research facility for a physical examination, and blood tests. Face to face visits will take place at one of two locations, either the Clinical Research Facility at the Nuffield Orthopaedic Centre, or the Experimental Medicine Clinical Research Facility (EMCRF), based at the Churchill Hospital site. Both of these facilities are run by the University of Oxford. We will let you know where to go before your visit.

Upon arrival you will have the opportunity to ask any further questions and, once you are happy that you fully understand what the study involves and before anything else takes place, the study doctor will ask you to sign a consent form. You will be given a copy of the consent form to take away and keep. The exact procedures that will happen in the study, and the timelines of involvement will depend on which study phase you are enrolled into—the main difference between these phases is the timing of follow-up assessments (see figure 1). We will make it clear what study phase applies to you before you sign any consent forms.

The study doctor will then go through a few administrative questions as well as detailed questions about your health. This will be followed by a physical examination and blood tests to see if you are suitable for this study (see more details below). You should allow approximately 1 hour for this first screening visit, and it will occur up to 90 days prior to enrolment in the study. You will receive financial compensation for this visit. We will ask to see some form of ID, such a driver's licence or passport.

<u>TOPS Registration</u>

You must not take part in too many studies because it's not good for you. So to help research units, the Health Research Authority keep a database of healthy volunteers and when they take part in studies--this is called TOPS. We will enter into the database your National Insurance number (if you're a UK citizen), or your passport number and country of origin (if you're not a UK citizen) and the date of your last dose of study medicine. If you withdraw from the study before you receive any study medicine, the database will show that you never received a dose. Only staff at the NIHR Oxford Clinical Research Facility 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 in TOPS is retained for the minimum period required and this is determined based on whether you receive a dose of the study medicine or not. If you receive a dose of the study medicine, this data will be retained in TOPS. If you do not receive a dose, your data will be retained in TOPS for two years. 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.

Medical examination and clinical observations

Medical examination of your skin, chest, abdomen, mouth and the lymph glands in your upper body will be performed. Your blood pressure, heart rate, and temperature will be recorded. We will record your weight and height. Additionally, for women of childbearing potential a urine pregnancy test will be performed.

Blood tests

To check that you are suitable for the study and that it is safe to take part, we will take blood to test for anaemia (low red blood cells), problems with your immune system, and kidney function. In addition, we will do a test to determine your 'HLA type' which is a genetically determined (inherited) characteristic which can influence an individual's immune response. We will take approximately 10mL (two teaspoons) of blood. These tests will be performed by Oxford University Hospitals NHS Foundation Trust, and will be linked to your NHS patient record (so will be visible to other healthcare professionals, such as your GP).

What happens if any of the tests are abnormal?

Sometimes test results are outside the usual ranges for healthy individuals. Depending on the results, you may not be eligible for the study, and you may be advised to contact your GP for further tests or review. In some cases, the study doctor may simply recommend that the blood tests be rechecked on a later date, before deciding on eligibility. You will be compensated for this additional blood test on a pro-rata basis.

Optional consent for further blood donation

At this visit you will be asked whether you would be happy to be contacted in the future to give further blood samples once the study is over, to better understand how the immune response to KLH changes over a longer period of time (up to 24 months). This is optional and does not oblige you to give a blood donation when contacted. If you do provide further blood donations, we will take up to 50mL of blood (approximately 3 tablespoons) per visit, and a maximum of 400mL (approximately two cups) in any 3 month period (similar to the limit used by the NHS blood and transplant service for regular blood donors). You will be compensated for the time and inconvenience of providing these additional blood samples.

Optional consent for further KLH injections

At this visit you will be asked whether you would be happy to be *contacted* in the future to undergo further injections of KLH into the skin of the forearms, similar to those given around day 28 of the study. This will consist of up to two injections (dose between 1-100mcg KLH) on the forearms or back. You will then return between 24-72 hours later (we will indicate when), for a clinical assessment, imaging, and up to two 'skin blister procedures'. Participation in these additional procedures would be subject to additional consent and there is a separate information sheet describing these procedures in more detail.

Optional consent for lymph node fine needle aspiration

If you consent to phase 3 of the study we may ask if you are willing to undergo a procedure called fine needle aspiration (FNA) of the lymph nodes on days 5 and 28 of the study. This is an optional extra, and you can participate in the study whether or not you agree to the FNA procedures. More info about the lymph node fine needle aspiration procedure is given below.

What happens if I decide not to take part at this stage?

There is nothing else you need to do—taking part if entirely your choice.

