PARTICIPANT INFORMATION SHEET

HEALTHY PARTICIPANTS 18-30

The **INSIGHT-AM** trial

INhaled Sargramostim In Groups of Healthy and inTensive care unit participants to study Alveolar Macrophage function

Introduction

You are being invited to take part in a research study. This is because you are a young, healthy individual and therefore eligible for participation. This document will provide you with more detail about the nature of the study itself and what your participation would involve. If anything remains unclear after reading this document or you would like further information, please feel free to ask.

This study involves healthy participants of two age ranges (18-30 and 60+) and critically ill patients in hospital intensive care units (ICUs). It is an educational project looking at the ways in which lung immunity changes as you age and when you are critically ill, and assessing if we can boost lung immunity using an intervention called GM-CSF.

Am I definitely eligible to participate?

We are looking to recruit 18-30 year olds who are in good health, and do not have any risk factors or habits that may cause any disease of the lungs. We therefore are looking for individuals who consider themselves healthy and do not take any regular medications (although contraceptives and skin creams are permitted*). Conditions such as hay fever are not a barrier to taking part, however some conditions such as diabetes or asthma may affect your ability to participate even if you are not on regular medications. We are more than happy to advise and answer any questions you may have and will include our contact details at the end of this document.

As we are studying sensitive cells within the lungs, we cannot recruit anyone who currently smokes or uses e-cigarettes, has smoked within the last year, or who has smoked an equivalent of 20 cigarettes a day for over 2 years of their life**. We will assess all potential participants to ensure they do not have any relevant undiagnosed medical problems.

* Certain other medications are permissible providing they are taken for controlled medical conditions. These include PPIs for acid reflux (such as lansoprazole, omeprazole), drugs for constipation, thyroid replacement (levothyroxine), paracetamol, codeine.

** This is deemed 2 'pack years' and could also be made up by a similar number of cigarettes smoked over a longer duration e.g. 10 cigarettes a day for 4 years, or even 2 cigarettes a day for 20 years.

What is the purpose of this study?

Despite the widespread availability of antibiotics, lung infections such as pneumonia remain a major cause of death and harm particularly in older people as well as critically ill patients in ICUs. Our lungs are unique; to allow us to breathe they must be in constant connection with the environment around them. In order to protect us, our lungs contain a special population of cells within the air pockets that sense the presence of germs, and act to eliminate them. These cells are called Alveolar Macrophages (AMs).

Unfortunately, we still know relatively little about AMs compared to other cells of the immune system. One key reason is that in order to study AMs we need to retrieve them from peoples' lungs using a procedure called a bronchoscopy that must be performed in a hospital. We believe that AMs work less well as you age and when you are critically ill, and the purpose of this study is to help us understand how and why this happens. Furthermore, and perhaps most crucially, we aim to determine if giving an inhaled intervention called GM-CSF can boost the function of AMs.

There is an urgent need to develop safe treatments for severe infections that are resistant to many common antibiotics, owing to years of heavy antibiotic use. GM-CSF, granulocyte-macrophage colony-stimulating factor, is a natural chemical produced in the body that helps AMs develop and function. It can also be produced and delivered as a treatment, called Sargramostim. If we can prove that this improves AM function there could be far-reaching benefits, and it would allow us to study GM-CSF as an alternative or additional treatment for severe lung infections and as a means of preventing lung infections in at-risk groups.

What would taking part involve?

We are looking for 20 healthy individuals within the 18-30 year old age bracket. Your first visit is called a screening visit and can occur any time from one month to one day before the study visits begin. On this occasion we would take formal written consent for your participation in the study, and perform some standard assessments to confirm that you are eligible and in good health. This would include a brief examination of your heart and lungs, measurement of your oxygen levels, an ECG (heart tracing) and spirometry (basic breathing test). A blood sample would also be taken. If we find any abnormal results these may prevent you from participating in the trial. We would inform you of this, as well as your GP, so any abnormalities can be appropriately investigated.

Following your screening visit, if you remain eligible to participate, we will arrange a time for you to come to the hospital on three consecutive days. The process for the first two days is identical. On attending we will again confirm your willingness to participate, briefly examine you, then you will receive either the GM-CSF or a placebo via a nebuliser (a device which can turn a liquid into a fine mist allowing it to be inhaled). The nebulisation takes 10 minutes and we will observe you for 30 minutes afterwards. This is a double-blind study, meaning that neither the researcher nor you as a participant will know whether you are receiving the placebo or the medication.

