

# INHALED nebulised unfractionated HEParin for the treatment of hospitalised patients with COVID-19 (INHALE-HEP): Protocol and Statistical Analysis Plan for an investigator-initiated international meta-trial of randomised studies

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## Abstract

Inhaled nebulised unfractionated heparin (UFH) has a strong scientific and biological rationale that warrants urgent investigation of its therapeutic potential in patients with COVID-19. UFH has antiviral effects and prevents the SARS-CoV-2 virus' entry into mammalian cells. In addition, UFH has significant anti-inflammatory and anti-coagulant properties, which limit progression of lung injury and vascular pulmonary thrombosis. Methods and intervention The INHALED nebulised unfractionated HEParin for the treatment of hospitalised patients with COVID-19 (INHALE-HEP) meta-trial is a prospective individual patient data analysis of on-going randomised controlled trials and early phase studies. Individual studies are being conducted in multiple countries. Participating studies randomise adult patients admitted to the hospital with confirmed SARS-CoV-2 infection, who do not require immediate mechanical ventilation, to inhaled nebulised UFH or standard care. All studies collect a minimum core dataset. The primary outcome for the meta-trial is intubation (or death, for patients who died before intubation) at day 28. The secondary outcomes are oxygenation, clinical worsening and mortality, assessed in time-to-event analyses. Individual studies may have additional outcomes. Analysis We use a Bayesian approach to monitoring, followed by analysing individual patient data, outcomes and adverse events. All analyses will follow the intention-to-treat principle, considering all participants in the treatment group to which they were assigned, except for cases lost to follow-up or withdrawn. Trial registration, ethics and dissemination The meta-trial is registered at ClinicalTrials.gov ID NCT04635241. Each contributing study is individually registered and has received approval of the relevant ethics committee or institutional review board.

*INHALE* d nebulised unfractionated *HEP* arin for the treatment of hospitalised patients with COVID-19

## (INHALE-HEP): Protocol and Statistical Analysis Plan for an investigator-initiated international meta-trial of randomised studies

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Authors' contributions: Chief Investigator FvH drafted the manuscript with advice from senior statisticians AR and HJY. All authors contributed to revision and finalisation of the manuscript. All authors read and approved the final draft for submission.

Meta-trial Combined Protocol and Statistical Analysis Plan **date and version** : 14 December 2020, INHALE-HEP meta-trial version 2.0

**Sponsor meta-trial:** INHALE-HEP Collaborative Research Group (CRG). Each individual investigator of every contributing trial is a member of the INHALE-HEP CRG.

**Role sponsor:** The INHALE-HEP CRG's executive committee is responsible for the meta-trial's study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication. Investigators from individual trials have ownership of their trial data. A collaboration and data sharing agreement between investigators facilitates and governs the collecting and analysing of de-identified individual patient data from individual trials and sets out eligibility for authorship.

## Declarations

Funding: No funding has been obtained for the meta-trial. Individual contributing studies/countries are responsible for their own funding.

Availability of data and material: The datasets used for the current manuscript are available from the corresponding author on reasonable request.

## Conflicts of interests

AA and MCR report a research grant for preclinical research from Grifols and from Fisher&Paykel, and payment as Scientific Advisor for Grifols, outside the submitted work. JL reports receiving an Academic Collaboration grant funded by Science Foundation Ireland and Aerogen Inc. for a different study (CHARTER-Ireland). JS is Scientific Advisor for and has shares in Ockham Biotech Ltd, which holds patents around the use of inhaled heparin. TW is Chief Investigator of the ACCORD COVID Research Programme. DS reports personal fees from AstraZeneca, personal fees from Boehringer Ingelheim, personal fees from Chiesi, personal fees from Cipla, personal fees from Genentech, personal fees from GlaxoSmithKline, personal fees from Glenmark, personal fees from Gossamerbio, personal fees from Menarini, personal fees from Mundipharma, personal fees from Novartis, personal fees from Peptinnovate, personal fees from Pfizer, personal fees from Pulmatrix, personal fees from Theravance, personal fees from Verona, outside the submitted work. CP reports receiving personal fees from Cipla, Immune Regulation, EpiEndo and Glycosynnovation, and has equity in Verona Pharma, outside of the submitted work. All other authors have nothing to disclose.

