The CHARTER-Ireland trial: Can nebulised heparin reduce acute lung injury in patients with SARS-CoV-2 requiring advanced respiratory support in Ireland: a study protocol and statistical analysis plan for a randomised control trial.

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Abstract

- **Background:** COVID-19 pneumonia is associated with the development of acute respiratory distress syndrome (ARDS) displaying some typical histological features. These include diffuse alveolar damage with extensive pulmonary coagulation activation. This results in fibrin deposition in the microvasculature, leading to the formation of hyaline membranes in the air sacs. Well conducted clinical trials have found that nebulised heparin limits pulmonary fibrin deposition, attenuates progression of ARDS, hastens recovery and is safe in non-COVID ARDS. Unfractionated heparin also inactivates the SARS-CoV-2 virus and prevents entry into mammalian cells. Nebulisation of heparin may therefore limit fibrin-mediated lung injury and inhibit pulmonary infection by SARS-CoV-2. Based on these findings, we designed the CHARTER-Ireland Study, a phase 1b/2a randomised controlled study of nebulised heparin in patients requiring advanced respiratory support for COVID 19 pneumonia.

- **Methods:** This is a multicentre, phase 1b/IIa, randomised, parallel group, open label study. The study will randomise 40 SARs-CoV-2 positive patients receiving advanced respiratory support in a critical care area. Randomisation will be via 1:1 allocation to usual care plus nebulised unfractionated heparin 6 hourly to day 10 while receiving advanced respiratory support or usual care only. The study aims to evaluate whether unfractionated heparin will decrease the procoagulant response associated with ARDS up to day 10. The study will also assess safety and tolerability of nebulised heparin as defined by number of severe adverse events; oxygen index and respiratory oxygenation index of intubated and unintubated respectively; ventilatory ratio; plasma concentration of interleukin (IL)-1 β , IL6, IL-8, IL-10 and soluble tumour necrosis factor receptor 1, C-reactive protein, procalcitonin, Ferritin, Fibrinogen and lactate dehydrogenase as well as the ratios of IL-1 β /IL-10 and IL-6/IL-10. These parameters will be assessed on days 1, 3, 5 and 10; time to separation from advanced respiratory support, time to discharge from the intensive care unit and number tracheostomised to day 28; survival to day 28, 60 and to hospital discharge, censored at day 60. Some clinical outcome data feeding into the CHARTER and INHALE-HEP international meta-trials.

- **Discussion:** This trial aims to provide evidence of potential therapeutic benefit while establishing safety of nebulised heparin in the management of ARDS associated with SARs-CoV-2 infection.

Trial registration:

ClinicalTrials.gov, ID: NCT04511923. Registered on 13 August 2020.

Protocol Version 7, 22 February 2021

Protocol Identifier: NUIG-2020-003

EudraCT registration number: 2020-003349-12 9 October 2020

Introduction

Background and rationale {6a}

SPIRIT guidance: Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention.

SARS-CoV-2 generates a robust immune response, with inflammatory cytokine generation and excessive coagulation activation.(1) Excess coagulation leads to increased fibrin formation, resulting in deposition of hyaline membranes in the alveolar spaces and microvascular thrombi, contributing to the development of ARDS and multiorgan failure. (1,2) A rise in d-dimer level associated with the extent of fibrin formation correlates well with the severity of ARDs.(1)

There is scientific rationale for the use of nebulised heparin in the treatment of SARS-CoV-2.(3) Administration of nebulised heparin to mechanically ventilated patients at risk of developing ARDs has been shown to reduce the Murray Lung Injury Score and development of ARDS along with improving outcomes at day 60.(4) This indicates that nebulised heparin limits fibrin deposition, preventing progression of ARDS and may help improve recovery from ARDS.(4) Further, SARS-CoV-2 spike glycoprotein has been found to bind heparin, causing a conformational change which preventing the virus entering the cell.(5)

This is a preliminary efficacy and safety study, as such d-dimer level is being used as an intermediate marker of efficacy. Higher d-dimer levels are correlated with more severe ARDS in SARS-CoV-2 infection. (6) Lower mean d-dimer levels were found in survivors of SARS-CoV-2 vs non-survivors.(7) This study aims to test the hypothesis that nebulised heparin will cause a reduction in pulmonary microvascular thrombosis, using as a reduction in d-dimer as a surrogate marker. Recent studies using nebulised Heparin have not shown an increased rate of adverse outcomes when compared with placebo, this study aims to confirm these findings.(4,8)

A number of previous clinical trials in patients with, or at risk for, ARDS or with related conditions, report that nebulised heparin is safe, and may have therapeutic potential, limiting pulmonary fibrin deposition, reducing acute lung injury progression, and facilitating recovery. Furthermore, the potential exists for heparin to directly inactivate SARS-CoV-2. Given these findings, we believe a that a safety and feasibility study of nebulised heparin therapy for the treatment of COVID-19 is warranted.

Objectives {7}

SPIRIT guidance: Specific objectives or hypotheses.

Our hypothesis is that nebulised heparin will decrease severity of lung injury in SARS-CoV-2 through multiple mechanisms as shown above, and this will be shown through a decrease in pro-coagulant markers such as d-dimer.