If you decide not to participate in the challenge part of the study, we might ask if you are willing to provide a one-off blood sample, to help us develop laboratory tests of the immune response, and compare the results of these tests with people who receive KLH in the study. This is optional, and you will be compensated for your time and inconvenience. In this circumstance we will not perform any other the study procedures detailed below, but we will ask if you are willing to be contacted in the future to provide further blood samples, or to see if you are interested in taking part in any future studies—this is also optional.

7.3. Study phase

If you consent to take part in the study, you will be invited to attend for up to 6 further in-person visits. The exact schedule of visits will depend on the phase of study which you are recruited to—you can only participate in one of the study phases. We will make it clear to you which study phase we are recruiting into before you agree to take part. Figure 1, and the following sections gives an overview of the study visits for each phase of the study, and the types of biological samples we will take at each visit.

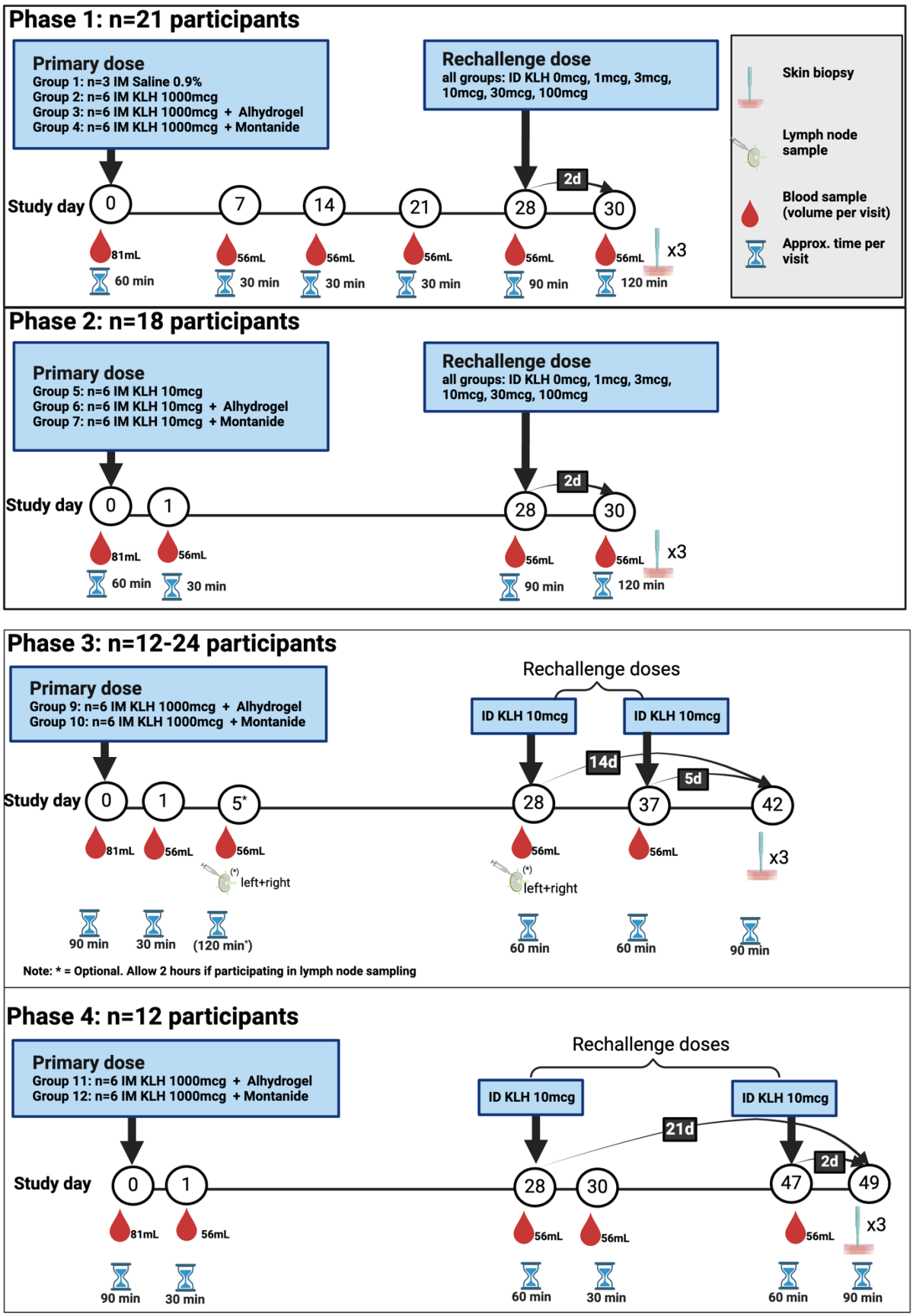


Figure 1 Overview of study visits and biological sampling

Study phase 1

We will randomly assign you to one of 4 different groups using a computerised process, similar to flipping a coin. Each group will receive slightly different study regimens, with an intramuscular (IM) injection of KLH or placebo (saline), with or without an adjuvant, into the deltoid muscle of the shoulder on day 0 of the study (see Figure 1). You will then return for study visits on days 7, 14, and 21, where we will take blood samples and perform assessment for any potential issues, such as adverse events. On day 28 of the study you will be given 6 injections into the skin ('intradermal') of the forearms with different doses of KLH or saline. Finally, on day 30, you will return for assessment of the skin response. This will involve measuring the size of any response using a ruler, specialised imaging devices, and by performing three skin biopsies at the sites of the intradermal injections. More information about the study procedures is given in section 7.4.

Study phase 2

We will randomly assign you to one of 3 different groups using a computerised process, similar to flipping a coin. Each group will receive slightly different study regimens, with an intramuscular (IM) injection of KLH, with or without an adjuvant, into the deltoid muscle of the shoulder on day 0 of the study (see Figure 1). You will then return the following day ('day 1') where we will take blood samples and perform assessment for any potential issues, such as adverse events. On day 28 of the study you will be given 6 injections into the skin ('intradermal') of the forearms with different doses of KLH or saline. Finally, on day 30, you will return for assessment of the skin response. This will involve measuring the size of any response using a ruler, specialised imaging devices, and by performing three skin biopsies at the sites of the intradermal injections. More information about the study procedures is given in section 7.4.

Study Phase 3