On the third day you will have a test called a bronchoscopy. This involves a small flexible telescope containing a fibre-optic camera being passed through the nose or the mouth to examine the inside of the lungs. Using this scope, we can take washings from one of your lung lobes in order to obtain a sample of AMs. We typically observe people for a few hours following this procedure. Further detailed information on the bronchoscopy test is contained later in this document.

We will phone you the day after your bronchoscopy to check if you have experienced any side effects. We will remain in contact so that we can arrange a date for you to return after a gap of at least a month. On your return you will again come to the hospital on three consecutive days, receiving a nebulised intervention on the first two days (either GM-CSF or Placebo, whichever you did not receive on your first visits) and a bronchoscopy on day three.

It is important to note that participation is entirely voluntary. You are free to withdraw from the study at any time, and without giving a reason. A decision not to take part, or to withdraw, will in no way affect the health care you receive now or in the future. While we obviously prefer participants to complete all the tests, including the return visit, you are under no obligation to do so.

What happens to the samples you provide?

Blood samples taken during the study are for two purposes. Some of the samples will be taken and processed at the NHS laboratories at the hospital to ensure there are no issues that you prevent you from participating (such as anaemia). Some of the samples taken will be transferred to the laboratories at Newcastle University for further processing as part of the trial as we will also look at the effect that the inhaled GM-CSF has on some of the immune cells within your blood. Although our focus is on immune cells from the lungs, we will be performing a smaller range of tests on a type of immune cells from the blood called neutrophils. It is likely that only small amounts (samples of up to 30mls, about two tablespoons, taken on up to 4 occasions) will be required, however If we have any excess blood that is not required then with your permission it will remain anonymously in our lab to assist future research by the team.

The samples of lung fluid that we obtain from your bronchoscopy will be transported immediately to the laboratories at Newcastle University for analysis. Small volumes of the sample may be transferred to a laboratory in Ghent, Belgium to perform tests that are unavailable locally. These will be labelled only with a study number, and no identifiable information. With your permission, both the blood and lung fluid samples may be frozen and stored in an anonymised form after the completion of the trial, for use in future ethically approved research. Occasionally, as new information becomes available there can be good reasons to perform further tests on the materials we obtained during this study. If this situation should arise, testing will only proceed with your permission, approval from an ethics committee, and the resulting information will remain anonymous.

There are no plans to do any genetic testing on the samples we obtain.

Involvement of GP

Should you consent to participate we will inform your GP of your inclusion in our study. If any abnormal clinical test results emerge during your tests, we would inform you and your GP. This will enable further action to be taken on the results if required.

What are the benefits of taking part?

There is no immediate or direct benefit to you. Your contribution is extremely valuable to us however, and we hope that the results of this study will lead to wider benefits in the future.

What are the potential disadvantages of taking part?

As a healthy participant, you will be opting to receive a medical intervention (inhaled GM-CSF) and procedure (bronchoscopy) that are not clinically necessary. You will also have blood samples taken however we do not anticipate any significant risks from the procedure itself, nor from the volume of blood we would take during the course of your study visits (a maximum of 120mls over four visits, or around 8 tablespoons). Bronchoscopy is an extremely safe procedure that is regularly performed in the NHS. There is a dedicated section later in this document outlining the procedure.

GM-CSF is a medication with a well-established safety profile. It is approved for use as an injection to help the immune system recover after chemotherapy or bone marrow transplants, and it is given as an inhaled medication in a rare lung condition called autoimmune Pulmonary Alveolar Proteinosis. We are aware that side effects can occur with any

medication and ensuring the wellbeing of the participants in this trial is our absolute priority. As a precaution, we will perform breathing tests after any dose of the GM-CSF, and observe participants for 30 minutes. Minor side effects may occur, including headache, fever and muscle aches. It is not safe to use GM-CSF in anyone with a known allergy to yeast-derived products, or any previous reactions to the medication itself. Any reactions that do occur will be formally recorded as part of the trial. We are happy for participants to take paracetamol during their study participation, though ideally not on the morning before their bronchoscopy. We ask participants to refrain from using ibuprofen during the study period.

A final risk to be aware of is the possibility of an incidental clinical findings during your study visits. If we were to find an abnormality on your blood tests, procedure or examinations we would communicate this to you verbally before sending written documentation to you and your GP.

What if there is a problem?

We do not expect anything to go wrong as a result of you taking part in this research study. In the event that something goes wrong and you are harmed during the research due to someone's negligence, then you may have grounds for a legal action for compensation against the Newcastle upon Tyne Hospitals NHS Foundation Trust but you may have to pay your legal costs.