The objective of this safety and feasibility study is to determine if treatment with nebulised heparin, compared to standard care, reduces the severity of the procoagulant response in intensive care unit (ICU) patients with SARS-CoV-2 requiring advanced respiratory support and to assess safety of nebulised heparin in patients with COVID-19 induced severe respiratory failure.

Trial design {8}

SPIRIT guidance: Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory).

This is an investigator led prospective, phase 1b/IIa, multi-centre, randomised, parallel-group, open label proof of principle study. The study will recruit 40 adult patients infected with SARS-CoV-2 who require advanced respiratory support across multiple centres in Ireland. Randomisation will be 1:1 allocation to usual care plus nebulised unfractionated heparin 6 hourly to day 10 while receiving advanced respiratory support or usual care only. The study is designed to evaluate whether nebulised unfractionated heparin will decrease the procoagulant state related to ARDS. The study will measure safety outcomes for the administration of heparin via this device as a co-primary endpoint and will assess clinical outcomes as secondary endpoints.

Methods: Participants, Interventions And Outcomes

Study setting {9}

SPIRIT guidance: Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained

The study will take place in selected intensive care units in Ireland where patients with COVID 19 are being treated: University Hospital Galway, Connolly Hospital Blanchardstown and Beaumont Hospital, Dublin.

Eligibility criteria {10}

SPIRIT guidance: Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists).

Patients with Confirmed SARS-CoV-2 infection receiving advanced respiratory support in an intensive care environment. See Table 1.

Table 1

Eligibility criteria for participants.

Inclusion Criteria	Exclusion Criteria
Confirmed or suspected COVID-19 If 'suspected', results must be pending or testing intended	Enrolled in another clinical trial that is unapproved for co-enrolment
Ability to obtain informed consent/assent to participate in study	Heparin allergy or heparin-induced thrombocytopenia
Age 18 years or older	APTT > 100 seconds
Requiring high flow nasal oxygen or positive pressure ventilator support or invasive mechanical ventilation in the ICU for a time period of no greater than 48 hours	Pulmonary bleeding, which is frank bleeding in the trachea, bronchi or lungs with repeated haemoptysis or requiring repeated suctioning
D-dimers > 200 ng/ml	Platelet count < 50 x 10 ⁹ per L
Acute opacities on chest imaging affecting at least one lung quadrant 'Acute opacities' do not include effusions, lobar/lung collapse or nodules	Uncontrolled bleeding
Currently in a higher level of care area designated for inpatient care of patients where therapies including non-positive pressure ventilatory support can be provided.	Pregnant or suspected pregnancy (Urine or serum HCG will be recorded)
	Receiving or about to commence ECMO or HFOV
	Myopathy, spinal cord injury, or nerve injury or disease with a likely prolonged incapacity to breathe independently e.g. Guillain-Barre syndrome
	Usually receives home oxygen
	Dependent on others for personal care due to physical or cognitive decline prior to this illness (premorbid status)
	Death is imminent or inevitable within 24 hours
	The clinical team would not be able to set up the study nebuliser and ventilator circuit as required including with active humidification
	Clinician objection.
	The use or anticipated use of nebulised tobramycin during this clinical episode
	Any other specific contraindication to anticoagulation including prophylactic anticoagulation not otherwise listed here.

Relapse in clinical condition in patient that had fully weaned from advanced respiratory support
Receiving any Direct / Novel Oral Anticoagulant

Who will take informed consent? {26a}

ST guidance: Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)

Informed consent is taken by an investigating doctor conducted in accordance with the ethical principles outlined in the declaration of Helsinki. For trial participants who are unable to give consent due to illness severity, informed assent is obtained from next of kin. Due to the pandemic situation some modifications to the assent process were required and approval was received from the Irish Health Research Consent Declaration Committee to allow phone assent to be obtained when next of kin was unable to attend the hospital. If or when these patients regain capacity, their informed consent to continue to participate in the study will then be sought, with this consent then superseding the consent declaration and assent

Additional consent provisions for collection and use of participant data and biological specimens {26b}

SPIRIT guidance: Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable

Provisions for consent/assent to use patient data and biological specimens in future ancillary studies is included in our study protocol and has similar approvals in place.

Interventions

Explanation for the choice of comparators {6b}

SPIRIT guidance: Explanation for choice of comparators

As a phase 1b/2a study of a new treatment for this disease, the comparator chosen was standard care in our participants.

Intervention description {11a}

SPIRIT guidance: Interventions for each group with sufficient detail to allow replication, including how and when they will be administered.

Participants assigned to ‘nebulised heparin’ will receive 5ml heparin sodium 5,000 I.U./ml (25,000 I.U. in 5 ml), manufactured by Pinewood laboratories, Ballymacarbry, Clonmel, Co. Tipperary. This will be administered via the Aerogen solo nebuliser every 6 hours from enrolment to day 10, in addition to the standard care required as determined by the treating team. Participants assigned to ‘standard care’ will receive the standard care required as determined by the treating team and will not be treated with nebulised heparin.

Criteria for discontinuing or modifying allocated interventions {11b}

SPIRIT guidance: Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease).

Outlined in table 2.

Table 2

Indications for withholding and recommencement of nebulised heparin.