We will randomly assign you to one of 2 different groups using a computerised process, similar to flipping a coin. Each group will receive slightly different study regimens, with an intramuscular (IM) injection of KLH, with one of two different adjuvants (montanide or alhydrogel), into the deltoid muscle of the shoulder on day 0 of the study (see Figure 1). You will then return the following day ('day 1'), and on day 5, where we will take blood samples and perform assessment for any potential issues, such as adverse events. Following this, you will receive one injection of KLH into the skin of the forearms on each of two occasions – one injection on day 28, and one on day 37. You will attend follow-up visits on day 37 and 42 where the skin response will be assessed using a ruler and specialised imaging devices. We will perform skin biopsies over the sites of these injections, plus a 'control' site (which did not receive any injections) at the day 42 visit. More information about the study procedures is given in section 7.4.

Optional: Participants in this phase of the study will be asked for additional consent to undergo a procedure called fine needle aspiration of the lymph nodes in both armpits (axillary lymph nodes). This is an optional extra part of the study, i.e. you can participate in the study whether or not you agree to lymph node fine needle aspiration. If you do agree to this, the fine needle aspiration procedure will be carried out by a trained doctor on day 5 and 28 of the study. More information about this procedure is given in section 7.4

Study Phase 4

We will randomly assign you to one of 2 different groups using a computerised process, similar to flipping a coin. Each group will receive slightly different study regimens, with an intramuscular (IM) injection of KLH, with one of two different adjuvants (montanide or alhydrogel), into the deltoid muscle of the shoulder on day 0 of the study (see Figure 1). You will then return the following day ('day 1'), where we will take blood samples and perform assessment for any potential issues, such as adverse events. Following this, you will receive one injection of KLH into the skin of the forearms on each of two occasions – one injection on day 28, and one on day 47. You will attend follow-up visits on day 30, 47, and 49 where the skin response will be assessed using a ruler and specialised imaging devices. We will perform skin biopsies over the sites of these injections, plus a 'control' site (which did not receive any injections) at the day 49 visit. More information about the study procedures is given in section 7.4.

7.4. Study procedures

On days where KLH is administered, when you arrive at the study site, we will ask you questions to confirm you are still healthy and suitable for the study. Your blood pressure, heart rate, and temperature will be recorded. For women of childbearing potential a urine pregnancy test will be performed.

Blood tests

We will take blood samples to measure the status of your immune system, as a baseline prior to the first injection of the challenge agent. We will also do tests for evidence of previous infections with viruses which very commonly infect people as children or in early adulthood (cytomegalovirus), as these viruses may affect the immune response to KLH, or provide additional insight into the way your immune system reacts to infection/inflammation. The total volume of blood taken on this occasion will be approximately 80mL (about 5 tablespoons).

