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Investigating the effects of a novel inhaled intervention on the function of alveolar macrophage cells in the lung

Submission date 10/01/2024	**Recruitment status** Recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 11/01/2024	**Overall study status** Ongoing	
Last Edited 18/11/2026	**Condition category** Respiratory	

Plain English summary of protocol

Background and study aims

Human lungs contain specialised cells (alveolar macrophages, AMs) that detect inhaled germs. In mice, AM function depends on a molecule called GM-CSF. How GM-CSF influences human AM function is poorly understood. Older people and critically ill patients are at increased risk of pneumonia, potentially because their AMs function less well. It is therefore possible that inhaled GM-CSF could boost AM function and prevent pneumonia and similar diseases in people at high risk. This study aims to learn more about the role of GM-CSF in human AM function, why AMs function less well as you age or while you are critically unwell, and to determine if giving GM-CSF as an inhaled intervention may offer protection against pneumonia and similar diseases. The study will provide entirely novel information about human AM function. A beneficial, safe role for inhaled GM-CSF may suggest future trials assessing whether this treatment can safely prevent pneumonia in patients at the highest risk.

Who can participate?

Young and healthy non-smoking participants (age 18-30), older and healthy non-smoking participants (aged 60 and over), adult participants who are critically unwell from intensive care units, and healthy non-smoking participants aged 18 or over for a final element of the study.

What does the study involve?

Twenty healthy young people who answer an advert and provide informed, written consent will inhale GM-CSF or a “dummy” treatment (placebo) on two consecutive days. Neither the participant nor the research team will know which has been inhaled. On the third day, the participant’s lungs will be “washed” in the hospital to retrieve AMs. These will be taken to a laboratory where their capacity to kill bacteria will be tested, with the identification of molecules involved in these processes. Participants will repeat this process after at least a month, except if they inhaled GM-CSF last time, they will inhale a placebo next time (and vice versa).

Twenty healthy older people will complete the same procedures as described above.

Twenty critically ill patients will receive inhaled GM-CSF or the placebo on two days and have their lungs washed on the third (i.e. they will undergo the procedures once only).

Finally, the study will determine whether laboratory-derived AM-like cells can faithfully mimic human AM function (to potentially avoid washing peoples' lungs to get AMs in the future) – therefore, up to twenty healthy people will have a lung wash with no inhalation procedures and function in AMs and AM-like cells with be compared.

What are the possible benefits and risks of participating?
For the healthy participants, there are not expected to be any direct benefits to the individual. There are risks involved with receiving a medical intervention and procedure that are not clinically required. The inhaled GM-CSF has a well-established safety profile. Side effects such as fever, headaches, wheezing or allergic reactions are rare. Participants will be monitored all after they receive the intervention. The bronchoscopy can be uncomfortable for some people and can cause minor side effects such as cough, sore throat and fever. While the study is reliant on the generosity of potential participants a small reimbursement will be planned for their time and inconvenience.

The critically ill participants may theoretically derive a benefit should they be randomised to receive GM-CSF and it is proved to help augment the function of their AMs. There is, however, no guarantee that they will derive any benefit at all. Patient safety is a priority and neither the nebulised intervention nor the bronchoscopy will be given if there are concerns about the safety of the participant given their critical illness state.

Where is the study run from?
The Newcastle upon Tyne NHS Foundation Trust (UK)
Supplemental recruitment for critically ill participants is expected from the ICU at Sunderland Royal Hospital (UK)

When is the study starting and how long is it expected to run for?
February 2023 until April 2026

Who is funding the study?
Medical Research Council (MRC) Experimental Medicine grant scheme (UK)
National Institute for Health and Care Research (NIHR) (UK)

Who is the main contact?
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Additional identifiers

Integrated Research Application System (IRAS)
319303

Central Portfolio Management System (CPMS)
58971

Study information

Scientific Title
INhaled Sargramostim In Groups of Healthy and inTensive care unit participants to study Alveolar Macrophage function - a clinical trial (INSIGHT-AM trial)

Acronym
INSIGHT-AM

Study objectives
1. A high Rac1/RhoA ratio promotes effective human AM phagocytosis.
2. In ageing and critical illness increased RhoA activation impairs AM phagocytosis.
3. GM-CSF restores the Rac1/RhoA ratio and efficient phagocytosis in AMs.
4. iPSC-like AMs share more phenotypic and functional similarities with AMs from younger people than with AMs from older people.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 22/12/2023, Wales REC 6 (Floor 4, Institute of Life Science 2, Swansea University, Swansea, SA2 8PP, United Kingdom; +44 (0)2920 785738; Wales.REC6@wales.nhs.uk), ref: 23/WA/0298

Primary study design
Interventional

Study design
Randomized controlled trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied

Respiratory

Interventions

1. Healthy young participants.
Adverts will be distributed in Newcastle University by email and poster, and through appropriate other channels, seeking healthy participants aged 18-30. Those responding will be sent a participant information sheet and invited to a screening visit within the Newcastle upon Tyne Hospitals trust. A study doctor will take a short history and perform a cardiorespiratory examination. Written, informed consent will be taken before any study-related procedures. The doctor will also measure the participant's blood oxygen saturation (this involves placing a probe on a finger), and spirometry (this involves taking the deepest breath one can, then blowing out into a tube as fast as one can and for as long as one can). A blood sample will be taken, and an ECG (electrocardiogram) performed (this involves placing electrodes on the chest and an electrical recording of the heart measured). The purpose of the screening visit is to check whether the participant is healthy, whether they have any features of infection, and whether they understand the study. If no features of illness are present, they will be invited to return for 3 visits at some point within the next month. Participants will be randomised (1:1) to Sargramostim or placebo.

VISIT 1 - The same procedures carried out in the screening visit will be repeated (except ECG, and blood tests if done within the last week). A COVID lateral flow test will be performed (the participant will proceed no further if this is positive), and anyone of childbearing potential will be asked to perform a pregnancy test (if this is positive the participant will not proceed in the study). The participant will then inhale Sargramostim/placebo via a special nebuliser then they will be observed clinically for at least half an hour with oxygen saturations and spirometry repeated. The participant will be asked to return the next day. The whole visit is expected to take approximately an hour (including the period of observation).

VISIT 2 - Everything in visit 1 will be repeated except the COVID and pregnancy tests, i.e. the participant will again receive nebulised Sargramostim or placebo, and be asked to return the next day, having had no food or drink for 4 hours (sips of water are allowed). A blood test will be performed.

VISIT 3 - Cardiorespiratory examination, spirometry, oxygen saturations and blood taking will be repeated, and it will be confirmed that the participant has not eaten for 4 hours or drank for 2 hours. The participant will then have bronchoscopy and bronchoalveolar lavage (BAL) performed by an experienced respiratory physician in the Endoscopy Unit, RVI. The participant will have an intravenous cannula sited in a vein, supplemental oxygen will be delivered via their nose throughout, and continuous ECG monitoring will be performed, as is standard clinical practice. Local anaesthetic gel and/or spray will be applied to the mouth and nose to reduce discomfort and the participant will be offered an intravenous sedative (e.g. midazolam) as part of routine clinical practice. If the participant accepts a sedative they will be informed that they must not drive, operate moving machinery or drink alcohol for the rest of that day, and they must be accompanied home after the procedure by a friend or by taxi.

When the participant is comfortable a flexible fibre-optic bronchoscope will be passed through the mouth (via a mouthguard) or nose and into a sub-segment of the lung under direct vision. Twenty millilitres of normal saline will be instilled via the bronchoscope, gently aspirated back, and the fluid discarded (the "bronchial/bronchiolar sample"), then 120 mL of normal saline will be instilled (3 aliquots of 40 mL typically). The bronchoscope will then be removed. The participants will be taken to a recovery area and observed for up to 4 hours and allowed home if they are well, as judged by doctors in the research team. They will be issued with a contact

number to call if they feel unwell. The BAL fluid will be immediately taken to the lab for analysis. The next day the participant will be phoned by a clinical member of the study team to check that they feel well.

After at least 1 month, the participant will return and repeat visits 1-3 (with the telephone check-up the following day), the only difference being that if they received Sargramostim on visits 1 and 2, they will now receive a placebo (and vice versa). The research team will remain blinded to this allocation.

2. Older healthy participants.
The procedures are the same as for healthy, young participants with the exception that adverts will be distributed via different sources including the Clinical Research Network, the NIHR Biomedical Research Centre for Ageing and Long-Term Conditions, bowling clubs, Lions Clubs, Rotary Clubs, and to other organisations frequented by fit, older people. Adverts will be for participants aged ≥60.

3. Patients in intensive care units (ICUs).
Patients in the ICUs will be screened by clinical and research staff in the ICU. Patients who are intubated and mechanically ventilated (i.e. they are unconscious and having their breathing assisted by a ventilator machine) and who are not being treated for pneumonia will be eligible. Exclusion criteria will be assessed. A cardiorespiratory examination will be performed. As the patients are unconscious written, informed assent will be sought from a personal legal representative (usually the family member considered as the next-of-kin). Where such a person is not identified, a professional legal representative may provide the assent. If and when the patient recovers capacity they will be asked to provide informed, written consent after being provided with details of the trial. If patients are eligible and if assent/consent has been provided, the patients will be randomised (1:1) to receive nebulised Sargramostim or placebo. On day 1, a blood sample will be taken, the nebuliser will be entrained into the patient's ventilator circuit and the patient will inhale Sargramostim or placebo, and this will be repeated on day 2. On day 3, a bronchoscopy and BAL will be performed as described above with the only differences being that the level of sedation and oxygen to be given will be determined by the doctors delivering routine care to the patient and that the bronchoscope will be passed through the endotracheal tube (the tube going into the lung) rather than through the mouth or nose. As the patient is sedated and under good clinical care there is no phone call the next day. Unlike in 1 or 2, no further procedures take place after this point.