Nebulised heparin should be withheld if any of the following occurs:	Nebulised heparin should be recommenced if:
More than 10 days have elapsed since randomisation	Having been withheld because the patient was outside the ICU, the patient returns to ICU
The patient is outside of higher-level care setting	Having been withheld because the patient was not receiving advanced respiratory support, advanced respiratory support is reinstituted
The patient is not receiving advanced respiratory support	Having been withheld because the APTT was unacceptably prolonged, the APTT becomes acceptable
The treating physician deems that there is a clinically unacceptable increase in APTT (>100s)	Having been withheld because there was excessive bloodstaining of respiratory secretions, the bloodstaining of the respiratory secretions has resolved
The treating physician deems that there is excessive bloodstaining of respiratory secretions	Having been withheld for suspected HIT, the patient is found not to have this condition
There is pulmonary bleeding, major bleeding or suspected or confirmed HIT	Having been withheld for ECMO, the treatment with ECMO is stopped
The patient is receiving ECMO or HFOV.	Having been withheld for HFOV, the treatment with HFOV is stopped

Each participant has the right to withdraw from the trial at any time. Where the participant gives a reason for withdrawal (they are not obliged to provide a reason), the reason for withdrawal will be recorded. Equally, the investigator may decide to withdraw a patient from the study at any time – in this case the reason for withdrawal will be recorded. If a patient withdraws from the study, they will be encouraged to complete the follow up aspect of the study. Also, if a patient withdraws from the study due to a safety event, mandatory follow up of that event until its resolution will occur.

Strategies to improve adherence to interventions {11c}

SPIRIT guidance: Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests).

As a phase 1b/2a study, any issues that arise with adherence to intervention will be reported and will be addressed during the study. These may include staffing issues due to the pandemic or any supply or administration issues related to drug and equipment which may arise. In general, we anticipate high levels of adherence as the intervention is provided in the ICU by ICU staff.

Relevant concomitant care permitted or prohibited during the trial {11d}

SPIRIT guidance: Relevant concomitant care and interventions that are permitted or prohibited during the trial.

Patients receiving or anticipated likely to receive nebulised tobramycin are prohibited from enrolling in the trial or must be withdrawn if this therapy is commenced. Patients receiving direct oral anticoagulants are also prohibited from enrolment.

Treatment with any or all the following therapies *is not* of itself reason to withhold nebulised heparin: deep vein thrombosis prophylaxis with unfractionated heparin or non-heparin anticoagulants; anti-thrombotic medications; protamine; prone positioning; and inhaled nitric oxide.

Provisions for post-trial care {30}

SPIRIT guidance: Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation.

There will be no formal provision of the intervention beyond the trial period, as recommended by the World Health Organisation (WHO) interim guidance that any specific therapy targeted to SARS-CoV-2 infection should be provided only as part of a research protocol.(11) All subsequent requirement of both SARS-CoV-2 and unrelated needs will be under the existing healthcare system in the recruiting centres.

Outcomes {12}

SPIRIT guidance: Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended.

The co-primary efficacy outcomes are:

1. A between group difference in d-dimer levels over time.
2. A between group difference in the occurrence of serious adverse events (SAEs) as listed in the safety analysis

Secondary efficacy outcomes include analysis of between group differences in:

1. Oxygenation index (OI) = $(\text{FiO}_2 \times \text{M}_{\text{PAW}}) / \text{PaO}_2$, will be recorded every 6 hours
2. Pulmonary compliance
3. Inflammatory and coagulation markers
 - a. IL-1 β , IL-6, IL-8, IL-10, soluble tumour necrosis factor receptor 1, C-reactive protein, procalcitonin, Ferritin, Fibrinogen and lactate dehydrogenase LDH will be assessed
 - b. Area under the curve (AUC) on days 1, 3, 5 and 10 as part of an exploratory outcome to assess for any potential markers of COVID 19 ARDS
 - c. Ratio of IL-1 β /IL-10 and IL-6/IL-10
4. Time to separation from invasive ventilation to day 28, where non-survivors to day 28 are treated as though not separated from invasive ventilation.
5. Number tracheotomised to day 28
6. Time to separation from the ICU to day 28, where non-survivors to day 28 are treated as though not separated from invasive care
7. Survival to day 28; Survival to day 60; and Survival to hospital discharge, censored at day

Additional outcomes include:

1. Time to separation from invasive ventilation to day 28, among survivors
2. Number treated with neuromuscular blockers instituted after enrolment to day 10
 1. Any administration of neuromuscular blocking drugs will be recorded
3. Number treated with prone positioning instituted after enrolment to day 10
4. Number treated with extra-corporeal membrane oxygenation instituted after enrolment to day 10
5. Time to separation from the ICU to day 28, among survivors
6. Number residing at home or in a community setting at day 60
7. Number residing at home or in a community setting at day 60, among survivors

Safety outcomes include:

1. Air quality samples from an infection control perspective
2. Number of patients transfused red blood cells to day 10
3. Volume of red blood cells transfused to day 10

4. Number who record major bleeding

- a. Major bleeding' is defined as: bleeding that results in death and/or; bleeding that is symptomatic and occurs in a critical area or organ (intra-cranial, intra-spinal, intra-ocular, retroperitoneal, intra-articular, or intramuscular with compartment syndrome) and /or; bleeding that results in a fall in haemoglobin of 20g/L or more, or results in transfusion of two or more units of whole blood or red cells.

5. Number of patients who record clinically relevant non-major bleeding

6. Number who record heparin-induced thrombocytopenia (HIT)

7. Number who record other adverse events and reactions

Participant timeline {13}

SPIRIT guidance: Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see figure at <http://www.spirit-statement.org/publications-downloads/>).