Lymph node ultrasound

We will use an ultrasound machine to look at the lymph nodes in your axilla (armpits)—we use gel to help improve the ultrasound pictures. The ultrasound procedure is painless and harmless.

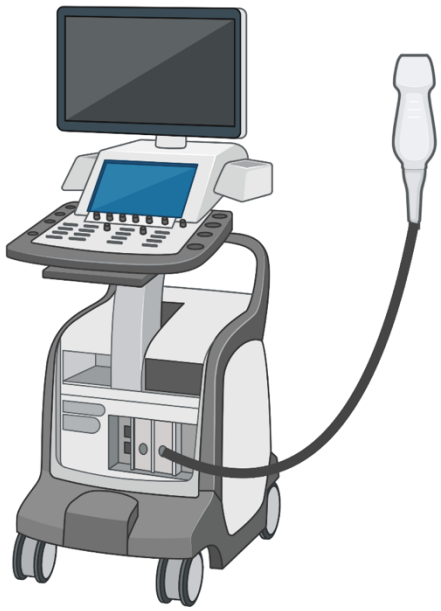


Figure 2 Ultrasound machine

SARS CoV2 (COVID-19) Testing

If you have symptoms which may be caused by COVID-19 (e.g. new cough, fever, or other cold-like symptoms) we will administer a SARS CoV2 lateral flow test (nasal swab), to check for COVID-19 infection.

KLH or placebo administration

Prior to your arrival on day 0 you will have been randomly allocated to one of the study groups (see figure 1 above). We will not tell you which group you have been assigned to—this increases the scientific validity of the study. We will give you an injection into the deltoid muscle of the arm (see Figure) with KLH or placebo, with or without adjuvant, according to your group assignment.

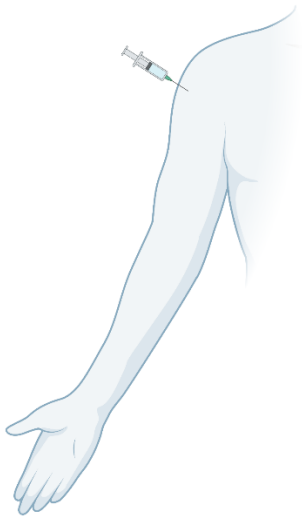


Figure 2: Site of first study injection

After the injection, we will ask you to wait at the study site for 20 minutes, to check you do not have a reaction to the injection (this is very unlikely).

Lymph node fine needle aspiration (optional: offered to groups 9 and 10 only)

A fine needle aspiration (FNA) involves taking cells and fluid from a lymph node (gland). It is a procedure commonly performed in outpatient clinics to help diagnosis in patients with different health conditions, for example for lumps or swollen glands. It will be performed by a doctor or trained sonographer.

The whole visit can take up to 90 minutes but the FNA procedure itself takes only a few minutes. You will have an examination to feel for the lymph nodes (glands) under the arm. Once a suitable gland has been identified, the area will be cleaned and numbed using local anaesthetic. Using the ultrasound scan for guidance, a needle will be used to collect a small amount of fluid and cells from the gland. You should not feel significant pain or discomfort but may feel some pressure. The procedure will then be repeated on the opposite side.

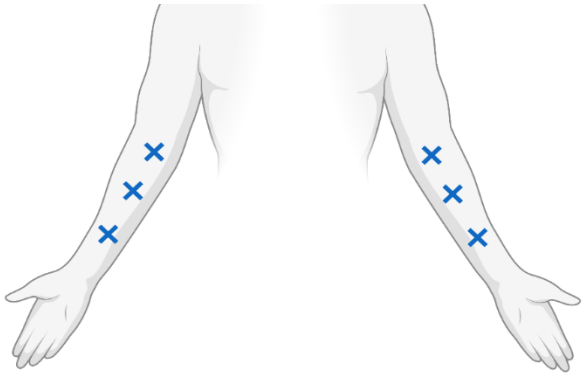
7.5. Assessments at follow-up study visits

Following your first study visit, you will return for follow-up visits. The schedule of visits depends on which group you are enrolled to as shown in figure 1. The approximate duration of these visits is also described in figure 1. If it is difficult for you to attend these visits we may be able to conduct them at a suitable alternative location. We will ask you questions about your current health, and any possible reactions to the study agents. If necessary, we will do a brief physical examination or check your vital signs, e.g. if you have a skin reaction to the injection. We will perform a brief ultrasound to assess the lymph node reaction in the armpits and take a blood sample to measure the immune response to KLH. On these visits we will take approximately 56 mL (about 4 tablespoons) of blood.