If you have a concern about any aspect of this study, you can speak to a member of the study team who will do their best to answer your questions. Further contact details are included at the end of this information leaflet.

If you are unhappy or have any concerns about any aspect of the study and wish to complain formally and confidentially, you can do so through the NHS complaints procedure. To discuss your concerns or make a complaint you can contact a member of the PALS (Patient Advice and Liaison Service) on 0800 0320 202, or Text/SMS: 0781 5500015 or by visiting northoftynepals@nhct.nhs.uk

Is there any reimbursement for taking part?

Yes. While we are reliant on the generosity of participants we will also reimburse you for time and inconvenience. Following your first bronchoscopy you will receive £150, while after your second bronchoscopy you will receive £200. Payments will be given in the form of gift vouchers, although we may also be able to pay you via bank transfer.

Can I access the results of the research?

Yes, we will be happy to send you a summary of the results after the study is complete. If you would like for us to do this please contact the study email address or either Dr Davidson / Professor Simpson via their email addresses (see Contacts) or inform us during one of your study visits. We will add you to a mailing list and contact you when results are available. We will also publish updates on the designated section of the study website: https://research.ncl.ac.uk/insightam.

We intend for the results of this study to be published in medical and scientific journals and presented at national / international meetings. All information within the public domain will be entirely anonymised. We hope that further research will be funded and performed based on the findings of this study.

Who is organising and funding the study?

The study is funded by the Medical Research Council via their experimental medicine scheme. The research team is made up of staff and clinicians from Newcastle University and Newcastle Hospitals. The research sponsor is The Newcastle upon Tyne Hospitals NHS Foundation Trust.

Who has reviewed the study?

An independent group of people called a Research Ethics Committee (REC) review all research taking place in the NHS. They seek to protect the safety, rights, well-being and dignity of patients and research participants. They have reviewed the INSIGHT-AM trial and given a favourable opinion. The study has also been reviewed by at least 5 independent specialists and a scientific panel chaired by the Medical Research Council prior to their decision to award funding. All aspects of the study are conducted in accordance with the ethical principles originating with the Declaration of Helsinki, and in accordance with Good Clinical Practice (GCP).

How will we use information about you?

We will need to use information from you and from your medical records for this research project. This information will include your name, initials, date of birth, NHS number and contact details. People will use this information to do the research or to check your records to make sure that the research is being done properly. People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead. We will keep all information about you safe and secure. Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

What are your choices about how your information is used?

- You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.
- We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

Where can you find out more about how your information is used?

You can find out more about how we use your information

- at www.hra.nhs.uk/information-about-patients/
- our leaflet available from www.hra.nhs.uk/patientdataandresearch
- by asking one of the research team
- by sending an email to nuth.dpo@nhs.net

Contacts for Further Information

Study email: Insight.am@newcastle.ac.uk

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We offer an independent contact if you wish to discuss the project and your potential participation with an expert who has no involvement of any kind in the trial. They are a fully qualified medical practitioner with a detailed understanding of the medical aspects involved:

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FURTHER SUPPORTING INFORMATION

Full timeline of participation

A breakdown of each study visit follows, showing what each visit would involve, their estimated duration and where these would occur. Some of the procedures mentioned, such as bronchoscopy, will be outlined in greater detail later in this section of the document. Typically, study visits 2-4 are on Tuesday-Thursday with the Endoscopy taking place early on a Thursday morning.

Study Visit 1
Screening visit.
Newcastle upon Tyne Hospitals
Duration: 30 minutes

- Written consent for participation
- Brief history and medical examination of heart and lungs
- Spirometry (simple breathing tests)
- Oxygen saturation (recording of blood oxygen levels taken using a finger probe)
- ECG (simple recording of heart's electrical activity)
- Blood sample
- Agreement of date for future study visits

Study visit 2
Inhaled intervention.
Newcastle upon Tyne Hospitals
Date: Between 1 and 31 days from Study visit 1.
Duration: 45-60 minutes

- Brief history (to ensure you are well on the day)
- Brief examination of heart and lungs
- Oxygen saturation measurement
- Blood sample if screening visit >1 week ago
- COVID lateral flow test
- Spirometry
- A pregnancy test will be required for all women of childbearing potential
- Nebulised intervention will be administered (approximately 10 minutes)
    - You will have been randomised by the research team to receive either GM-CSF or a placebo (a mix of sterile water and salty water called saline) prior to study visit 2.
    - Neither you nor the researcher will know which intervention you are receiving.
- You will be observed for 30 minutes following administration