## Study approvals and registration

The Brazilian study protocol was approved by the Institute of Biomedical Sciences (ICB) Ethics Committee, Sao Paulo (ID 38660320.0.0000.5467). The Argentinian study protocol was approved by the Independent Ethics Committee for Clinical Pharmacology Trials, Buenos Aires (ID N 3183). The Egyptian study protocol was approved by the Ethics committee, Faculty of Medicine, Alexandria University (ID 2158\_11456.-4737). Each contributing study is also registered individually as follows: PACTR202007606032743 (Egypt),

NCT04530578 (Argentina). Registration and ethics approval are pending in other countries.

Keywords: COVID-19, ARDS, SARS, inhaled heparin, nebulised heparin, unfractionated heparin, SARS-CoV-2, respiratory failure, pandemic, randomised controlled trial, meta-trial

### What is already known about this subject?

- Unfractionated heparin (UFH) has antiviral properties against SARS-CoV-2 at therapeutically relevant concentrations, as well as anti-inflammatory and anticoagulant effects.
- Inhaled nebulised UFH has shown to improve outcomes in pre-pandemic experimental and clinical studies of acute lung injury and ARDS.
- There is a strong scientific rationale for urgent investigation of the therapeutic potential of inhaled nebulised UFH for COVID-19.

### What this study adds?

- This meta-trial is a prospective individual patient data analysis of on-going randomised trials and early phase studies, to determine whether inhaled nebulised UFH improves outcomes in hospitalised patients with COVID-19.
- The collective goal of this meta-trial is to reach a conclusion about the efficacy of inhaled UFH in COVID-19 as quickly as possible by pooling information from multiple clinical trials not originally configured as a network.
- The pragmatic design effectively deals with recruitment difficulties that could occur in individual studies given the uncertainties of the international dynamics of the COVID-19 pandemic.
- Individual studies contributing to the meta-trial are conducted in multiple countries, which improves effect size estimates across different conditions as well as the external validity of the results.

## Abstract

### Introduction

Inhaled nebulised unfractionated heparin (UFH) has a strong scientific and biological rationale that warrants urgent investigation of its therapeutic potential in patients with COVID-19. UFH has antiviral effects and prevents the SARS-CoV-2 virus' entry into mammalian cells. In addition, UFH has significant anti-inflammatory and anti-coagulant properties, which limit progression of lung injury and vascular pulmonary thrombosis.

### Methods and intervention

The *INHALE* d nebulised unfractionated *HEP* arin for the treatment of hospitalised patients with COVID-19 (*INHALE-HEP*) meta-trial is a prospective individual patient data analysis of on-going randomised controlled trials and early phase studies. Individual studies are being conducted in multiple countries. Participating studies randomise adult patients admitted to the hospital with confirmed SARS-CoV-2 infection, who do not require immediate mechanical ventilation, to inhaled nebulised UFH or standard care. All studies collect a minimum core dataset. The primary outcome for the meta-trial is intubation (or death, for patients who died before intubation) at day 28. The secondary outcomes are oxygenation, clinical worsening and mortality, assessed in time-to-event analyses. Individual studies may have additional outcomes.

### Analysis

We use a Bayesian approach to monitoring, followed by analysing individual patient data, outcomes and adverse events. All analyses will follow the intention-to-treat principle, considering all participants in the treatment group to which they were assigned, except for cases lost to follow-up or withdrawn.

### Trial registration, ethics and dissemination

The meta-trial is registered at ClinicalTrials.gov ID NCT04635241. Each contributing study is individually registered and has received approval of the relevant ethics committee or institutional review board. Results of

this study will be shared with the WHO, published in scientific journals and presented at scientific meetings.

## Introduction

In December 2019, a novel coronavirus (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) emerged in China and has since spread globally. Nearly 20% of patients with coronavirus disease 2019 (COVID-19) experience hypoxaemia, which is the primary reason for hospitalisation.[1] A significant proportion of patients admitted to hospital for COVID-19 develop acute respiratory failure, with 12-24% requiring intubation for invasive mechanical ventilation.[2-6]

The pathophysiology of COVID-19 associated lung injury is characterised by diffuse alveolar damage, hyperinflammation, coagulopathy, DNA neutrophil extracellular traps (NETS), hyaline membranes and microvascular thrombosis.[7]