4. Bronchoscopy only
For the comparison of alveolar macrophages to laboratory-derived alveolar macrophage-like cells, volunteers aged 18 and over (identified by the mechanisms described in 1 and 2) will come for a screening visit as described above. If they remain eligible and have provided written, informed consent, they will return on a day within the next month. On the day of the visit, they will have a cardiorespiratory examination, spirometry, oxygen saturations, an ECG, and a blood sample. They will then have a bronchoscopy and BAL as described above. A clinical member of the team will phone the next day to check that they remain well.

Intervention Type
Procedure/Surgery

Primary outcome(s)

The proportion of alveolar macrophages phagocytosing ≥2 zymosan particles measured using laboratory phagocytosis assays in each bronchoscopy sample obtained for the duration of the study

Key secondary outcome(s)
1. Bronchoscopy Safety measured by recording oxygen saturations and continuous ECG monitoring following standard clinical SOPs during each bronchoscopy
2. Safety of nebulised interventions measured by the recording of oxygen saturations, post-inhalation spirometry and the recording of serious adverse reactions during each nebulisation
3. The function of alveolar macrophages measured using functional assays (including phagocytosis, efferocytosis and bacterial killing), cell signalling analyses, receptor expression and cell surface marker analyses, cytokine levels, transcriptomics and proteomics after each bronchoscopy
4. The function of neutrophils in blood measured using phagocytosis assays, bacterial killing, reactive oxygen species generation, and flow cytometry for cell surface markers after blood sampling in each participant
5. The function of monocytes in blood measured using flow cytometry to measure mHLA-DR after blood sampling in each participant

Exploratory outcome measurements (applicable to parallel group element only):
Safety will be measured using data collected through a review of patient records at day 30 following inclusion. This will include the following variables:
1. 30-day all-cause mortality
2. Length of ICU stay (data collected at day 30 and not beyond)
3. Frequency of serious adverse reactions overall and between groups (SAEs will be collected from the start of the first nebulisation until 24 hours after the BAL)
4. Duration of intubation and mechanical ventilation (data collected at day 30 and not beyond)
5. Blood tests at 24 hours post-intervention for toxicity assessment (blood white cell count, blood neutrophil count, serum liver transaminases and serum creatinine)
6. Respiratory infections (data collected at day 30 and not beyond; principally to assess the safety of BAL in parallel group element).

Completion date
30/04/2027

Eligibility

Key inclusion criteria
Younger healthy participants:
1. Aged 18-30 years old
2. World Health Organization (WHO) Performance Status Score 0
3. Provision of informed, written consent from the participant
4. A negative highly sensitive urine pregnancy test for women of childbearing potential (WOCBP) *
(*A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile**. The post-menopausal state is defined as “no menses for 12 months without an alternative medical cause.” When it cannot be confirmed that a participant is post-menopausal a pregnancy test will be conducted.
**Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.)

Older healthy participants:
1. Aged > = 60 years old
2. WHO Performance Status Score 0
3. Provision of informed, written consent from the participant
4. A negative highly sensitive urine pregnancy test for women of childbearing potential (WOCBP)

Patients in the ICU:
1. Patients intubated and mechanically ventilated in ICU for > = 2 days
2. Provision of informed, written consent from a personal or legal representative
3. A negative highly sensitive urine pregnancy test for WOCBP

Bronchoscopy only:
1. Aged 18 or over old
2. WHO Performance Status Score 0
3. Provision of informed, written consent from the participant
4. A negative highly sensitive urine pregnancy test for women of childbearing potential (WOCBP)

Participant type(s)
Healthy volunteer, Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 Years

Upper age limit
80 Years

Sex
All

Total final enrolment
0

Key exclusion criteria
Younger healthy participants:
1. SARS-CoV-2 positive
2. Current smoker of cigarettes or e-cigarettes
3. Past smoking history of > = 2 pack-years
4. Any smoking in the last year
5. Pregnancy or lactation
6. Temperature > = 38°c
7. Systolic blood pressure < 90 mmhg
8. Evidence of atrial or ventricular arrhythmia on ecg
9. Oxygen saturations < 94% breathing room air
10. FEV1 < 80% of predicted