Day 0: Screening, Consent/next of kin assent, enrolment and randomisation

Day 1: The following baseline data will be recorded on the baseline electronic case report form (eCRF):

- Eligibility criteria
- Intubation date and time; and intubation setting
- Birth date; sex; height; and weight
- History of tobacco smoking; hypertension; diabetes mellitus; asthma; and chronic obstructive pulmonary disease
- Hospital admission date; ICU admission date and time; and acute physiology and chronic health evaluation (APACHE) III score, ICU diagnosis.
- Treatment in the 24 hours prior to randomisation with unfractionated heparin, intravenously or subcutaneously; LMWH, intravenously or subcutaneously; lopinavir-ritonavir; remdesivir; hydroxychloroquine; interferon- β ; interleukin antagonists; oseltamivir, laninamivir, zaninamivir or peramivir; macrolide; non-macrolide antibacterial; antifungal; and corticosteroid
- Treatment at the time of randomisation with inotrope or vasopressor infusion; renal replacement therapy; neuromuscular blocker; and prone positioning

- Serum creatinine and bilirubin, blood haemoglobin, white cell count and platelet count, and blood activated partial thromboplastin time (APTT) and international normalised ratio (INR), collected closest to and before randomisation
- For the chest radiograph or computerised tomography (CT) of chest performed closest to and before randomisation: the number of lung quadrants with acute opacities that are not fully explained by effusions, lobar/lung collapse or nodules; whether the opacities are present bilaterally; whether, given all the medical information about the patient, the opacities are entirely attributable to cardiac failure or fluid overload; whether the patient was exposed to any risk factor for acute lung injury in the previous 7 days and; whether there is objective evidence to exclude the possibility of cardiac failure or fluid overload
- Arterial blood gas (pH, PaCO₂, PaO₂, bicarbonate and lactate) and corresponding ventilation parameters (respiratory rate, FIO₂, peak airway pressure, positive end expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) and tidal volume) closest to and before randomisation.

Days 0 to 10: the following data are gathered from health records at the treating institution:

- Type of respiratory support – high flow nasal O₂ / non invasive ventilation / invasive mechanical ventilation
- Dose of nebulised unfractionated heparin
- Treatment with unfractionated heparin, intravenously or subcutaneously; LMWH, intravenously or subcutaneously; lopinavir-ritonavir; remdesivir; hydroxychloroquine; interferon-β; interleukin antagonists; oseltamivir, laninamivir, zaninamivir or peramivir; macrolide; non-macrolide antibacterial; antifungal; corticosteroid; inotrope or vasopressor infusion; renal replacement therapy; neuromuscular blocker; prone positioning; and extra-corporeal membrane oxygenation
- Volume of packed red cells and whole blood transfused
- Highest APTT
- Blood samples will be collected for inflammatory marker and coagulation parameter assessment as per the primary and secondary outcomes, on days 0, 3, 5 and 10.

Day 28: The following data are gathered from health records at the treating institution and, where necessary, other healthcare providers:

- Date of first diagnosis of COVID 19 (Clinical diagnosis)
- Date of first positive respiratory sample for SARS-CoV-2 and the sample type
- Acute hospital discharge status at day 28 and, if discharged, the date of discharge and discharge destination including deceased

- Readmission to ICU during the acute hospital admission and prior to day 28
- ICU status at day 28 and, if not in the ICU at the end of day 28, the final date and time of ICU discharge
- Invasive ventilation status at day 28 and, if not receiving invasive ventilation at the end of day 28, the final date and time that invasive ventilation was stopped
- Tracheotomy and, if performed, the procedure date

Day 60: The following data are gathered from health records at the recruiting institution and, where necessary, other healthcare providers and the patient or proxy:

- Vital status at day 60 and, if deceased, the date of death and whether death related (directly or indirectly) to COVID-19 infection
- Place of residence at day 60
- If not discharged from the acute hospital discharge status by day 28, the acute hospital discharge status at day 60 is ascertained and, if now discharged, the date of discharge and the discharge destination including whether deceased.

Sample size {14}

SPIRIT guidance: Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations.

This is a phase 1b/2a study aiming to evaluate the effect of nebulised unfractionated heparin on procoagulant markers and the safety of nebulised heparin in patients receiving advanced respiratory support for COVID-19 lung disease. This has not been studied previously, and as such, data does not exist to power the study accurately to assess clinical outcomes. We have chosen to base our power analysis on some of our own in house data for d-dimer levels in covid patients who required ICU care (12 patients) and those who didn't (26 patients).

Based on a calculation that nebulised heparin may reduce the d-dimer levels in ICU patients (mean = 944.8ng/ml [SD = 485.3]) to those experienced in ward patients (mean = 436.5ng/ml[SD = 604.0]), with an alpha level of 0.05 and a power of 90% to detect a type II error 19 patients per group would be required. Increasing the number by 1 per group to allow for potential dropout gives a sample size of 20 patients per arm of the study, with a total of 40 patients to be enrolled. The safety profile of administering nebulised heparin to invasively ventilated patients with COVID 19 will be a co-primary outcome, but power analysis will not be done for this outcome.

Recruitment {15}

SPIRIT guidance: Strategies for achieving adequate participant enrolment to reach target sample size.

