Study Protocol

Exploratory Clinical Study of Microdosing NAP for Optical Molecular Imaging in Human Lungs

NAP

Co-sponsors	University of Edinburgh & NHS Lothian ACCORD The Queen's Medical Research Institute 47 Little France Crescent Edinburgh EH16 4TJ
Funder	Medical Research Council
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Chief Investigator	Dr Kev Dhaliwal
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EudraCT number 2011-006169-17

Signatures

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Professor Tim Walsh		05/02/2015
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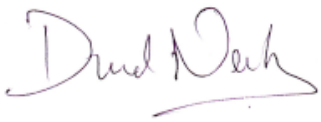
Professor Dave Newby		05/02/2015
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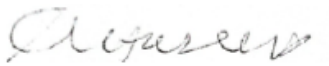
Professor Chris Haslett		05/02/2015
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LIST OF ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for University of Edinburgh and NHS Lothian
ABG	Arterial Blood Gas
AE	Adverse Event
ALI	Acute Lung Injury
ARDS	Adult Respiratory Distress Syndrome
AR	Adverse Reaction
CRF	Case Report Form
CRP	C Reactive Protein
CTA	Clinical Trials Authorisation
CXR	Chest X-Ray
DMSC	Data Monitoring and Safety Committee
DPFS	Developmental Pathway Funding Scheme
ECG	Electrocardiogram
ECRF	Edinburgh Clinical Research Facility
FBC	Full Blood Count
FC	Functional Capacity
FDG PET	Fludeoxyglucose Positron Emission Tomography
FEV1	Forced Expiratory Volume (1 second)
FiO2	Inspired Oxygen Concentration
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
HIV	Human Immunodeficiency Virus
HNE	Human Neutrophil Elastase
ICU	Intensive Care Unit
IMP	Investigational Medicinal Product
ISF	Investigator Site File
LFTs	Liver Function Tests
MHRA	Medicines Health Regulatory Authority
MI	Molecular Imaging
MRC	Medical Research Council
NAP	Neutrophil Activation Probe
PaO2	Partial Pressure of Arterial Oxygen
PCLE	Probe Based Confocal Endomicroscopy
PEEP	Positive End Expiratory Pressure
PISRC	Phase I/First-in-Human Study Review Committee

QP	Qualified Person
R&D	Research and Development
RIE	Royal Infirmary of Edinburgh
REC	Research Ethics Committee
RML	Right Middle Lobe
RLL	Right Lower Lobe
SAE	Serious Adverse Event
SpO2	Oxygen Saturations of pulsatile blood
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
TOPS	The Over Volunteering Prevention System
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TSE	Transmissible Spongiform Encephalopathy
UAR	Unexpected Adverse Reaction
U&Es	Urea and Electrolytes
VAP	Ventilator Associated Pneumonia
WGH	Western General Hospital

INVESTIGATOR STATEMENT

Exploratory clinical study of microdosing NAP for optical molecular imaging in human lungs

I agree to conduct the study according to this protocol, the principles of Good Clinical Practice (GCP) and the applicable regulatory requirements. Any changes in procedure will only be made if necessary to protect the safety, rights or welfare of the participants.

I agree to take responsibility for the conduct of the study and to ensure that all other staff involved are adequately informed about the protocol and amendments, and their study-related duties and functions.

Signature

Dr Kev Dhaliwal

27/07/2015

Chief Investigator	Signature	Date

LAY SUMMARY

Seriously ill patients may develop a complication called acute lung injury (ALI), a form of inflammation in which lung tissue is filled by fluid containing white blood cells called neutrophils. ALI is common and is often fatal (for example in the USA it is estimated that 190,000 patients develop ALI per annum, of whom 75,000 die). No pharmacological treatment has been shown to improve ALI.

Data from animal models and patients strongly suggest that neutrophils are central to disease progression. However no bedside methods exist to rapidly and accurately determine in seriously ill patients if neutrophils are present and if they are releasing damaging enzymes such as elastase. As such, the investigating team have developed and synthesised, to clinical grade, an imaging agent called NAP (Neutrophil Activation Probe). This detects activated neutrophils and also the damaging enzyme, human neutrophil elastase (HNE). We have extensively tested NAP in animal models for efficacy and safety. It reliably detects activated neutrophils and is not toxic.

NAP is a small molecule that is delivered in tiny doses (called microdoses) to areas of inflammation in human lungs through a bronchoscope. The activity of NAP is visualised by imaging though a tiny camera that is also introduced through the bronchoscope. This camera system is now widely used throughout the world in over 150 sites.

We therefore aim to test the utility and safety of NAP in an exploratory clinical study. The study involves the delivery of NAP to 6 healthy volunteers followed by delivering NAP to 3 patients in ICU with suspected ALI.

In the healthy volunteers study, healthy male volunteers recruited from the University of Edinburgh will be invited to participate.

In the ICU study, patients will be recruited from the ICU in the Royal Infirmary of Edinburgh (RIE) and the Western General Hospital (WGH), Edinburgh.

If the study (which is supported by the Medical Research Council) demonstrates safety and also the ability to image activated neutrophils, we have secured further follow on funding to perform a clinical validation study.

PROFESSIONAL SUMMARY

Acute lung injury (ALI)/adult respiratory distress syndrome (ARDS) is clinically important (16% of mechanically ventilated patients acquire ALI, of whom one third die), yet no pharmacological therapy has been shown to impact significantly on outcome. This is in part due to inadequate stratification of patients with neutrophil predominant ALI/ARDS and the inability to determine disease activity and hence target therapy.

Molecular Imaging (MI) offers a potential strategy to visualize neutrophil activity *in vivo in situ*. Indeed FDG PET has been used to image neutrophil activity but it is not a bedside modality, and moving critically ill patients to remote scanners is dangerous and expensive and there there are currently no bedside 'smart' MI solutions that can guide, at the cellular/functional level, the diagnostic or therapeutic pathway in patients with inflammatory lung disease. Indeed, in ICU, there is a specific need to rapidly diagnose patients with deteriorating gas exchange, particularly those with chest X-ray (CXR) shadowing. Such CXR infiltrates result from numerous causes including cardiac failure, fluid overload, secondary pneumonia and ALI/ARDS. All require different treatments but, at present, options to distinguish these conditions are severely limited, resulting in empirical 'blunderbuss' antimicrobial therapy and non-correction of the primary condition. There is now a pressing need to rapidly stratify such patients to inform focused implementation of specific targeted therapies.