KLH re-challenge visits

For groups 1-7 (study phase 1 and 2), on day 28 of the study we will give you further small injections of KLH under the skin. We will give you a total of 6 small injections into the skin of the forearms, as shown in Figure 3. One of these injections will be saline, and the rest will be different doses of KLH. We will ask you to stay at the study site for a minimum of 20 minutes after the injections, to check you do not have a reaction to them. If you are in groups 9-12 the procedure will be very similar, but instead we will give you just two injections of KLH into the skin of the forearms (10mcg per dose in the upper part of the forearms), on the study days depicted in figure 1 and described in section 7.3.

Figure 3: Sites of KLH re-challenge injections (groups 1-7)



7.6. Study visit following KLH re-challenge

Following the skin injections we will perform the assessments also performed at previous visits (e.g. clinical assessments and blood tests). In addition, at each of these visits we will assess the skin response to the KLH injections given from day 28 onwards at each of the injection sites.

Assessment of KLH re-challenge

We will measure the skin reaction to the injections using a ruler, and a special camera called a laser Doppler imager (LDI), which measures blood flow in the skin. You will be given a special set of glasses to wear while the LDI is being used to protect your eyes. We will also take photos of the skin reaction—these will be close up photos of the skin and will not include any identifiable detail.

Skin biopsy

We will take up to samples of skin (a skin biopsy), using a special device called a punch biopsy. The timing of these biopsies depends on what group you are enrolled into, and is shown in figure 1. The skin will be taken from either areas

where you were given the saline and KLH injections, or from a ‘control’ site where no injections were administered. In all cases the biopsies will be taken from forearms. To take the biopsy we will clean the skin with antiseptic, and then give an injection of local anaesthetic to minimise discomfort. The punch biopsy takes a tiny circular amount of skin (4-6mm in diameter, about the size of 2-3 grains of rice side by side). We will then close the skin with special plasters (steristrips), or a single dissolvable stitch, if necessary. We will then put a dressing over these biopsy sites, which can be left on until it falls off, or removed carefully after 48h.

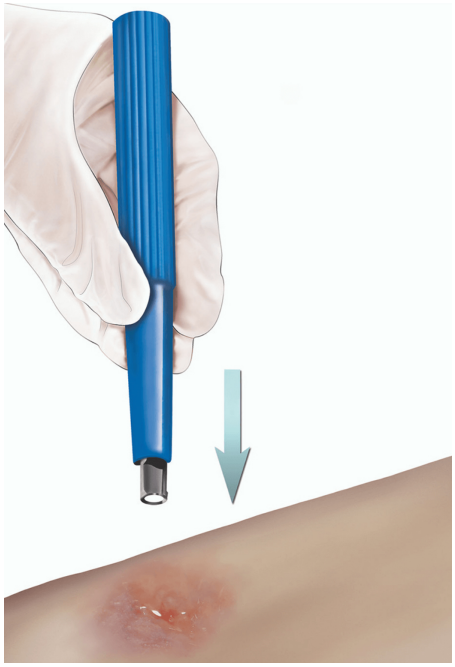


Figure 4 Punch skin biopsy procedure. From https://www.healthdirect.gov.au/surgery/punch-biopsy-of-a-skin-lesion

After the biopsy you will be asked to keep the area dry for 48h, then you can bathe/swim normally. If a stitch has been used, this will dissolve and fall out on its own in about 10 days. If a steristrip is used, it should fall off by itself, or it can be removed by soaking and gently removing at after 10 days.

Participant experience questionnaire

On your final visit will ask you about your experience in the study to date, e.g. how you found the study procedures, and whether you would volunteer for similar studies in the future, based on your experience in this study.

End of the study

Following your final visit we will make sure that you have contact details for the study team in case there are any problems after this, such as any concern around the healing of the punch biopsy sites (this is very unlikely).

Contact for repeat rechallenge and skin blister procedure

Following your final visit, if you have consented for further contact from us, we may contact you to return for further KLH injections and skin blistering procedures. This may occur up to 24 months following your first dose of KLH. Further information about this is given in a separate information sheet – the study team will provide this to you if you are interested in participating in this aspect of the study.

8. What are my responsibilities?

It is important to consider whether you can commit to coming for all study visits, as far as possible.

If you take part in the study we will ask you to avoid the following activities, within 72h of primary and re-challenge KLH doses (or placebo):

- Sunbathing and use of sunbeds
- Contact sports, weight lifting, and any other moderate/high intensity exercise lasting >30 minutes
- Consumption of more than 3 units of alcohol per day
- Smoking of tobacco or cannabis, or use of vapes
- Consumption of non-steroidal anti-inflammatory drugs and antihistamines
- Use of topical creams, ointments, or gels containing corticosteroids or non-steroidal anti-inflammatory drugs.

