Participant information sheet

Experimental Human Pneumococcal Challenge:

Effect of asthma on immune response to pneumococcus

What is the purpose of the study?

Pneumonia is a common condition, and a leading cause of death. It is most commonly caused by a bacteria called Pneumococcus.

Very young children and adults who are elderly or have other medical conditions such as asthma are more likely to become ill due to pneumonia. We are not sure why the risk is increased in asthma and would like to study the immune response to this bacteria in asthma. This will help us understand why there is an increased risk of pneumonia in asthma.

Small numbers of these bacteria are often found in the nose. Usually, the carrier does not know the bacteria are there.

Our research team want to study what happens when small numbers of a bacteria (pneumococcus) are put up the nose of people with asthma. We have already studied this in more than 500 volunteers, and have found this type of study to be safe.

This is part of a larger project looking at developing vaccines. We may be able to protect people against severe disease from pneumococcus using a vaccine which could be sprayed into the nose of people with asthma. We don't yet know if this will work.

Do I have to take part?

No. Taking part in this study is voluntary.

Why have I been asked to take part?

We are looking for volunteers who have:

- Mild, well controlled asthma,
- Do not smoke
- Not had a life threatening asthma attack
- Not in close contact with children under 5

We ensure that it is safe for you to take part that your participation will provide helpful information to us. If we find any reason you may be at higher risk of infection, then we will not invite you to take part.

You will not be eligible if:

- You are aged more than 50 years
- You are a regular smoker or have a significant history of daily smoking
- You are in close contact with those who have lower immune levels (such as young children and people with chronic ill health)
- You have taken part in similar research before
- You are allergic to penicillin

- You have heart disease, or lung disease due to smoking
- The study doctor thinks that a health condition, or medication means that you are at increased risk of infection
- If you are pregnant. (We would advise you to use contraception during the study)

What happens if I choose to take part?

1. **Health check** – for safety, we check that you are healthy. This includes a clinical assessment and checklist (as above).
2. **Consent** –We ask you to sign a consent form when you are sure you want to take part.
3. **Taking samples** – We take samples from the nose, throat and blood *(see below)*. We also do a heart tracing (ECG) and breathing tests (described later in the leaflet) again this is to check that you are well enough and to confirm a diagnosis of asthma if not done previously.
4. **Being given drops of pneumococcus in the nose** - We put a few drops of liquid with a small number of bacteria in your nose.
5. **Monitoring**– we will ask you to contact us daily (by phone or text) to make sure you are well
6. **Monitoring visits** – We take samples from your nose to see whether the bacteria is present and if your asthma is affected

This study takes less than four weeks. After six to twelve months we will invite some participants to repeat this study.

A small number of participants may be allocated at random to receive drops of water in their nose rather than pneumococcus bacteria. This is called a **placebo**, and will help us determine if people develop symptoms (e.g. runny nose) *because* of the pneumococcus bacteria, or simply as a reaction to our other study procedures. You will not know if you have received pneumococcus or a placebo until the end of the study, and all participants will follow the same study protocol.

7. We will ask you to complete a symptom questionnaire for seven days during the study. It asks simple questions such as do you have a cough, wheeze etc.

8. We will also ask you to provide details of someone who can be contacted in an emergency, as mentioned in the consent form.

What kind of samples do you take?

- Samples from the ***nose*:**
  1. ***Nasosorption***: To collect cells from your nose we place a small piece of blotting paper inside your nostril for a few minutes

2. ***Nasal probe:*** We run a small plastic rod along the inside of each nostril

3. ***Nasal wash****:* We squirt a little salty water into your nose. After a few seconds the water runs out into a sample bowl. This will tell us about the bacteria in your nose and your immunity.

- **Throat swab**: We wipe the back of your mouth with a sterile swab (like a cotton bud). The laboratory can use this to find out if there are any bacteria or viruses.
- **Blood samples**: We take blood samples from a vein in your arm. We will never take more than 10 teaspoons (50 mls).
- **Breathing tests:** These tests are part of asthma care and you may have had them done before

1. ***Spirometry***: This is a basic breathing test which measures the amount of air that can be blown out of the lungs. This is done using a spirometer and you will be asked to take a deep breath in and blow into the Spirometer as hard and fast as you can, until your lungs are completely empty. This routine will be repeated to ensure the results are consistent. Depending on the results you may be given an inhaler (bronchodilator) and have the test repeated 15-20 minutes later to see if there is any improvement. This is called reversibility.

2. ***FeNO***: This is a breathing test, done using a special machine. It involves blowing air out of the lungs into a machine at a steady rate. This test measures the inflammation in the lungs and is routinely used for diagnosis and monitoring of asthma in clinical practice.