Study visit 3
Inhaled intervention.
Newcastle upon Tyne Hospitals
Date: The day after study visit 2
Duration: 45 minutes

- Brief history (to ensure you are well on the day)

- Brief examination of heart and lungs
- Oxygen saturation measurement
- Blood sample
- Spirometry
- Nebulised intervention will be administered (approximately 10 minutes)
    - This will be a second dose of the same intervention you received on study visit 2.
- You will be observed for 30 minutes following administration

Study visit 4
Bronchoscopy
Newcastle upon Tyne Hospitals
Date: The day after study visit 3
Duration: 4 hours

- Brief history (to ensure you are well on the day)
- Brief examination of heart and lungs
- Further consent form specific to bronchoscopy
- Oxygen saturation measurement
- Spirometry
- Blood sample / insertion of cannula (to allow administration of any medications if required during bronchoscopy)
- Bronchoscopy and lavage (washings from lung)
- Observation following procedure

Telephone follow-up
Date: The day after study visit 4

- Phone call to confirm you feel well and have not experienced any issues following your bronchoscopy.
- We may agree a date for your return visits in ≥1 month.

Return visit 1
Inhaled intervention.
Newcastle upon Tyne Hospitals
Date: At least 1 month following study visit 4
Duration: 45-60 minutes

- Brief history (to ensure you are well on the day and no other circumstances have changed in the elapsed time)
- Brief examination of heart and lungs
- Oxygen saturation measurement
- Blood sample
- Spirometry
- A pregnancy test will be required for all women of child bearing potential
- Nebulised intervention will be administered (approximately 10 minutes)
    - Following your previous randomisation, you will now receive the other intervention (i.e. GM-CSF if you received placebo previously.
    - Neither you nor the researcher will know which intervention you are receiving.
- You will be observed for 30 minutes following administration

Return visit 2
Inhaled intervention.
Newcastle upon Tyne Hospitals
Date: The day after return visit 1
Duration: 45 minutes

- Brief history (to ensure you are well on the day)
- Brief examination of heart and lungs

- Oxygen saturation measurement
- Blood sample
- Spirometry
- Nebulised intervention will be administered (approximately 10 minutes)
    - This will be a second dose of the same intervention you received on return visit 1.
- You will be observed for 30 minutes following administration

Return visit 3
Bronchoscopy
Newcastle upon Tyne Hospitals
Date: The day after return visit 2
Duration: 4 hours

- Brief history (to ensure you are well on the day)
- Brief examination of heart and lungs
- Further consent form specific to bronchoscopy
- Oxygen saturation measurement
- Spirometry (simple breathing tests)
- Blood sample / insertion of cannula (to allow administration of any medications if required during bronchoscopy)
- Bronchoscopy and lavage (washings from lung)
- Observation following procedure

Telephone follow-up
Date: The day after return visit 3.

- Phone call to confirm you feel well and have not experienced any issues following your bronchoscopy.

Nebulisations

Nebulisation is a means of turning a liquid into a fine mist, or aerosol, allowing it to be inhaled. The aerosol is composed of tiny particles, making it a very effective way of delivering medications to the lungs. A nebuliser is the device which transforms the liquid into an aerosol. They are commonly used in breathing disorders, such as asthma. There are different types of nebulisers which function in different ways. Perhaps the most commonly seen type is called a jet nebuliser, which uses air or oxygen to aerosolise the liquid. For this study, we will be using a small hand-held device called a Vibrating Mesh Nebuliser (VMN) to give the inhaled intervention or placebo. This is a relatively new form of nebuliser that has significant advantages over previous technology. A vibrating mesh creates a small mist out of a liquid medication so it can be inhaled evenly throughout your lungs. It is typically much quieter and quicker to use than a traditional jet nebuliser, and you breathe through a small mouthpiece rather than a larger face mask. Both the GM-CSF and placebo will be administered as 4mls of clear, colourless liquid.

Bronchoscopy and Bronchoalveolar lavage (BAL)

A bronchoscopy is a routine medical procedure typically done to diagnose and investigate various lung disorders. It involves a thin, flexible plastic tube (the scope) being passed via the nose or mouth into the lungs. The tube has a fibre-optic camera to allow us to see inside your lungs, and a small port through which we can insert and retrieve fluid from your lungs.