Recruitment will be organised and supervised by intensive care research and clinical research facilities within recruiting centres and in line with national and international standards and guidelines, and local standard operating procedures. The Research Nurses/Coordinators and Investigators at each site will work with clinicians to identify potential candidates for enrolment. A screening log will be maintained of patients who met the inclusion criteria but were not enrolled, with the reason for exclusion recorded on the log. If a patient is deemed eligible, the patient's next of kin will be contacted, and a patient information leaflet will be sent to them or given to them in person if possible.

Assignment of interventions: allocation

Sequence generation {16a}

SPIRIT guidance: Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions.

Allocation will be carried out after consent is confirmed, via a central, secure web randomisation process hosted by the contract research organisation (CRO). Allocation will be in a one to one ratio, with variable block size randomisation.

Concealment mechanism {16b}

SPIRIT guidance: Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned.

Blocks of variable size and a random seed will be used to ensure allocation concealment cannot be violated by deciphering the sequence near the end of each block. To further protect from deciphering, block size will not be revealed to site Investigators. Site level randomisation will be used. At randomisation each participant is assigned to nebulised heparin or standard care. There is a one to one allocation ratio.

Implementation {16c}

SPIRIT guidance: Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions.

Research nurses and investigators at each site will work with clinicians to identify potential candidates for enrolment. Investigators will generate allocation sequence and assign participants to interventions via the eCRF.

Assignment of interventions: Blinding

Who will be blinded {17a}

SPIRIT guidance: Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how.

Not-applicable- this is an open label trial

Procedure for unblinding if needed {17b}

SPIRIT guidance: If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial

Not-applicable- this is an open label trial

Data collection and management

Plans for assessment and collection of outcomes {18a}

SPIRIT guidance: Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol

Data will be collected by trained staff at each site under the supervision of the principal investigator using a case report form and data dictionary developed by the management committee (Attachment CRF). Baseline data will be gathered from health records at the treating institution. It may also be necessary in a small number of cases to obtain information from other healthcare providers. Daily data for days 0 to 10 while in intensive care: Data are gathered from health records at the treating institution for each day that the patient is in ICU up to and including day 10. Day 28 and day 60 data are gathered from health records at the treating institution and, where necessary, other healthcare providers. Adverse event or adverse

reaction data are gathered from health records at the recruiting institution and, where necessary, other healthcare providers and the patient or proxy.

The study will be conducted in accordance with the current approved protocol, International Conference on Harmonisation (ICH) Good Clinical Practice (GCP), relevant regulations and standard operating procedures. All effort shall be taken to ensure that data collected is accurate, complete and reliable. The site must facilitate all required monitoring and respond to queries in a timely manner. All data will be reviewed for completeness and logical consistency by the data management team. Data queries will be generated via the electronic data capture system to correct or clarify data or request missing information. The designated site staff will be required to respond to these queries in accordance with data entry and data query timelines for the study.

Plans to promote participant retention and complete follow-up {18b}

SPIRIT guidance: Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols.

N/a- participation is while in ICU only. Intention to treat study design

Data management {19}

SPIRIT guidance: Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol.

All electronic information held will be kept on a password protected, audited server maintained by the CRO, accessible only to authorised study personnel and compliant with ICH GCP.

All study material, including case report forms and the study database, will be stored for a minimum period of 15 years after the conclusion of the study or as per national/European legislation.

Source documents are the documents or media where the patients data are first recorded, and from which the data participants' entered into the eCRF data is obtained. These include, but are not limited to, data gathered from health records at the treating institution, medical records from other institutions where applicable.

Sources of data will be identified and pre-specified on a study-specific source data agreement relevant to the study site. The source data agreement will be verified by the Principal Investigator with a copy of the agreement to be filed within the Site File.

The site investigator(s) will facilitate the permit of study-related monitoring, audit, research ethics committee approval review and regulatory inspection by the relevant national authority/international, providing direct access to source documents where possible.

Data collected will be pseudo-anonymised; on all study-specific documents other than the signed consent, the subject will be referred to by the study subject identification number/code.

Subject participation and subject progress should also be recorded in the subject medical records to ensure relevant healthcare providers have knowledge of the subject's participation in the study.

Data from medical records will be entered by authorised and delegated site personnel into the electronic case report form. The data will be verifiable against original records and source notes by the Monitor during monitoring visits. Data reported on the eCRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained.

eCRF completion instructions will be provided and any questions about recording specific information on the eCRF should be directed to the investigator. Each participating centre will maintain a subject identification log of enrolled patients that includes patient identifiers. Patient identifiers are not transferred to the study coordinating centre.

Confidentiality {27}

SPIRIT guidance: How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial.

Only authorised study staff will be permitted access to the password protected study database where study specific data will be stored. Paper documents will be stored in a locked site with restricted access. On all trial-specific documents, other than the signed consent form and the enrolment log, the participant will be referred to by the unique participant code, not by name. Patient Identifiable data will not leave the site, as per the Data Protection Act. Access will be granted to authorised representatives from the sponsor and the regulatory authorities to permit trial-related monitoring, audits and reports.

Subject confidentiality will be maintained at all times and no documents containing the subject's name or other identifying information will be collected by the sponsor on the study database. It may be necessary for the sponsor's representatives, the ethics committee and regulatory authority representatives to have direct access to the subject's medical records.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

SPIRIT guidance: Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable.