3. ***Peak Expiratory Flow rate (PEFR)***: It is a measure of the fastest rate of air (airflow) that you can blow out of your lungs. It records airflow in litres per minute (L/min). It is measured using a peak flow meter, which is a small device that you blow into. Participants will be shown how to take a peak flow reading. They will be explained to put the marker to zero, take a deep breath, seal their lips around the mouthpiece, and then blow as hard and as fast as they can into the device. They will be asked to note the reading on the chart provided. Each time we will ask them to check the reading three times and record the best of these three.

4. ***Histamine Challenge Test:***

This requires you to inhale a very small dose of a substance called histamine, after which a breathing test is done. . If your breathing does

not change with the first dose, you will be asked to inhale progressively larger doses of histamine. If your airways tighten at any point, you will be given an inhaled bronchodilator that will re-open your airways. The test is stopped if a drop of 20 percent is observed in your breathing test. This test is routinely done to diagnose asthma in clinical practice. This test is optional and may only be carried out in very few participants if required.

You may choose to gift your samples for future research. This may be used to study the DNA from your blood sample, as mentioned in your consent form. If you choose not to donate your DNA you may still take part in the study.

What will happen to my samples?

We will process your samples in laboratories at the Liverpool School of Tropical Medicine (LSTM) and at the Royal Liverpool University Hospital. We will measure the levels of bacteria and viruses in your nose, and we will look in detail at how your immune system responds to the pneumococcus bacteria.

To make full use of your samples, we will store the remainder. In the future, we can then go back to them with new tests to answer new questions. For some specialist tests, we may send samples to laboratories in the UK and abroad.

What will happen at each visit of the first study?

Initial Visit, Pre-screen and Screening appointments (spread over about two weeks)

We explain the study in detail, obtain your signed consent and ask some basic questions to ensure that you are eligible and do some breathing tests. We will also write to your GP to confirm some aspects of your medical history (e.g. which vaccinations you have had before), and inquire about asthma tests.

At the next visit, we will do some more test as detailed earlier, check your blood pressure, temperature and listen to your heart and lungs, breathing tests (FeNO) and blood tests. We will also give you a PEFR meter to measure and record these at home.

If you are well enough to take part in the study, we do the throat swab, nasal samples and other blood tests.

We then book your next appointments. If you have problems and can't come on a specific date, we can be flexible to accommodate you.

⇩ *Between one to seven days after Visit 3:*

Appointment for being given pneumococcus up the nose

We collect samples as described earlier.

We use a dropper to put a small amount of water containing a small number of bacteria into each nostril. Usually, volunteers have no symptoms afterwards. There will be a doctor or nurse available by telephone 7 days a week to answer questions. We will give you a course of antibiotics to keep with you, in case you are unwell, as well as a thermometer to check your temperature at home. ***Every day for the next week, we will need to be in contact with you by phone or text to check that all is well. We advise following your personal asthma plan at all times, and to seek medical help as necessary.***

⇩ *Up to six visits over the next five weeks*

Clinic Appointments on days 2, 7, 9 14, 22 and 29

At each visit, a number of samples will be taken, which may include throat swab, nasal swab, nasal wash, nasal probe and blood tests

⇩

End of the first study	If our laboratory test finds that the pneumococcus bacteria stays in your nose, at this stage we will ask you to take a course of antibiotics to clear it, and we may ask you to be in the re challenge study.

What about the re challenge?

We think that having small number of bacteria in your nose—even for a short time—might protect you against illness from this bacteria, possibly for a long time. But we cannot be certain. To test this, we may ask you to have the pneumococcus put into your nose a second time, after a few months. Y*ou do not have to take part in the re challenge if you do not want to*. These visits will take about 2 to 3 weeks.

What will happen at each visit of the re challenge??

Re=challenge study: pre screen	We make sure you are still fit to take part in the study, by repeating the questions and examination done at the start of the first study. We do the throat swab, nasal wash and blood test, and ask you to monitor PEFRs
	⇩ *1-7 days later*
Appointment for being given pneumococcus up the nose	We use a dropper to put a small amount of water containing a small number of bacteria into each nostril, just like before. Each day for the next week we will ask you to contact the research team by phone or text for seven days to ensure that all is well and to check your temperature reading (again, antibiotics and a thermometer are provided in the study).
	⇩ *Daily phone call or text message for 7 days*
Clinic appointments days 2, 7 and 14	Samples as explained earlier
	⇩

Visit 5: End of the study

At the end of the re challenge, after a final throat swab and nasal wash, if our laboratory confirm that you have had pneumococcus in your nose, we will ask you to take the antibiotic course to clear it.