To ensure your safety during the procedure we ask that you do not consume solid food for 4 hours before the test. You can continue to drink clear fluid until 2 hours before the test. This is to make sure that your stomach is empty and there is no risk of food entering your lungs when your main windpipe is numb.

The preparation for the procedure takes longer than the actual test itself. You will have the test in a dedicated room in the endoscopy department. We will give you low dose of oxygen to breathe through the nose and your heart and breathing will be monitored throughout. A local anaesthetic spray is given to your mouth to numb the back of your throat to prevent any discomfort. This wears off after 1-2 hours. A small plastic tube called a cannula will be inserted into one of your veins. At this point, we will give you a sedative injection if this is your wish. The goal is to make you relaxed and sleepy during the test. We will put a mouth guard in to protect your teeth and the bronchoscope, and the test will begin when you are comfortable.

The actual procedure is typically brief, lasting only around 10-15 minutes. The scope is passed through your mouth (or nose if you prefer) to your voice box. At this point, we spray local anaesthetic down the scope to numb your vocal cords and airways. This will initially trigger a cough, briefly feeling as if you have swallowed a small amount of liquid down the wrong way. Once your cough has eased we pass the scope into the lungs and perform the bronchoalveolar lavage. This involves washing sterile saline (a medical solution of salty water) into a single segment of your lung. There are 19 segments in total, and only one will be involved in the procedure. We gently suck the saline back up through the scope into specimen pots. This fluid now contains cells from deep inside your lungs that can be analysed in our labs. We remove the scope as soon as we have collected the fluid samples.

Bronchoscopy is considered an extremely safe procedure, even more so in healthy volunteers. The monitoring of your heart and breathing is routine practice in the NHS, and enables us to give you more oxygen in the extremely unlikely event that your oxygen levels cause any concern. We would stop the procedure immediately if so.

The biggest drawback of the procedure is that some people find it temporarily unpleasant. We will outline some of the elements that people may find difficult:

- We numb the mouth with a throat spray that has a bitter taste. It may make your eyes water briefly and can leave the sensation that your mouth is ‘swollen’ and it is hard to swallow. In reality there is no swelling, this is merely the sensation of having a numb throat. We do ask you not to eat / drink until your sensation has returned. This can vary from individual to individual but usually takes around 2-3 hours.
- Some people have a very strong gag reflex that triggers before we reach the vocal cords. This eases once we have applied more local anaesthetic to the vocal cords. In the rare situation that you find the test intolerable, we will simply stop the procedure.
- Most people have a bout of coughing when we first numb the vocal cords, or when we pass the scope into the lungs for the first time. Some people even feel it to be a choking sensation. It is almost invariably less than 10 seconds in duration and does not affect your breathing or oxygen levels. We may ask you to do simple things like count slowly to 10, as this has proven to be an effective means of reassurance through a very brief discomfort.
- People rarely cough much during the lavage, though it does occur on occasions.

A note on sedation:

- While people generally find bronchoscopy perfectly tolerable with just local anaesthetic as described above, some patients prefer to have a sedative (midazolam) before the procedure. This is more common in clinical practice when we are performing longer and more complicated bronchoscopies in the presence of lung disease.
- If you would like to have sedation, this is perfectly acceptable however there are added precautions to consider following the test.
- If you have received sedation**, you must be accompanied home by a friend or relative.**
- If you have received sedation, **you must not return to work duties, drive, cycle, operate moving machinery, or sign any legal document for the remainder of that day**. This is because sedation can have subtle effects on your judgement and memory for a few hours.

Following the procedure:

- You will rest and be observed in the recovery room of the endoscopy suite. The staff will monitor your pulse, blood pressure, temperature and oxygen levels.
- After 2-3 hours you should be allowed to eat, once the effects of the local anaesthetic throat spray have worn off. Your throat may feel a little sore at first, but this is typically mild and eases quickly.
- A doctor will see you and confirm you are safe to return home, unless any unexpected findings arise.
- Following a bronchoscopy and BAL some people experience a rise in temperature later in the day / night. This is not a cause for alarm and is usually brief. Paracetamol is a simple and effective treatment for this.
- Occasionally people find themselves coughing more frequently for approximately 24 hours after a bronchoscopy, and very occasionally they can find specks of blood in their phlegm. This is also entirely normal and not a cause for concern.
- People are typically able to resume full normal activities the day after a bronchoscopy with no limitations.
- We will contact you by telephone the following day to ensure you are well, and answer any questions you may have.