Following the skin biopsy (and any skin blistering procedures) you will need to take care to not disturb the skin too much until the skin is healed.

We will ask you to inform us if you develop symptoms that may be consistent with COVID-19 infection (e.g. a high temperature, new continuous cough, and/or a change in sense of smell or taste). If these occur, we will ask you to come to the research facility for a COVID-19 test. We will also ask you to provide results of any tests that you may have done elsewhere.

You should not donate blood within 3 months of the study, as the total amount of blood donated during this study is similar to that of a standard blood donation.

<u>Women of childbearing potential</u>

For female participants, we consider you to be of childbearing potential unless you have had previous surgical sterilisation (e.g. hysterectomy, bilateral salpingectomy, bilateral oophorectomy). Female participants of childbearing potential are required to use a **two** effective forms of contraception from the day of first administration of KLH until 60 days after the last administration of KLH. Acceptable forms of contraception for participants of childbearing potential include:

- Established use of oral, injected or implanted hormonal methods of contraception
- Placement of an intrauterine device (IUD) or intrauterine system (IUS)
- Barrier methods of contraception (condom or occlusive cap with spermicide).
- Male sterilisation, if the vasectomised partner is the sole partner of for the subject.
- True abstinence (defined as refraining from heterosexual intercourse) when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence and withdrawal are not acceptable methods of contraception.

9. Are there any possible disadvantages or risks from taking part?

The disadvantages of taking part relate to the inconvenience of attending for study visits, and the small risk of adverse effects of the study procedures. You should consider the following risks before agreeing to take part:

9.1. Potential risks of the challenge agents

Keyhole Limpet Haemocyanin (Immucothel)

KLH is a highly purified protein obtained from the blood of an inedible shellfish. It has been used for over 50 years for challenge studies similar to ours, at doses up to 5 times greater than those used in our study. The specific product we are using (Immucothel) is a registered medicine in some countries.

Expected common adverse effects are limited to mild responses at the injection site e.g. pain, redness, warmth, swelling, tenderness or itching. Other potential foreseeable risks would be similar to those seen with standard vaccinations, including mild systemic reactions e.g. flu-like illness with feverishness, fatigue, malaise, arthralgia, sore muscles and headache. In almost all cases we would expect these to last no more than a few days. In very rare cases, local reactions could be more severe. If this were to occur we would not give any further injections and would withdraw you from the study, while also providing any appropriate medical care that you might need, or referring you to your GP or other NHS service as required.

There are some very rare but serious adverse effects that can occur with commonly used vaccinations. Although KLH is not a vaccine, it is similar to a vaccine in that it is foreign to the body and provokes an immune response, and it is therefore reasonable to expect a similar potential for these adverse effects. These include severe allergy (anaphylaxis) and problems with nerves such as Guillain-Barre Syndrome. The risk of these is extremely low.

Aluminium hydroxide adjuvant (Alhydrogel)

Aluminium hydroxide is a class of drugs called ‘adjuvants’—these drugs are included in many registered vaccines due to their ability to boost the immune

response. Aluminium hydroxide has been administered as a component of millions of doses of vaccine worldwide, and is considered very safe. Local, transient reactions may be observed including swelling, redness and itch. The combination of KLH with aluminium hydroxide adjuvant has been used in multiple previous studies, with no report of significant additional side effects compared to KLH alone.

Montanide ISA-51

Montanide ISA-51 is a mineral oil-based adjuvant, extensively studied for enhancing vaccine responses. Montanide ISA-51 can cause transient local skin reactions, including swelling, redness, pain, and itch. Occasionally Montanide ISA-51 has been associated with systemic effects such as fatigue, and fever, which would be expected to disappear in no more than a day or two. In rare situations, more severe local reactions have been observed. These side effects were not reported in the two previous studies which combined KLH with Montanide ISA-51 at the same doses used in this study, thus the risk of these more severe side effects is considered to be low.

9.2. Potential risks of tests performed as part of the study

To minimize the risk of problems all study procedures will be performed by experienced professionals using appropriate precautions and equipment.