Activated neutrophils and their histotoxic products, particularly human neutrophil elastase (HNE), have been specifically implicated in the pathogenesis of ALI/ARDS, and there is considerable clinical interest in new drugs in this area. However, there is currently no way of rapidly determining whether new therapeutic candidates are exerting their predicted effects *in situ* in the human lung prior to embarking upon major clinical trials. Such a solution would inevitably accelerate the pathway of new drugs to clinical application.

The Proposed Solution: probe-based confocal laser endomicroscopy (pCLE) combined with direct intra-pulmonary instillation of microdoses (pharmacologically-inactive and non-toxic) of a highly specific and sensitive 'smartprobe' (***NAP***) will detect neutrophil activity and the presence of active HNE in the lungs of ventilated ICU patients.

pCLE itself safely provides high-resolution, real-time images of the human lung at cellular resolution *in situ*. Alone, however, it provides no functional or molecular information. We have therefore embarked on a discovery programme to synthesise highly sensitive smartprobes, detectable by pCLE and specifically directed against key inflammatory events. This provides a new dimension of clinical application for this cutting-edge technology. *NAP,* the prototype has now been validated *in vitro* and *in vivo* where it is effective at a dose of <10µg and generates a powerful fluorescent signal in <30 sec. Our pilot study aims are to apply the combined utility of pCLE and NAP in healthy volunteers and patients with inflammatory lung disease. The study will also provide a prototypic foundation that can be applied to future smartprobes, not only in the lung but also in any organ accessible to endoscopy.

The primary end-point will be to visualise the delivery of a microdose of NAP in 6 healthy volunteers and 3 ICU patients. Demonstration of activated neutrophils by pCLE in ICU would be expected to lead directly to clinical validation trials in patients with ALI/ARDS.

1 INTRODUCTION

1.1 BACKGROUND

Critically ill patients commonly develop acute lung injury (ALI) characterised by accumulation of neutrophil polymorphs in the alveolar space with attendant fluid 'leak' across the alveolar-capillary membrane.[1] The complication develops secondary to a wide range of primary pathologies, broadly classifiable into ALI secondary to pulmonary disease (e.g. pneumonia or aspiration of gastric contents) or extra-pulmonary disease (e.g. major extrathoracic trauma or sepsis). An American European Consensus Conference provided a pragmatic clinical definition for ALI[2] fulfilled by,

- acute onset,
- the development of bilateral infiltrates on a frontal chest x-ray,
- impaired oxygenation (a PaO_2:FiO_2 ratio of ≤ 300mmHg) and
- the absence of left atrial hypertension (either on clinical grounds or by a measured pulmonary arterial wedge pressure of ≤18 mmHg).

A more severe form of ALI, adult respiratory distress syndrome (ARDS), fulfills the same criteria but requires a PaO_2:FiO_2 ratio of ≤ 200mmHg. ALI and ARDS therefore represent continua of the same clinical spectrum.[2]

ALI is common and has a high mortality. For example, a comprehensive study in the USA estimated that 190,000 Americans develop ALI each year, approximately 74,000 of whom die.[3] High rates of ALI have also been described in intensive care units (ICUs) in Europe and the UK.[4-6] To place the clinical significance of ALI in context, it has been estimated that the mortality due to ALI is similar to that attributable to conditions such as human immunodeficiency virus (HIV), breast cancer or asthma.[7] It is increasingly recognised that ALI/ARDS not only causes high mortality but consigns a high proportion of survivors to chronic morbidity and ill health.[8,9]

Despite significant research efforts using a wide and logical range of drugs, no pharmacological treatment has yet been shown to impact significantly upon mortality from ALI/ARDS.[10] Indeed the only medical intervention yet shown to influence mortality has been a 'protective' mechanical ventilation strategy.[11] ALI therefore remains common, with an unacceptable associated mortality and morbidity. The lack of effective treatment may reflect the crucial role played by the blood neutrophil in the pathogenesis of ALI. Neutrophils are white blood cells, which are rapidly recruited to sites of inflammation during infection where they ingest and clear bacteria. In ALI this reaction appears inappropriate or over-exuberant and the neutrophil releases toxins which directly injure the lung.[12] Reduction in neutrophil accumulation remains difficult to achieve by pharmacological means.

1.2 RATIONALE FOR STUDY

Our group has an interest in the factors regulating the recruitment of neutrophils to the inflamed lung.[13-15] We have also had a long interest in imaging neutrophils [16-18]. Recently a multidisciplinary collaboration has been formed with Professor Mark Bradley in the Department of Chemistry to develop novel methodologies to image neutrophil activation. Funded by a MRC DPFS award, we have generated a compound that is non-toxic and functional as an optical imaging agent to detect activated neutrophils. It is delivered as a microdose locally in the alveolar space and neutrophil activity imaged using pCLE [19-21]. (A microdose [22] is so small that it is not intended to produce any pharmacologic effect when administered to humans and therefore is also unlikely to cause an adverse reaction. For practical purposes this dose is defined as 1/100th of that anticipated to produce a pharmacological effect, or 100 micrograms, whichever is the smaller) It is envisaged NAP will be widely used in the future to detect neutrophil activity within the human lung in ICU to direct diagnostic and therapeutic decisions.

The tools and the expertise available locally, present a unique opportunity to assess the effectiveness and safety of delivering NAP to healthy volunteers and patients in ICU as a prelude to larger definitive clinical validation studies.

The study has 2 parts

Part A will evaluate the imaging parameters and safety of delivering NAP to 6 healthy volunteers within the MHRA accredited phase I unit at the Edinburgh Clinical Research Facility (ECRF)

In Part B we shall assess NAP delivery to 3 patients in ICU with suspected ALI/ARDS and pulmonary infiltrates at the RIE and WGH.