What are the risks of being in the study?

Risks of being given live bacteria

Because the bacteria are alive, there is a very small risk of infection to you or your close contacts. We do not expect anyone to develop an infection but this is why we choose participants carefully, and monitor them closely. We have experience of using this model safely in more than 500 healthy volunteers, with no reported symptoms.

We provide a thermometer and antibiotics that treat these bacteria. We give you a separate leaflet which explains the safety precautions, and what to do if you feel unwell. If you carry the pneumococcus bacteria in your nose at the end of the study, we will ask you to take the antibiotics to kill the bacteria.

Risks of medical tests during the study

The only side effect of nasal sampling is a little discomfort. Some people experience a runny nose. Some people can feel light-headed after blood tests, and sometimes may have a bruise. All other tests are standard for asthma. If these are outside the normal values, we will inform your GP.

What if there is a problem?

You can contact the research team 7 days a week by phone, to answer your questions and arrange to see you as necessary. We would recommend using and following your personal asthma action plan at times.

What if I wish to complain?

If you wish to complain about any aspect of the study, you can contact the study doctor. You may also use the Royal Liverpool University Hospital's independent complaints department (contact number 01517064903). Making a complaint will not affect the medical care you receive now or in the future.

What if I change my mind, or want to stop?

Even if you do start in the study, you are free to stop at any time and without giving a reason. If you decide not to take part, or to withdraw from the study, this will have no effect on your future health care.

If you decide to stop, we will continue to use the samples and information that we have already collected unless you tell us not to. You will be paid for the visits completed up to that point.

Will my details be kept confidential?

Yes. For safety, we collect information about your medical history and contact details before you take part. The clinical research team use this information to check you are healthy, and to contact you when needed. We will ask your permission to ask your GP to share some of your medical history with us.

We will also collect information which allows us to understand more about the samples, for example, you age or sex. However, those outside of the clinical team are never given information that can identify you. Your samples are given a unique number, and your name is not used.

We do not expect to find anything which would affect your health care. If we do, we will let you and your GP know about it.

All data will be collected and stored at the Royal Liverpool University Hospital and the Liverpool School of Tropical Medicine. It will be stored for a minimum period of 10 years. Your medical notes and research data are may be looked at by those who monitor the research.

Are there any benefits to taking part?

There are no direct benefits to you. You will be a part of what we believe is a valuable research study that may help us to improve medical care of people with asthma.

How much will I get paid?

The money you are paid is compensation for inconvenience, loss of income, and your time. The first payment will be made at the end of part one. If you are eligible and choose to take part in the second study you will receive a second payment at the end of part two. If you receive a placebo instead of pneumococcus, the payment is unchanged. Our payments are listed below:

First Study	**Visit length**	
Initial Visit	45 min	-
Pre-screen appointment	60 min	£40
Screening appointment	30 min	£30
Inoculation with pneumococcus appointment. This includes you making daily telephone/text message contact for the first 7 days. (We will withhold £5 per day if you do not contact us)	30 min	£50
Clinic appointments for samples on days 2 and 7	30 min	£20
Clinic appointment for samples on day 9	20 min	£15
Clinic appointments for samples on days 14 and 22 (*not all participants will be called for day 22)*	15 min	£10

Clinic appointment for samples on day 29	25 min	£20
Re-challenge		
Re-challenge study pre-screen.	45 min	£30
Inoculation with pneumococcus appointment. This includes you making daily telephone/text message contact for the first 7 days. (We will withhold £5 per day if you do not contact us)	30 mins	£50
Re challenge study clinic visit day 2, 7 and 14	20 min	£15

After you have had time to read the information leaflet, a member of our team will discuss the study with you: please ask us if you have questions. You may want to talk to other people about the study: please do so. Take your time to decide if you want to be involved

Contact details

General questions: please contact the research team on 0151 706 3381 during normal working hours.

The Chief Investigator for this study is Dr Jamie Rylance. You may contact him at the Liverpool School of Tropical Medicine, Pembroke Place, Liverpool, L3 5QA, UK. Telephone: 0151 705 3775. This research is sponsored by the Liverpool School of Tropical Medicine and the Royal Liverpool and Broadgreen University Hospitals. It is funded by the Medical Research Council. The research has been reviewed for scientific content by an external panel.
Royal Liverpool University Hospital Independent Complaints Department 01517064903
The National Research Ethics Service Committee has reviewed the study and given approval for it to take place.