Blood donation

If you take part in the study and complete all follow-up the total amount of blood taken will be about 400mL, which is similar to a standard blood donation. As such it would not be expected to cause problems for an otherwise healthy volunteer. The blood donation itself requires the use of a needle into a vein of the arm, and this can cause minor bruising, tenderness, and occasionally feeling faint or actually fainting. Very rarely sites of blood tests can become infected and require antibiotic treatment. The blood tests will be taken by experienced members of the study team which should minimize the risks of side effects.

Intramuscular injection

Intramuscular injection is a commonly performed procedure for the administration of medicines, including vaccines. The potential risks include minor discomfort on injection, minor bruising, tenderness, and occasionally feeling faint or actually fainting. There can also be discomfort for a few days afterwards due to bruising related to the injection, and due to the body's response to the KLH (+/- adjuvant) injection. Very rarely sites of injections can become infected and require antibiotic treatment. The injections will be performed by experienced members of the study team which should minimize the risks of side effects.

Intradermal injection

The risks of intradermal injection are similar to those of intramuscular injection. Intradermal injections can cause stinging at the time of injection. There can also be discomfort, redness, and itching for a few days afterwards. Very rarely a small sore can form at the time of injection which can longer to heal or cause scarring.

Skin punch biopsy

Skin punch biopsy is a commonly performed diagnostic procedure. The potential risks include minor bruising, bleeding, and skin discomfort. A 4-6mm punch biopsy will be performed using local anaesthetic to reduce discomfort. The injection of anaesthetic can cause stinging during injection which fades quickly as the anaesthetic takes effect. It is common for a minute scar or persistent skin discoloration to be visible once the skin has healed—this usually fades over time but may be permanent. In rare cases, certain individuals can develop more prominent scars (called keloids). We will exclude people from the study who are known to have developed keloids previously, or have a family history of this, because we know this increases the risk of keloids. There is a very small risk of infection following skin biopsy—this is minimized by use of skin antiseptic at the time of biopsy, and careful technique of the doctor performing the biopsy.

Phase 2 participants only (optional): Lymph node fine needle aspiration

FNA is a safe and well-tolerated procedure but, as with any medical intervention, it carries some risks, which the doctor will discuss:

- Pain: The FNA should not be any more uncomfortable than a blood test. Any tenderness afterwards will resolve. You can take a simple painkiller like paracetamol if you need it but avoid aspirin as this may increase the risk of bruising.
- Bleeding: The needle used is fine but bleeding under the skin may sometimes occur after the FNA. It should stop quickly by itself. Any bruising will fade within 2 weeks.
- The risk of bleeding is higher if you are taking any medications that make your blood thinner such as warfarin, aspirin or clopidogrel. Because we are seeking healthy volunteers for the study, it is unlikely that you will be eligible for the study if you have conditions which require these medications, but please let us know before the procedure if you take any blood thinning medications.
- Not enough sample: If the person performing the FNA is not able to collect enough sample, they may decide to repeat the FNA with your permission.
- Infection after the FNA is rare. If you get redness, pain and/or tenderness in the days afterwards you may need antibiotic treatment.

10. Will my General Practitioner (GP) be informed of my participation?

We will send a letter to your GP informing them of your participation in the study. If we incidentally find an issue during the study that may be important for your health (e.g. high blood pressure, blood test abnormalities), we will inform your GP, or ask you to contact them, to ensure appropriate follow-up can be arranged.

11. Will my taking part in the study be kept confidential?

All information that is collected about you during the course of the study will be kept strictly confidential. It is available only to the study team. Responsible members of the University of Oxford may be given access to data for monitoring and/or audit of the study to ensure that the research is complying with applicable regulations.

To help keep your information confidential, your sample and any information recorded about you in this study will be 'de-identified' and assigned a study code. which will be used on all study documents and any electronic database(s). All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

12. Will I be reimbursed for taking part?

You will be compensated for your travel costs, time and inconvenience related to taking part in this study. The total amount of compensation you receive will depend on your degree of involvement:

- £20 if you attend the screening visit, but do not enter the main study (either due to your choice or decision of the study team).
- £75 if you attend the screening visit, and take part in the visit 1 study procedures, but do not complete all study procedures and follow-up (e.g. If you withdraw from the study, either due to your choice or the decision of the study team).
- Phase 2 participants (groups 5-7 only): £400 for completing all study procedures and follow-up.
- Phase 3 and 4 participants (groups 9-12 only): £600 for completing all study procedures and follow-up.
- Phase 2 participants (groups 9 and 10 only): if you provide additional consent to attend for fine needle aspiration of the lymph nodes in your armpits (both sides) on days 5 and 28 of the study, you will be compensated an additional £200 for the time and inconvenience of attending for these procedures (i.e. £800 for full study participation).