2 STUDY OBJECTIVES

2.1 OBJECTIVES

2.1.1 Primary Objective

The primary objective is to deliver NAP as a microdose to 6 healthy volunteers and 3 patients in ICU and to test if ***activated neutrophils within the alveolar space can be detected with NAP and pCLE over background autofluorescence***

2.1.2 Secondary Objectives

The secondary objective is to deliver NAP and to observe if ***NAP is non-toxic.***

2.2 ENDPOINT MEASURES FOR EXPLORATORY CLINICAL STUDY

2.2.1 Primary Endpoint

- Visualise the delivery of a microdose of NAP in healthy volunteers and ICU patients.
- Delineate the presence of activated neutrophils within CXR infiltrates in ventilated patients with suspected ALI/VAP.

2.2.2 Secondary Endpoints

Safety and tolerability as assessed by occurrence of adverse events (AEs) and serious adverse events (SAEs).

3 REGULATORY REQUIREMENTS

The protocol will be submitted to the REC for ethical approval. Local R&D Management and Edinburgh Clinical Research Facility (ECRF) phase I committee (PISRC) approval before the first participant is recruited. The study is 'First in Man' but the maximum dose level required is defined as a microdose within the relevant ICH M3(R2) guidelines. A CTA will be submitted to the MHRA.

4 STUDY DESIGN

The study is designed in 2 parts;

Part **A**) is a dose escalation in 6 healthy volunteers to deliver NAP and designed to assess the imaging parameters of NAP in the healthy lung and to monitor any unexpected serious adverse events (SAEs). No volunteer will be permitted to take part more than once.

Only if part A is successfully completed and the data monitoring and safety committee (DMSC) permit, part B will be undertaken. The REC will be informed of the outcome of part A and the DMSC decision to proceed.

Part **B**) is an exploratory clinical study in ICU to provide preliminary 'proof of concept' in 3 patients with suspected inflammatory lung disease.

4.1 A) Delivery of NAP to healthy volunteers

Volunteers will return on a morning agreed after the screening medical described in Section 7.1 below. A brief history (pertaining to upper and lower respiratory tract symptoms) and respiratory examination will be repeated. Spirometry will be performed before proceeding.

For Volunteers, 1-4, they will be bronchoscoped and pCLE performed of the right middle lobe (RML). Immediately following this, NAP will be instilled via microcatheter into the RML and pCLE performed again of the RML.

Bronchoscopy will be performed using a standardised protocol and procedure employed throughout our work thus far.[14] Briefly, local anaesthesia will be applied topically to the throat. Sedation with intravenous midazolam will be optional. Electrocardiogram (ECG) trace and SpO_2 will be monitored continuously. A flexible fibreoptic bronchoscope will be passed per-orum or nasally and the bronchoscope wedged into the medial segment of the right middle lobe. The alveoflex will be passed down the working channel and alveoscopy performed with upto 4 transbronchial passes. Following this, the alveoflex will be withdrawn and a microcatheter passed into the medial segment of the RML and NAP instilled. Immediately following this pCLE will be performed as described above.

For volunteers, 5 and 6, they will be bronchoscoped and pCLE performed of the right lower lobe (RLL) and right middle lobe (RML). Immediately following this, NAP will be instilled via microcatheter into the RLL and RML and pCLE performed again of the RLL and RML. The dose of NAP will be divided between 2 segments in the RLL and one segment in the RML. The volunteer will receive a total of 80mcg (+/-20%) NAP.

Bronchoscopy will be performed using a standardized protocol and procedure employed throughout our work thus far.[14] Briefly, local anesthesia will be applied topically to the throat. Sedation with intravenous midazolam will be optional. Electrocardiogram (ECG) trace and SpO_2 will be monitored continuously. A flexible fibre-optic bronchoscope will be passed per-orum or nasally and the bronchoscope wedged into right lower and middle lobes. The alveoflex will be passed down the working channel and alveoscopy performed with upto 4 transbronchial passes per segment. Following this, the alveoflex will be withdrawn and a microcatheter passed into the RLL and RML and NAP instilled. Immediately following this pCLE will be performed as described above.

The volunteer will return to the ECRF after the procedure and will be monitored for a further 2 hours after which he can eat and drink. Volunteers will remain within the ECRF overnight. In the morning if, on assessment, volunteers observations are within acceptable parameters and they have a satisfactory cardio-respiratory examination, they will be discharged from the ECRF, with a number to contact should they feel unwell. The volunteers will be telephoned 3 days after dosing to enquire about any possible late unexpected adverse events.

6 volunteers will receive a dose escalation of NAP (below) on 6 separate days (each at least 6 days apart). After each episode, data will be submitted to the DMSC for approval to proceed to the next volunteer. The DMSC opinion will be documented and available to the ECRF prior to subsequent dosing events.

Table 1

Volunteer number	Dose of NAP (+/- 20%) (mcg)	Volume of NAP (mls)(80mcg/5mls)
1-2	5	0.312
3-4	10	0.625
5-6	80	5

Blood will be drawn just before bronchoscopy and delivery of NAP (t=0) and at t= 4 hours (±30mins). For participants 5 and 6 an additional blood sample (less than 5 ml) will be collected

at t=1 hour (±30 mins) for analysis to demonstrate the systemic uptake, or lack thereof, of the IMP. For participants 5 and 6, the first and second urine voiding following dosing will be collected for the same purpose. Spirometry will then be repeated 4 hours (±30mins) after NAP delivery and the following morning. Bloods will be taken again in the morning. After each dosed volunteer has completed the 3-day follow up, clinical and laboratory data will be checked by the sponsor's representative prior to submission to the DMSC by the investigatory team. All data will be recorded on paper case report forms (CRFs). A summary of assessments and events is shown in table 2 below.