Blood samples collected for analysis of interleukin and tissue necrosis factor levels will be stored during the study and processed once all patients have been enrolled and all samples collected, as these are not standard assays carried out in our laboratories. Unused portions of these samples will be destroyed.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

SPIRIT guidance: Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol

(Demographic and baseline characteristics of the study population will be summarized using appropriate graphical and numerical summaries for each treatment group and by site. Both an intention to treat analysis set and per protocol and safety analysis set will be included. For effectiveness analysis we will use the 2-sample t-tests for the between group difference in d-dimer levels and generalized linear (or non-linear as appropriate) mixed effects models for the analysis of longitudinal data, using appropriate link functions depending on type of outcome variable. This analysis will be used to compare the treatment effect, while adjusting for patient characteristics (e.g. Horowitz index of lung function (P/F ratio), sequential organ failure assessment (SOFA) Score, body mass index (BMI), sex and age) as appropriate for all primary and secondary efficacy outcomes. A Cox Proportional Hazards model will be used to model time to event responses. Generalized Linear Models will be used for the analysis of safety outcomes. Primary and secondary outcome data will be suitable for meta-analysis to further assess clinically relevant outcomes. Interval estimates (95% confidence intervals) for the treatment effect will be reported accordingly.)

Interim analyses {21b}

SPIRIT guidance: Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial.

There is no plan to carry out an interim analysis as the primary outcome is not a clinical outcome, and the numbers recruited are small.

Methods for additional analyses (e.g. subgroup analyses) {20b}

SPIRIT guidance: Methods for any additional analyses (eg, subgroup and adjusted analyses).

Results will be presented as per protocol and intention to treat analysis groups. Results will also be presented for ventilated at enrollment and non-ventilated at enrollment subgroups, although due to the sample size the numbers in each group will be small.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

SPIRIT guidance: Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation).

All participants who are enrolled will be included in the analysis. Any participants who withdraw and wish to have their data withdrawn will not be included. Analysis will be carried out using the intention to treat principle where patient's data will be analysed as members of the group they were randomised to, irrespective of their compliance with the treatment as specified in the protocol. A separate per-protocol analysis will be carried out including all patients who complied with the protocol in terms of exposure to planned treatment, availability of measurements and absence of major protocol deviations. Any deviation(s) from the original statistical plan will be described and justified in the final report. [An analysis of all missing data will be carried out to identify the likely missing data mechanism (e.g. missing completely at random, missing at random, and missing not at random) and to investigate

reasons for missingness as a useful outcome for the corresponding subsequent definitive trial.] Multiple Imputation using chain equations will be used to handle missing data (due to outcome values missing in some visits for some of the participants) in the primary and secondary outcome analysis.

Plans to give access to the full protocol, participant level-data and statistical code {31c}

SPIRIT guidance: Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code.

The full protocol is available on application to the investigators, with the summary protocol published here. The statistical code will be published as an addendum to the results paper after completion of the study. Participant level data will be maintained confidentially, with some clinical outcome data feeding into the CHARTER and INHALE-HEP international meta-trials. (9,10) Reasonable requests for access to the

data from other investigators will be considered by the investigators, taking into account general data protection regulation (GDPR) compliance.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {5d}

Trials guidance: Provide information on the composition, roles and responsibilities of the coordinating centre and trial steering committee and all groups providing day to day support for the trial. There will always be a group running the trial day-to-day and providing organisational support and knowing how often they will meet, plus information on other committees providing oversight such as a Trial Steering Committee, and how often they will meet over the course of the trial, is what we need for item 5d. We do not need names of staff.

SPIRIT guidance: Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)

The Health research board clinical research facility (HRB-CRFG) Galway will be the coordinating centre, taking overall responsibility for the conduct of the trial. All members of the investigator team and research group will have appropriate GDPR and ICH GCP training, which will be documented in a delegation log. Regular meetings between each site and the coordinating center, facilitated by the CRO, will allow communication of progress, highlighting of adverse reactions and discussion of technical issues. A detailed plan of sponsor oversight with regular site audit has been devised.

Composition of the data monitoring committee, its role and reporting structure {21 a}

SPIRIT guidance: Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed.

An independent international Data Safety Monitoring Committee (DSMC) will oversee the conduct of the trial and verify the correct implementation of the clinical trial design. Just as with a traditional trial design, the role of the DSMC is to ensure the design is implemented with integrity, that the original design remains scientifically and ethically appropriate in light of the accumulating data and any external

information, and to protect research participants from avoidable risk. The DSMC for this trial will include expertise in critical care, biostatistics and clinical trials.

The responsibilities of the DSMC are to advise on all matters related to the safety of subjects enrolled in this study, integrity of trial data and conclusions and the appropriateness of continued trial conduct.

The aims of the DSMC include:

1. To identify any trends, such as increases in un/expected events, and take appropriate action
2. To seek additional advice or information from investigators where required
3. To evaluate the risk of the trial continuing and take appropriate action where necessary

The researchers will provide the DSMC with an interim report of adverse events and early results. The DSMC will also undertake a review of enrolments and withdrawals according to the DSMC Charter, to ensure adequate study safety, and minimal risk to participants. Where necessary, the DSMC will make recommendations for corrective action which may include early termination, suspension or modification of a trial, or changes in consent processes. However, the final decision will rest with the Sponsor.