You will receive additional compensation if you agree to return for additional study procedures:

- If you agree to be contacted to provide a blood donation in the future for research related to this study, you will be compensated £20 to attend an appointment and provide this sample.

13. What will happen to the samples I give?

Blood and skin samples that you give will be primarily stored and analysed in facilities based at NDORMS, University of Oxford. De-identified samples may be analysed in other hospitals, universities, non-profit institutions or commercial laboratories worldwide by other laboratories, including those overseas.

We will ask for your consent for the use of your samples to be stored indefinitely, and used in future ethically approved studies. If you agree to this, your anonymised samples will be used mainly by local researchers (if applicable), but ethically approved research projects may take place in hospitals, universities, non-profit institutions or commercial laboratories worldwide. If you agree to your samples being used in future research, your consent form will be held until the samples have been depleted or destroyed.

14. What will happen to my data?

UK 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, based in the United Kingdom, is the sponsor for this study, and the data controller and is responsible for looking after your information and using it properly.

We will be using information provided by you in order to undertake this study and will use the minimum personally-identifiable information possible. We will keep identifiable information about you for 12 months after the study has finished. Your bank details will be stored for 7 years in accordance with University of Oxford financial policy. This excludes any research documents with personal information such as consent forms which will be held securely at the University of Oxford for 3 years after the end of the study.

Blood tests sent to local NHS Trust laboratories (including screening and visit 1 blood tests) will be registered using your NHS number, and will thus be visible to other healthcare professionals and retained indefinitely, but only members of the study team will be able to link these results to the other results related to your involvement in this study (via your unique anonymised study identification number).

UK 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://compliance.web.ox.ac.uk/individual-rights

You can find out more about how we use your information by contacting the Chief Investigator, Dr James Fullerton, or Dr Philip Drennan (contact details at the top of this sheet)

15. What will happen if I don't want to carry on with the study?

Participation is entirely voluntary. If you change your mind you can withdraw at any time without giving a reason and without penalty. If you withdraw from the study, any samples and data collected before your withdrawal will be used for research as detailed in this participant information sheet, unless you specifically request otherwise. However, if any of your anonymised data has been incorporated into the study, it will not be withdrawn or erased in order to maintain the scientific integrity of the study.

16. What happens at the end of the study?

The results of this project will be disseminated via standard scientific channels: publication in scientific journals, poster and oral presentations at scientific conferences. The data will contribute to the fulfilment of doctoral research project and presented in the thesis. You will not be able to be identified in any of these. When you enter the study we will ask if you would like to be informed of the results when they become available, and how you would like to receive them (e.g. email, post, and/or link to a website).

17. What if we find something unexpected?

If we incidentally find an issue during the study that may be important (e.g. high blood pressure, blood test abnormalities), we will inform your GP, or ask you to contact them, to ensure appropriate follow-up can be arranged.

18. 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 the Chief Investigator, Dr James Fullerton (contact details at the top of this form) or you may contact the University of Oxford Research Governance, Ethics & Assurance (RGEA) office on 01865 616480, or the director of RGEA, email rgea.complaints@admin.ox.ac.uk.

19. Who is organising and funding the study?

- This study is sponsored by the University of Oxford. It is being funded by The Kennedy Trust for Rheumatology Research, donations to the Oxford University

Botnar Research Centre (The John Climax Donation), the NIHR Oxford Biomedical Research Centre, and Bristol Meyers Squibb.

- All researchers involved in this study are employees of the University of Oxford. No members of the study team will receive additional payments for enrolling you in this study.

20. Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect participants' interests. This study has been reviewed and given favourable opinion by **East of England - Cambridgeshire and Hertfordshire Research Ethics Committee (reference 22/EE/0150)**.

21. Participation in future research:

At the end of the study, we will ask you if you are willing to be approached to be involved in future studies, or to provide additional blood samples for research related to this study. Your contact details will be held separately on password protected computer servers maintained by NDORMS, University of Oxford. Agreeing to be contacted does not oblige you to take part in future research, and you can be removed from this register at any time you wish. If you consent, we will retain a copy of your consent form until such time as your details are removed from our database. The consent form and your details will be kept separate.

22. Further information and contact details:

Please contact Dr James Fullerton (Chief Investigator and Clinical Pharmacologist) or Dr Philip Drennan (Co-Investigator, Clinical Pharmacologist, and Clinical Research Fellow, NDORMS) using the details at the top of this form if you would like further information or to ask any questions

Thank you for reading this information sheet and for considering taking part in this research study.