Table 2

	Day of screening	Study day on arrival	Following NAP delivery	1 hour after NAP delivery (± 30mins)	4 hours after NAP delivery (±30 mins)	Overnight	24 hours (±30 mins)
CXR	✓						✓
Cardiorespiratory examination	✓	✓			✓		✓
Bloods: FBC, U&Es, LFTs, CRP	✓	✓			✓		✓
Additional blood test for IMP level (Volunteers 5 and 6 only- non safety)				✓			
Spirometry	✓	✓			✓		✓
Informed consent	✓						
Urine collection for IMP level (non safety)			✓				
Observations, pulse, temperature, oxygen saturation	✓	✓	✓	✓	✓	✓	✓

4.2 B) Delivery of NAP to 3 patients in ICU with pulmonary infiltrates

ICU patients will be screened daily by ICU research nurses. If they fit the inclusion criteria described in Section 5.3, they or their personal/professional legal representative will be approached by a member of the research team to obtain consent. The attending consultant will also be approached and only after also gaining permission from the attending consultant will the patient be considered for inclusion into the study.

The pulmonary infiltrates will be identified on a CXR, which has been performed as part of routine clinical care and bronchoscopy and pCLE performed as above. A CXR will be performed immediately before the procedure. pCLE will be performed on areas without infiltrates as well as the affected segment/s. Following this, NAP will be instilled into the affected segment/s and unaffected segment/s via a microcatheter . A total of 80 mcg (+/-20%) of NAP will be delivered

to the patient divided between the affected and unaffected segments. pCLE will be subsequently performed on the segments in which NAP has been delivered. We have performed bronchoscopy in over 70 patients in ICU over the last 5 years [14]. The whole procedure including delivery of NAP will take approximately 30 minutes. The table below summarise the events and data to be collected before and after the procedure.

In addition, we intend to collect an additional sample (less than 5 ml) at t= 7.5 mins (±2.5 mins) for analysis to demonstrate the systemic uptake, or lack thereof, of the IMP. For these participants, the urometer will be emptied at the time of bronchoscopy and then any urine passed over the next 2 hours will be collected to demonstrate the systemic uptake, or lack thereof, of the IMP.

Table 3

	Day of screening	Immediately pre procedure (within 1 hour)	7.5 mins (+/- 2.5mins)	2 hours (+/- 30 mins)	6 hours (+/- 30 mins)	24 hours (+/- 30 mins)
CXR	✓	✓				✓
Cardiorespiratory examination	✓					
NAP blood sampling (non-safety)			✓			
Bloods: FBC, U&E's, LFTs, CRP	✓			✓	✓	✓
ABG		✓		✓	✓	✓
Urine Collection for IMP (non-safety)			✓	✓		
Attending ICU consultant permission	✓					
Informed consent	✓			✓	✓	✓
Observations, pulse, temperature, oxygen saturation	✓	✓		✓	✓	✓
All ventilator settings, PEEP, oxygenation, P:F ratio	✓	✓		✓	✓	✓

5 STUDY POPULATION

Part A: The study population will be comprised exclusively of healthy male volunteers.

Part B: The study population will be comprised of male patients in ICU (RIE and WGH) with pulmonary infiltrates.

5.1 NUMBER OF PARTICIPANTS

A total of 6 participants will be recruited for Part A.

A total of 3 patients will be recruited for Part B.

5.2 INCLUSION CRITERIA FOR PART A

For part A, healthy male volunteers aged between 18 and 40.

5.3 INCLUSION CRITERIA FOR PART B

5.4 Ventilated male patients over the age of 18 in the ICU.

5.5 EXCLUSION CRITERIA FOR PART A

A patient will not be eligible for inclusion in the study if any of the following criteria apply at entry:

1. Age < 18 or >40 years
2. History of any chronic or ongoing acute illness (with particular reference to asthma, upper respiratory tract infection, lower respiratory tract infection, bronchiectasis, congenital heart disease, ischaemic heart disease, valvular heart disease, diabetes mellitus, chronic renal impairment, urinary tract infection)
3. Any current medication
4. Any history of previous reactions to flourescein or any other anaphylaxis
5. Abnormal physical signs detected at cardiorespiratory examination
6. Temperature >37.3 degrees Celsius
7. Oxygen saturation <95% breathing room air
8. Haemoglobin, white cell count or platelet count outside the normal laboratory reference range
9. Blood sodium, potassium, urea, creatinine, bilirubin, alanine aminotransferase, random glucose or C-reactive protein outside the normal laboratory reference range
10. Forced expiratory volume in one second (FEV1) or forced vital capacity (FVC) <80% predicted
11. FEV1:FVC ratio <70%
12. Any significant cardiorespiratory abnormality detected on chest x-ray
13. Peripheral venous access insufficient to support 14 gauge cannulae.
14. General practitioner confirmation of eligibility as a healthy volunteer not received
15. Failure to provide suitable identification (passport/driving licence)
16. Refusal to consent to enter details in 'The Over Volunteering Prevention System' (TOPS) database
17. Positive urine drug screen
18. Participation in any other interventional study or less than three months since their last participation in an interventional study
19. Female

5.6 EXCLUSION CRITERIA FOR PART B

1. Age <18years
2. Any contraindication for bronchoscopy [22,23]
3. Refusal for participation by attending consultant
4. Fi02 >70%
5. PEEP>10cm
6. Recent pneumothorax (whilst on ventilator)
7. Any history of previous reactions to flourescein or any other anaphylaxis
8. Participation in any other interventional study or less than three months since their last participation in an interventional study
9. Female

6 PARTICIPANT SELECTION AND ENROLMENT

6.1 APPROACHING AND IDENTIFYING POTENTIAL PARTICIPANTS FOR PART A

An advert will be placed on University of Edinburgh email lists and on University of Edinburgh notice boards. Potential participants will be asked to make contact with the research team only if they consider themselves to be healthy. Interested individuals will be invited to contact the research team who will send out information on the study (participant information sheets and consent forms). Participants sent such information will be invited to contact the research team to arrange a screening visit (section 6.3 below) or to decline participation. If no reply is received after 2 weeks, the research team will send a reminder.