Adverse event reporting and harms {22}

SPIRIT guidance: Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct.

Procedures for Recording Adverse Events

Reportable adverse events and reactions and reactions will be communicated by site investigators to the chief investigator. In general, this will occur in writing within than 3 days of the site investigator becoming aware of the event. The management committee will assess all safety reports received from investigators.

All adverse events occurring during the trial that are observed by the Investigator or reported by the participant, will be recorded on the eCRF, whether or not attributed to trial medication.

The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to trial medication, other suspect drug or device and action taken. Follow-up information should be provided as necessary. Only non-serious adverse events which are considered related to the investigational medicinal product will be recorded routinely on the adverse event eCRF from the time of informed consent (or enrolment into the study) up to 96 hours after the last dose of study drug has been received. All adverse events meeting “serious” criteria should be recorded on the SAEs CRF as per Section below.

Procedures for Recording and Reporting SAEs

All SAEs must be reported on the SAE reporting form to the Sponsor within 24 hours of the Study Team becoming aware of the event.

The Sponsor will perform an initial check of the report, request any additional information, and ensure it is reviewed by the Medical Monitor on a weekly basis.

Adverse events meeting the definition of SAEs must be reported using the SAE Report Form located in the investigator site file. All adverse events meeting “serious” criteria occurring in each patient should be reported from the time of informed consent (or enrolment into the study) up to 90 days after the last dose of study drug has been received. All SAE information must also be recorded on the SAE form within the eCRF. Additional and further requested information (follow-up or corrections to the original case) may be captured within the SAE form and eCRF. Follow-up/ new information is required within the same reporting timeline, i.e. within 24 hours of the Study Team becoming aware of the new information.

SAEs will also be reviewed by the DSMC, in accordance with their Charter.

Sponsor Responsibilities:

The Sponsor, National University of Ireland Galway (NUIG), will delegate appropriate adverse event reporting for the study according to the applicable regulatory guidelines.

NUIG will submit local suspected unexpected serious adverse reactions (SUSARs) on an expedited basis to the local regulatory authority and other Competent Authorities involved, concerned Ethics Committees, all participating investigators and the DSMC. NUIG sends annual Development Safety Update Reports to the concerned regulatory authority and Ethics Committee. Investigators will be informed of SUSARs.

For fatal and life-threatening SUSARS, this will be done no later than 7 calendar days after the Sponsor is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days.

Frequency and plans for auditing trial conduct {23}

SPIRIT guidance: Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor.

The trial will be conducted in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures. Regular monitoring will be performed according to GCP and as defined within the study Monitoring Plan. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. The Monitor will perform source document verification to verify

that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

A quality assurance audit/inspection may be conducted by the competent authority, sponsor, or an agent delegated responsibility.

Data will also be monitored by the DSMC in accordance with the DSMC Charter.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

SPIRIT guidance: Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators).

Protocol amendments will be reviewed for their impact (substantial or non-substantial) as per requirements and all substantial amendments will not be implemented prior to pre-approval by the competent authority and the ethics committees. Protocol amendments will be updated on relevant clinical trial registries by an appropriate delegated person the sponsor or the sponsors representative.

If a protocol amendment requires a change to the Informed Consent Form or any relevant document the Sponsor or their delegate will ensure that all related documents will be updated or considered for update, and all approvals sought as required.

Dissemination plans {31 a}

SPIRIT guidance: Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions.

The study site(s), represented by the primary investigator, will take responsibility to report the results in a scientific peer reviewed journal, according to the International Committee of Medical Journal Editors recommendations. Results of the study will be sent to participants on request (once available) and will be made available on a publicly available trial registry website, recognised by the World Health Organisation International Clinical Trials Registry Platform (WHO ICTRP) as a Primary Registry.

Discussion

Trials guidance: This should include a discussion of any practical or operational issues involved in performing the study and any issues not covered in other sections⁷ Nil extra.

Trial status

Trials guidance: Authors should report the protocol version number and date, the date recruitment began, and the approximate date when recruitment will be completed

The CHARTER-Ireland trial commenced December 23rd 2020 at University Hospital Galway, Ireland. Recruitment is proceeding using protocol version 7, 22 February. We expect to complete recruitment in Spring 2022.

Abbreviations

National University of Ireland, Galway (NUIG)

Acute respiratory distress syndrome (ARDS)

Tumour necrosis factor receptor 1 (sTNFR1)

Interleukin (IL)

Intensive care unit (ICU)

Activated partial thromboplastin time (APTT)

Lactate dehydrogenase (LDH)

Heparin induced thrombocytopenia (HIT)

Extracorporeal membrane oxygenation (ECMO)

High frequency oscillatory ventilation (HFOV)

Deep vein thrombosis (DVT)

Low molecular weight heparin (LMWH)

World Health Organisation (WHO)

Oxygenation index (OI)

Fraction of inspired oxygen (FiO₂)

Mean Airway Pressure (M_{PAW})

Partial pressure of arterial oxygen (PaO₂)

Area under the curve (AUC)

Electronic case report form (eCRF)

International normalising ratio (INR)

Computerised tomography (CT)

Partial pressure of carbon dioxide (PaCO₂)

Positive end expiratory pressure (PEEP)

Continuous positive airway pressure (CPAP)

International Conference on Harmonisation (ICH)

Good Clinical Practice (GCP)

Horowitz index of lung function (P/F ratio)

Sequential organ failure assessment (SOFA)

Body mass index (BMI)

General data protection regulation (GDPR)

Contract research organisation (CRO)

Health research board (HRB)

Data Safety Monitoring Committee (DSMC)

Serious adverse events (SAEs)

Suspected unexpected serious adverse reactions (SUSARs)

Declarations

Acknowledgements

Trials guidance: Please acknowledge anyone who contributed towards the article who does not meet the criteria for authorship including anyone who provided professional writing services or materials. Authors should obtain permission to acknowledge from all those mentioned in the Acknowledgements section. See our [editorial policies](#) for a full explanation of acknowledgements and authorship criteria. If you do not have anyone to acknowledge, please write "Not applicable" in this section.