11. FEV1:FVC ratio < 70% predicted
12. Haemoglobin < 10 g/L
13. Blood platelets < 100x109/L
14. Estimated GFR < 60ml/min/1.73m2
15. Any previous cardiovascular events
16. Diabetes
17. Known allergy to GM-CSF, yeast-derived products, mannitol, sucrose or tromethamine
18. Regular prescribed oral, inhaled, subcutaneous or intravenous medication with the following exceptions:
18.1. Topical skin treatments
18.2. Contraceptives
18.3. PPIs
18.4. Drugs for constipation
18.5. Levothyroxine
18.6. Aspirin
18.7. Paracetamol
18.8. Codeine

Older healthy participants:
1. SARS-cov-2 positive
2. Current smoker of cigarettes or e-cigarettes
3. Past smoking history of > = 2 pack-years any smoking in the last year
4. Pregnancy or lactation
5. Temperature > = 38°c
6. Systolic blood pressure < 90 mmhg
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12. Blood platelets < 100x109/L
13. Estimated GFR < 60ml/min/1.73m2
14. Any previous cardiovascular events
15. Diabetes
16. Known allergy to GM-CSF, yeast derived products, mannitol, sucrose or tromethamine
17. Regular prescribed oral, inhaled, subcutaneous or intravenous medication with the following exceptions:
17.1. Topical skin treatments
17.2. Contraceptives
17.3. Hormone Replacement Therapy
17.4. Antihypertensives (single agent only)
17.5. PPIs
17.6. Drugs for constipation
17.7. Levothyroxine
17.8. Aspirin
17.9. Paracetamol
17.10. Codeine

Participants in ICU:
The majority of the exclusion criteria relate to factors known to increase risk of complications at bronchoscopy and BAL.
1. Known allergy to GM-CSF, yeast derived products, mannitol, sucrose or tromethamine

2. Current treatment for pneumonia (i.e. If treating clinicians have prescribed antibiotics specifically to treat suspected or confirmed pneumonia)
3. Arterial partial pressure (pao2) less than 8 kpa on fio2 greater than 0·7
4. Positive end-expiratory pressure greater than 15 cmh2o
5. Peak airway pressure greater than 35 cmh2o
6. Heart rate greater than 140 beats per minute
7. Mean arterial pressure less than 65 mmhg
8. Bleeding diathesis (platelet count < 20×10^9/L or international normalised ratio > 3)
9. Intracranial pressure greater than 20 mmhg
10. Estimated GFR < 15 ml/min/1.73m2
11. Immunosuppressant medication (maintenance corticosteroids up to an equivalent of prednisolone 10mg once daily will be eligible for inclusion)
12. Pregnancy or lactation
13. ICU consultant considers bronchoscopy and bronchoalveolar lavage to be unsafe for the patient

Participants for Bronchoscopy-only element:
1. SARS-cov-2 positive
2. Current smoker of cigarettes or e-cigarettes
3. Past smoking history of > = 2 pack-years
4. Any cigarette smoking in the last year
5. Pregnancy or lactation
6. Temperature > = 38°c
7. Systolic blood pressure < 90 mmhg
8. Evidence of atrial or ventricular arrhythmia on ECG
9. Oxygen saturations < 94% breathing room air
10. FEV1 < 80% of predicted
11. FEV1:FVC ratio < 70% predicted
12. Haemoglobin < 10 g/L
13. Blood platelets < 100x109/L
14. Estimated GFR < 60ml/min/1.73m2
15. Any previous cardiovascular events
16. Diabetes
17. Regular prescribed oral, inhaled, subcutaneous or intravenous medication with the following exceptions:
17.1. Topical skin treatments
17.2. Contraceptives
17.3. Hormone Replacement Therapy
17.4. Antihypertensives (single agent only)
17.5. Ppis
17.6. Drugs for constipation
17.7. Levothyroxine
17.8. Aspirin
17.9. Paracetamol
17.10. Codeine

Date of first enrolment
22/01/2024

Date of final enrolment
31/03/2027

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Sunderland Royal Hospital
Kayll Road
Sunderland
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SR4 7TP

Study participating centre
Freeman Hospital
Freeman Road
High Heaton
Newcastle upon Tyne
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NE7 7DN

Study participating centre
Royal Victoria Infirmary
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NE1 4LP

Sponsor information

Organisation
Newcastle upon Tyne Hospitals NHS Foundation Trust

ROR
https://ror.org/05p40t847

Funder(s)

Funder type
Government

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, Medical Research Committee and Advisory Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
National Institute for Health and Care Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study will be published as a supplement to the results publication

IPD sharing plan summary
Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			18/11/2026	No	No
Study website		11/11/2025	11/11/2025	No	Yes