6.2 APPROACHING AND IDENTIFYING POTENTIAL PARTICIPANTS FOR PART B

After screening by members of the routine healthcare team in ICU, the patient or if incapacitated, their personal/professional legal representative will be approached by a member of the research team. A professional legal representative will be a clinician responsible for the medical treatment of the patient if they are independent of the study or a person nominated by the healthcare provider and will only be approached if a personal legal representative is not available. Direct face-to-face approach will be made. If the patient is conscious and the clinician in charge judges the patient to have capacity to provide informed consent then he will be approached directly. The first approach will always be by a member of the research team who is a qualified nurse or doctor.

6.3 SCREENING FOR ELIGIBILITY

For part A:
Volunteers who contact the research team will be invited to attend for a screening visit. This will take the form of;

- a short history
- cardiorespiratory examination
- full blood count
- urea & electrolytes, liver function tests, random blood glucose, C-reactive protein
- CXR
- spirometry
- oxygen saturation
- urine toxicology screen
- consent for the study
- consent for details to be submitted to the TOPS database
- Volunteer's GP being contacted regarding health status and suitability to participate

These are performed with the sole intention of identifying potential exclusion criteria as listed in section 5.4.
A medically qualified member of the research team will perform the history, examination and investigations.

For part B
ICU patients will be screened by the ICU research team for inclusion and exclusion criteria.

6.4 CONSENTING PARTICIPANTS

For healthy volunteers, eligible subjects will be asked to consider giving written consent. This will be taken by a medically qualified member of the research team.
In ICU, patients who are ventilated and are judged by the clinician in charge to be able to provide informed consent- they will be given a written information sheet fully explaining the procedure with expected benefits and potential outcomes and risks. Consent will be obtained by clinically qualified members of the team. For ventilated patients who are not able to consent,

their personal/professional legal representative will be approached by the research team in person-they will be given a written information sheet fully explaining the procedure with expected benefits and potential outcomes and risks.

Consent will be obtained by clinically qualified members of the team. One original will be signed and 2 copies made. The original will be filed in the patient's notes along with the Information sheet. One copy will be given to the patient/patients personal/professional legal representative and one stored in the trial master file (TMF).

6.5 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

For ineligible patients and eligible volunteers who are not subsequently entered into the study, the reason for ineligibility or non-recruitment will be entered on the paper CRF. Only anonymised data will be entered on to the paper CRF and this will include gender, age, "ineligible" or "non-recruitment" and the associated reason.

6.6 WITHDRAWAL OF STUDY PARTICIPANTS

Participation in the study is voluntary. A participant has the right to discontinue or completely withdraw from the study at any time for any reason. The Investigator has the right to discontinue a participant from the study at any time if it is deemed to be in the volunteer's or patient's best interest. The reason and circumstances for premature discontinuation will be documented in the participant's Case Report Form (CRF).

6.6.1 Reasons for Discontinuing Participants

Reasons for discontinuation of the study **may** include

Bronchoscopy

- intolerance of the scope (i.e. unable to intubate the trachea)
- marked coughing

6.6.2 Discontinuation Procedures

If a participant chooses to withdraw completely from the study and all study assessments this will be recorded in the CRF. Any concerns expressed by the participant will be addressed by the research team.

7 INVESTIGATIONAL MEDICINAL PRODUCT AND PLACEBO

7.1 STUDY DRUG

7.1.1 Study Drug Identification

Neutrophil Activation Probe sterile solution (NAP)
The final dosage form of the investigational medicinal product (IMP) consists of 80 µg (+/- 20%) of the drug substance NAP dissolved in 5 mL of sterile Phosphate Buffered Saline (PBS) pH 7.4 solution, presented in sterile nitrogen filled glass vials. The solution is intended for direct instillation into the distal lung delivery via a microcatheter at microdose levels (<100 µg). Upon contact with neutrophils and/or the enzyme elastase, NAP will give a specific fluorescent signal that will be detected by pCLE.

7.1.2 Study Drug Manufacturer

The synthesis of NAP is carried out using standard solid phase chemistry at a GLP compliant manufacturing site, Aptuit Laurus, India. No materials at risk of transmitting transmissible spongiform encephalopathy (TSE) are used in the manufacturing process. NAP manufacture and filling, under aseptic conditions, and QP release are performed by Pharmacy Production Unit, Western Infirmary, 100 University Place Glasgow, G12 8TA, and are carried out according to Good Manufacturing Practices. The quality of the product is controlled by ensuring

compliance to internal specifications set with due regard to European guidance on the control of IMPs.

7.1.3 Labelling and Packaging

NAP labelling and packaging is being carried out by Pharmacy Production Unit, Western Infirmary, Glasgow.

7.1.4 Storage

The IMP is to be stored at room temperature. Stability studies have been conducted to confirm the stability of NAP formulation over the proposed study duration. NAP will be stored in the pharmacy at the RIE.

7.2 OTHER MEDICATIONS

7.2.1 Non-Investigational Medicinal Products

Paracetamol (in the event of significant symptoms of fever)

Salbutamol (in the event of bronchospasm)

Oxygen (in the event of hypoxia)

Adrenaline (in the event of anaphylaxis).

8 STUDY ASSESSMENTS

8.1 OUTCOME MEASURES

8.1.1 Primary Outcome Measures

This is an exploratory clinical study. The primary outcome measure is measurement of fluorescence and imaging parameters determined using pCLE and Cellvizio viewer software.

8.1.2 Other Measured Variables

Safety in part A and part B and initial proof of concept in ICU to detect neutrophil activation.

8.1.3 Processing and Analysis of Blood Samples

'Screening visit' and all other blood samples will be sent to the hospital laboratories for assessment of full blood count, urea and electrolytes, blood glucose, liver function tests and C-reactive protein.

8.2 SAFETY ASSESSMENTS

8.2.1 Clinical

In part A, Clinical assessment will be on a rolling basis throughout the study days (table 2). 'Vital signs' (pulse, blood pressure, temperature and oxygen saturation) will be measured on arrival and at least hourly (±10mins) over the course of the day. The only exceptions will be that monitoring will be suspended overnight if the volunteer is sleeping comfortably. In this exception, the volunteer can be observed directly and continuous heart rate monitoring will continue, and additional monitoring can be re-initiated immediately if there are any features of clinical distress. During bronchoscopy there is continuous monitoring of ECG trace and oxygen saturation. Spirometry in part A will be a primary safety assessment with a greater than 15% reduction from baseline defined as significant.