Group authorship (for manuscripts involving a collaboration group): if you would like the names of the individual members of a collaboration Group to be searchable through their individual PubMed records,

please ensure that the title of the collaboration Group is included on the title page and in the submission system and also include collaborating author names as the last paragraph of the “Acknowledgements” section. Please add authors in the format First Name, Middle initial(s) (optional), Last Name. You can add institution or country information for each author if you wish, but this should be consistent across all authors. Please note that individual names may not be present in the PubMed record at the time a published article is initially included in PubMed as it takes PubMed additional time to code this information.

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Authors' contributions {31b}

SPIRIT guidance: [31b] - Authorship eligibility guidelines and any intended use of professional writers.

Trials guidance: The individual contributions of authors to the manuscript should be specified in this section. Guidance and criteria for authorship can be found in our [editorial policies](#). Please use initials to refer to each author's contribution in this section, for example: "AB is the Chief Investigator; she conceived the study, led the proposal and protocol development. CD contributed to study design and to development of the proposal. EF was the lead trial methodologist. All authors read and approved the final manuscript

Study design and conception: Bairbre McNicholas, Frank van Haren, Alberto Alvarez-Iglesias, John Laffey, David Cosgrave; Patient recruitment and study implementation: John Robert Sheehan, Padraig Calpin, Ciara Hanley, Bairbre McNicholas, Camilla Giacomini, Catriona Cody, Shane McGeary, Gerard Curley, Maeve Kernan, Claire Kelly, Siobhan Casey, Darragh Murphy, John Laffey, David Cosgrave; Acquisition, analysis, and/or interpretation of data; John Robert Sheehan, Padraig Calpin, Ciara Hanley, Bairbre McNicholas, Camilla Giacomini, Catriona Cody, Shane McGeary, Gerard Curley, David Cosgrave, John Laffey; Drafting of the manuscript: John Robert Sheehan, Padraig Calpin, David Cosgrave, John Laffey; Critical revision of study design, Study supervision and critical revision of the manuscript: John Laffey, David Cosgrave.

Funding {4}

SPIRIT guidance: Sources and types of financial, material, and other support.

Trials guidance: All sources of funding for the research reported should be declared. You will be required to include a copy of the original funding document and an English translation of this document as an additional file on submission, which will be checked against this declaration. The role of the funding body

in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript should be declared.

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Availability of data and materials {29}

SPIRIT guidance: Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators.

Trials guidance: Please do not include any baseline or pilot data in your study protocol. The Editorial Office will ask you to remove this if it is included. Please declare here who will have access to the final trial dataset and disclose contractual agreements that limit such access for investigators.

The data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as agreed in the publication policy of this protocol. Individual requests for access to dataset will be considered in discussion with the local research ethics committee.

Ethics approval and consent to participate {24}

SPIRIT guidance: Plans for seeking research ethics committee/institutional review board (REC/IRB) approval.

Trials guidance: Trials do not consider study protocols for studies without ethical approval. You will be required to provide a copy of the original ethical approval document and an English translation of this document as an additional file on submission, which will be checked against this declaration. The name of the ethics committee that approved the study and the committee's reference number (if applicable) should be declared. Details of authors' intentions to obtain consent to participate in the study from participants (or their parent or legal guardian in the case of children under 16) should be declared. "eg. ABC Ethical Review Board ABC123456. Written, informed consent to participate will be obtained from all participants"

Written ethical approval was received from the COVID-19 National Research Ethics Committee (Ref No: 20-NREC-COV-104). Regulatory approval for the study was given by the Health Products Regulatory Authority (CT0900/650/001 Heparin Sodium). The patient consenting process for study participation was reviewed and approved by the Health Research Consent Declaration Committee (Ref: 20-026-AF1/COV). As detailed above, written informed consent/assent will be obtained from all participants.

Consent for publication {32}

SPIRIT guidance: Model consent form and other related documentation given to participants and authorised surrogates.

Trials guidance: Please do not include any baseline or pilot data in your study protocol. The Editorial Office will ask you to remove this if it is included. If you have included any details, images or videos relating to an individual person, written informed consent for the publication of these details must be obtained from that person (or their parent or legal guardian in the case of children under 18) and declared in this section. Please also state whether you will be willing to provide a model consent form on request. If this section does not apply, please state “Not applicable”.

Written informed consent or assent was obtained from all patients prior to inclusion in the trial for collection, storage, analysis and dissemination of the results of the trial. (attached)

Competing interests {28}

SPIRIT guidance: Financial and other competing interests for principal investigators for the overall trial and each study site.

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