In part B, patients will be within ICU and be continually monitored.

8.2.2 Blood Tests

In part A, blood tests (FBC, LFTs, U&Es, CRP) are submitted as outlined in table 2. In part B, blood tests are submitted as outlined in table 3.

9 ADVERSE EVENTS

The Investigator is responsible for the detection and documentation of events meeting the criteria and definitions detailed below.

Full details of contraindications and side effects that have been reported following administration of the IMP can be found in the Investigator's Brochure (IB).

Participants will be instructed to contact their Investigator at any time after consenting to join the trial if any symptoms develop. All adverse events (AE) that occur after joining the trial must be reported in detail in the Case Report Form (CRF) or AE form. In the case of an AE, the Investigator should initiate the appropriate treatment according to their medical judgment. Participants with AEs present at the last visit must be followed up until resolution of the event.

9.1 DEFINITIONS

An **adverse event** (AE) is any untoward medical occurrence in a clinical trial participant which does not necessarily have a causal relationship with an investigational medicinal product (IMP).

An **adverse reaction** (AR) is any untoward and unintended response to an IMP which is related to any dose administered to that participant.

A **serious adverse event** (SAE), **serious adverse reaction** (SAR). Any AE or AR that at any dose:

- results in death of the clinical trial participant;
- is life threatening*;
- requires in-patient hospitalisation^ or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- consists of a congenital anomaly or birth defect;
- results in any other significant medical event not meeting the criteria above.

*Life-threatening in the definition of an SAE or SAR refers to an event where the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.

^Any hospitalisation that was planned prior to inclusion into the study will not meet SAE criteria. Any hospitalisation that is planned post inclusion into the study will meet the SAE criteria.

A suspected unexpected serious adverse reaction (SUSAR) is any AR that is classified as serious and is suspected to be caused by the IMP, that it is not consistent with the information about the IMP in the Summary of Product Characteristics (SmPC) or Investigators Brochure.

9.2 IDENTIFYING AEs AND SAEs

In part A, all AEs and SAEs will be recorded from the time a participant signs the consent form to take part in the study until 3 days after the participant has been dosed.
For part A, a member of the research team will ask about the occurrence of AEs/SAEs during and on a surveillance call 3 days after the participant is dosed. Open-ended and non-leading verbal questioning of the participant will be used to enquire about AE/SAE occurrence. Participants will also be asked if they have been admitted to hospital, had any accidents, used any new medicines or changed concomitant medication regimens. If there is any doubt as to whether a clinical observation is an AE, the event will be recorded. If the healthy volunteer participant is unavailable by phone at this time, a reasonable number of attempts to contact the participant by telephone will be made to follow up on safety outcomes as described in the consent process.

In part B, all AEs and SAEs will be recorded from the time the NAP is delivered and until 3 days after dosing.

AEs and SAEs may also be identified via information from support departments e.g. laboratories. The laboratory may fax the results directly to ACCORD. Details of the fax number will be placed on the laboratory request form as well as the mobile phone number of the Chief Investigator.

9.3 RECORDING AEs AND SAEs

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event. The Investigator will then record all relevant information in the CRF and on the SAE form (if the AE meets the criteria of serious).

Information to be collected includes dose, type of event, onset date, Investigator assessment of severity and causality, date of resolution as well as treatment required, investigations needed and outcome.

9.4 ASSESSMENT OF AEs AND SAEs

Seriousness, causality, severity and expectedness will be assessed by the Chief Investigator. The Investigator is responsible for assessing each AE.

The Chief Investigator (CI) may not downgrade an event that has been assessed by an Investigator as an SAE or SUSAR, but can upgrade an AE to an SAE, SAR or SUSAR if appropriate.

9.4.1 Assessment of Seriousness

The Investigator will make an assessment of seriousness as defined in Section 9.1.

9.4.2 Assessment of Causality

The Investigator will make an assessment of whether the AE/SAE is likely to be related to the IMP according to the definitions below.

- Unrelated: where an event is not considered to be related to the IMP.
- Possibly Related: The nature of the event, the underlying medical condition, concomitant medication or temporal relationship make it possible that the AE has a causal relationship to the study drug. The assessment of causality will be made against the reference safety information found in the Investigators Brochure.

Where non Investigational Medicinal Products (NIMPs) e.g. rescue/escape drugs are given: if the AE is considered to be related to an interaction between the IMP and the NIMP, or where the AE might be linked to either the IMP or the NIMP but cannot be clearly attributed to either one of these, the event will be considered as an AR. Alternative causes such as natural history of the underlying disease, other risk factors and the temporal relationship of the event to the treatment should be considered and investigated.

9.4.3 Assessment of Expectedness

If an event is judged to be an AR, the evaluation of expectedness will be made based on knowledge of the reaction and the relevant product information documented in the IB.

The event may be classed as either:

Expected: the AR is consistent with the toxicity of the IMP listed in the IB.

Unexpected: the AR is not consistent with the toxicity in the IB.

9.4.4 Assessment of Severity

The Investigator will make an assessment of severity for each AE/SAE and record this on the CRF or SAE form according to one of the following categories:

Mild: an event that is easily tolerated by the participant, causing minimal discomfort and not interfering with every day activities.

Moderate: an event that is sufficiently discomforting to interfere with normal everyday activities.

Severe: an event that prevents normal everyday activities.

Note: the term 'severe', used to describe the intensity, should not be confused with 'serious' which is a regulatory definition based on participant/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe.

9.5 REPORTING OF SAEs/SARs/SUSARs

Once the Investigator becomes aware that an SAE has occurred in a study participant, the information will be reported to the ACCORD Research Governance & QA Office **immediately or within 24 hours**. If the Investigator does not have all information regarding an SAE, they should not wait for this additional information before notifying ACCORD. The SAE report form can be updated when the additional information is received.

The SAE report will provide an assessment of causality and expectedness at the time of the initial report to ACCORD according to Sections 10.4.2, Assessment of Causality and 10.4.3, Assessment of Expectedness.

The SAE form will be transmitted by fax to ACCORD on **+44 (0)131 242 9447** or may be transmitted by hand to the office or submitted via email to Safety.Accord@ed.ac.uk. Only forms in a pdf format will be accepted by ACCORD via email.

Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the investigator and request the missing information.

All reports faxed to ACCORD and any follow up information will be retained by the Investigator in the Investigator Site File (ISF).

9.6 REGULATORY REPORTING REQUIREMENTS

The ACCORD Research Governance & QA Office is responsible for pharmacovigilance reporting on behalf of the co-sponsors (Edinburgh University and NHS Lothian).

The ACCORD Research Governance & QA Office has a legal responsibility to notify the regulatory competent authority and relevant ethics committee (Research Ethics Committee (REC) that approved the trial). Fatal or life threatening SUSARs will be reported no later than 7 calendar days and all other SUSARs will be reported no later than 15 calendar days after ACCORD is first aware of the reaction.

ACCORD will inform Investigators at participating sites of all SUSARs and any other arising safety information.

An Annual Safety Report/Development Safety Update Report will be submitted, by ACCORD, to the regulatory authorities and RECs listing all SARs and SUSARs.

9.7 FOLLOW UP PROCEDURES

After initially recording an AE or recording and reporting an SAE, the Investigator will follow each participant until resolution or death of the participant. Follow up information on an SAE will be reported to the ACCORD office.

AEs still present in participants at the last study visit will be monitored until resolution of the event or until no longer medically indicated.

10 PREGNANCY

Pregnancy is not considered an AE or SAE; however, the Investigator will collect pregnancy information for female partners of dosed male participants who become pregnant while participating in the study. The Investigator will record the information on a Pregnancy Notification Form and submit this to the ACCORD office within 14 days of being made aware of the pregnancy.

Female partners of dosed male participants who become pregnant while participating in the study will be followed up until following the outcome of the pregnancy.

11 TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

11.1 TRIAL MANAGEMENT GROUP

The study will be co-ordinated by a Project Management Group, consisting of Dr Kev Dhaliwal, Professor Tim Walsh and Professor Chris Haslett.

A Delegation Log will be prepared for each site, detailing the responsibilities of each member of staff working on the trial.

11.2 DATA MONITORING AND SAFETY COMMITTEE

An independent DMSC will be established to oversee the safety of subjects in the study. ***They will be informed of every participant's response to NAP.*** The DMSC will comprise local and external experts who will be contacted at the end of each participant's involvement. A decision to proceed will be required after each dosed participant as detailed in a DMSC charter monitored by ACCORD. At the end of part A, a DMSC report will also be sent to the regional ethics panel for recording successful completion of part A.

11.3 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection(s). In the event of an audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

11.4 RISK ASSESSMENT

A comprehensive review and risk assessment of the study will be performed by the PISRC prior to the approval of the study. A contingency plan will be agreed and this will be audited by the CRF QA Manager once the study is underway. An independent risk assessment will be performed by an ACCORD Clinical Trials Monitor to determine if monitoring is required and if so, at what level. An independent risk assessment will also be carried out by the ACCORD Quality Assurance Group to determine if an audit should be performed before/during/after the study and if so, at what locations and at what frequency.

11.4.1 Potential Risks to Subjects and Measures in Place to Minimise Risk

11.4.1.1 Blood sampling/venous access

Venepuncture is associated with mild discomfort and bruising, and there is a small risk of vasovagal syncope. The number of venepuncture procedures to be performed will be minimised by drawing blood from venous cannulae wherever possible. Bruising will be minimised by ensuring that venepuncture is carried out by experienced personnel. Withdrawal of cannulae/needles will be accompanied by firm pressure on the puncture for at least one minute. The risk of syncope will be minimised by having subjects recumbent or semi-recumbent for all venepuncture.

11.4.1.2 NAP delivery

In part A, 5-80µg (+/- 20%) NAP will be delivered via a microcatheter instilled in the working channel of the bronchoscope. The exact time and dose delivered will be recorded. Delivery of fluorescein and other dyes have been reported with no recorded adverse effects.

Participants will be observed after NAP delivery and medications required to treat any adverse effects will be readily available (e.g. paracetamol in the event of significant symptoms of fever, salbutamol in the event of bronchospasm, oxygen in the event of hypoxia, adrenaline in the

event of anaphylaxis). The bronchoscopy suite and the ECRF are within the RIE and all resuscitation equipment and cardiac arrest teams are immediately to hand. Hence all the necessary facilities to safely undertake this procedure are available.

11.4.1.3 Bronchoscopy and pCLE

Participants will be closely monitored during and after the bronchoscopy. Healthy volunteers in part A will receive topical anaesthesia to the oral cavity (to prevent discomfort). The subject will also be offered light sedation in the form of intravenous midazolam.

Bronchoscopy can be associated with low oxygen levels (rarely). Prior to bronchoscopy subjects will be given supplemental oxygen. The test will be stopped if the oxygen levels fall significantly. Predefined stopping criteria are established and if oxygen levels as measured by pulse oximetry falls to <92% from baseline, bronchoscopy will be stopped.

Other risks of bronchoscopy include aspiration (in the rare event of vomiting while there are significant gastric contents) and arrhythmia if too much local anaesthetic is used. We have minimised the risk of vomiting firstly by offering 'non-sedated' bronchoscopy (thereby eliminating midazolam, the principal cause of nausea), and secondly by ensuring at least 8 hours between the patient's breakfast and bronchoscopy. The risk of arrhythmia will be minimised by limiting airway anaesthesia to ≤10ml 2% lignocaine and by the fact that we study healthy volunteers (in whom arrhythmia is extremely rare).[23]

For part A, bronchoscopy will be undertaken in a dedicated bronchoscopy suite. All the necessary facilities to safely undertake this procedure are available. For part B, bronchoscopy will be performed in ICU.

Subjects can experience cough and fever within 24 hours following bronchoscopy. Subjects will be advised how to manage symptoms (paracetamol as anti-pyretic and analgesia) and given a telephone number to contact a member of the study team if any symptoms develop after leaving hospital.

pCLE has been performed in over 500 patients worldwide with no recorded serious adverse events. It is now a routine procedure in many institutions. [19,20] We have performed it locally in ventilated animals and patients with no adverse events.

11.5 STUDY MONITORING AND AUDIT

An ACCORD Clinical Trials Monitor or an appointed monitor will visit the Investigator site prior to the start of the study and during the course of the study if required, in accordance with the monitoring plan. Risk assessment will determine if audit, by the ACCORD QA group, is required. Details will be captured in an audit plan. Audit of Investigator sites, study management activities and study collaborative units, facilities and 3rd parties may be performed. The CRF QA manager will perform audits at key stages of the protocol to ensure compliance with the PISRC decisions.

12 GOOD CLINICAL PRACTICE

12.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).

A favorable ethical opinion will be obtained from the appropriate REC and local R&D approval will be obtained prior to commencement of the study.

12.2 REGULATORY COMPLIANCE

The study will not commence until a Clinical Trial Authorisation (CTA) is obtained from the appropriate Regulatory Authority. The protocol and study conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended.

12.3 INVESTIGATOR RESPONSIBILITIES

The Chief Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

Delegated tasks must be documented on a Delegation Log and signed by all those named on the list prior to undertaking applicable study-related procedures.

12.3.1 Informed Consent

The Chief Investigator is responsible for ensuring informed consent is obtained before any protocol specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants must receive adequate oral and written information – appropriate Participant Information and Informed Consent Forms will be provided. The oral explanation to the participant will be performed by the Investigator or qualified delegated person, and must cover all the elements specified in the Participant Information Sheet and Consent Form.

The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be given sufficient time to consider the information provided. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant will be informed and agree to their medical records being inspected by regulatory authorities and representatives of the sponsor(s) but understand that their name will not be disclosed outside the hospital.

The Investigator or delegated member of the trial team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The participant will receive a copy of this document and a copy filed in the Investigator Site File (ISF) and participant's medical notes.

12.3.2 Study Site Staff

The Chief Investigator must be familiar with the IMP, protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the IMP, protocol and their trial related duties.

12.3.3 Data Recording

The Chief Investigator is responsible for the quality of the data recorded in the CRF at each Investigator Site. The source data plan identifies which source data correspond to CRF data and states which data are recorded directly into the CRF.

12.3.4 Investigator Documentation

Prior to beginning the study, each Investigator will be asked to provide particular essential documents to the ACCORD Research Governance & QA Office, including but not limited to:

- An original signed Investigator's Declaration (as part of the Clinical Trial Agreement documents);
- Curriculum vitae (CV) signed and dated by the Investigator indicating that it is accurate and current.
- Evidence of GCP training within the past two years.

The ACCORD Research Governance & QA Office will ensure all other documents required by ICH GCP are retained in a Trial Master File (TMF), where required, and that appropriate documentation is available in local ISFs.

12.3.5 GCP Training

The Chief Investigator has completed GCP training. The clinical research fellows directly attached to the study will be required to complete GCP training before the first patient is enrolled.

12.3.6 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the Sponsor, its designee, Regulatory Authorities, or the REC. The Chief Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

12.3.7 Data Protection

All Investigators and study site staff involved with this study will comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Access to collated participant data will be restricted to those clinicians treating the participants, representatives of the sponsor(s) and representatives of regulatory authorities.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

13 STUDY CONDUCT RESPONSIBILITIES

13.1 PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of a urgent safety measure, must be reviewed and approved by the Chief Investigator.

Substantial amendments to the protocol must be submitted in writing to the appropriate REC, Regulatory Authority and local R&D for approval prior to participants being enrolled into an amended protocol.

Where amendments result in changes to participant information sheets and/or consent forms, participants who have already signed a consent form and are still taking part in the trial will be asked to review the updated participant information sheets with the research team. Participants will be given the opportunity to ask any questions regarding their ongoing participation and will be asked to sign an updated consent form if they decide to continue with the study.

13.2 PROTOCOL VIOLATIONS AND DEVIATIONS

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, Regulatory Authority and local R&D for review and approval if appropriate.

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsors every 3 months. Each protocol violation will be reported to the sponsor within 3 days of becoming aware of the violation.

13.3 SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the co-sponsors (accord.seriousbreach@ed.ac.uk) must be notified within 24 hours. It is the responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and take the appropriate action.

13.4 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 15 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

13.5 END OF STUDY

In part A, the end of study is defined as 3 days after the last participant's dosing or the resolution of any on going AEs from any participant, whichever is later.

In part B, the end of the ICU study is defined as 3 days after the delivery of NAP in the last patient.

The Investigators and/or the trial steering committee and/or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC and Regulatory Authority within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved.

A summary report of the study will be provided to the REC and Regulatory Authority within 1 year of the end of the study.

13.6 CONTINUATION OF DRUG FOLLOWING THE END OF STUDY

NAP will only be administered once to each participant.

13.7 INSURANCE AND INDEMNITY

The co-sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the co-sponsors' responsibilities:

- The Protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.
- Sites which are part of the United Kingdom's Nation Health Service will have the benefit of NHS Indemnity.

14 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

14.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared in accordance with ICH guidelines.

14.2 PUBLICATION

The clinical study report will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study.

14.3 PEER REVIEW

The results of the study will be disseminated by peer review publication and presentation at national and international meetings.

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APPENDIX 1: Data Monitoring and Safety Committee

Name	Details	Contact Details	Agreed to take part
Dr Geoff Bellingan CHAIR	Medical Director, Critical Care, UCH London. ICU physician	Email: geoff.bellingam@uclh.nhs.uk Tel: 02034479008	✔
Professor Dave Singh	Professor of Respiratory Medicine and Clinical Pharmacologist. Director of Phase I Unit at Manchester University	Email: Dsingh@meu.org.uk Tel: 0161 946 4052	✔
Professor Peter Andrews	Professor of Critical Care, University of Edinburgh	Email: P.Andrews@ed.ac.uk Tel: 0131 537 1131	✔