Our group and others have previously outlined the scientific rationale for the use of nebulised unfractionated heparin (UFH) as a treatment for COVID-19.[8, 9] Nebulised UFH has anti-viral, anti-inflammatory, anticoagulant, and mucolytic effects. Our meta-trial of inhaled nebulised UFH as a repurposed drug for COVID-19 adheres to the five core principles and recommendations as described by the pharmacology community in its ASCEPT-BPS statement as follows.[10] Firstly, UFH has demonstrated antiviral activity in pre-clinical studies in concentrations relevant for administration to humans. The SARS-CoV-2 Spike S1 protein receptor binding domain attaches to UFH and undergoes conformational change that prevents it from binding to the Angiotensin Converting Enzyme 2 (ACE-2) receptor.[11, 12] It was recently demonstrated that spike protein binding to human epithelial cells requires engagement of both cell surface heparan sulphate (HS) and ACE-2, with HS acting as a co-receptor for ACE-2 interaction, and UFH blocked the binding and infectivity of SARS-CoV-2 to human bronchial epithelial cells.[13] The inhibition of SARS-CoV-2 infection of Vero E6 cells by an UFH preparation was found to be concentration dependent, occurred at therapeutically relevant concentrations and is significantly stronger compared to low molecular weight heparins (LMWHs).[14]

Secondly, the optimal concentrations of UFH can be achieved for the proposed mode of administration in the lungs (data on file in the Investigator's Brochure).

Thirdly, in our meta-trial we concurrently quantify in vivo dynamics and time course of COVID-19. Specifically, we collect and report patient-relevant clinical outcomes including rates of intubation, time course of disease progression and mortality.

Fourthly, previous studies have provided information relevant to posology optimisation for the immunomodulatory and anticoagulant effects of inhaled nebulised UFH in acute lung injury and acute respiratory distress syndrome, to ensure the appropriate intensity and timing of therapy. Animal studies of nebulised UFH in different acute lung injury models have consistently shown a positive effect on pulmonary coagulation, inflammation and oxygenation.[8] Small human studies indicate that nebulised UFH limits pulmonary fibrin deposition, attenuates progression of acute lung injury and hastens recovery.[8] Early-phase trials in patients with acute lung injury and related conditions found that nebulised UFH reduced pulmonary dead space, coagulation activation, microvascular thrombosis, improved lung injury and increased time free of ventilatory support.[15-19] In a pre-pandemic double-blind randomised study in 256 critically ill ventilated patients, nebulised UFH limited progression of lung injury including ARDS and accelerated return to home in survivors.[20] The anti-inflammatory effects of inhaled UFH are thought to reduce pulmonary hyperinflammation and the generation of DNA NETs, both of which contribute to COVID-19 lung injury. The anticoagulant actions of nebulised UFH limit fibrin deposition, hyaline membrane formation and microvascular thrombosis, which are also important features of COVID-19.

Finally, our meta-trial is innovative, robustly designed, and combines randomised controlled studies to determine efficacy and safety so that the benefit-harm balance of inhaled nebulised UFH is identified. We hypothesise that treatment with inhaled nebulised UFH of hospitalised patients with COVID-19 limits progression to acute respiratory failure requiring intubation, reduces the risk of death, reduces the risk of clinical worsening, and improves oxygenation. The collective goal of the proposed meta-trial is to reach a

conclusion about the efficacy of inhaled UFH in COVID-19 as quickly as possible by pooling information from multiple clinical trials not originally configured as a network.[21] This protocol and statistical analysis plan manuscript has been prepared in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 guideline and in accordance with published guidelines for the content of statistical analysis plans in clinical trials (Appendix 1 and 2).[22, 23]

## Objective

The primary objective of the meta-trial is to investigate whether inhaled nebulised UFH in hospitalised patients with COVID-19 who do not require immediate invasive mechanical ventilation, significantly reduces rates of intubation (or death, for patients who died before intubation) at day 28, compared to standard care alone. Primary outcomes for individual studies may be different clinical or biochemical endpoints and are listed in the individual trial protocols.

## Concept and design

A meta-trial employs prospective pooling of individual patient data from ongoing individual clinical trials and early phase studies.[21] The term “meta-trial” refers to a prospective pooled analysis planned to streamline data collection from multiple individual trials, allowing for faster accumulation of data for major clinical endpoints during the pandemic.[24] The meta-trial concept enables researchers to combine the agility of smaller national trials into a much larger international project in a short period of time.[24, 25] Meta-trial interim analysis enables to detect a positive or negative response to the scientific question as soon as an adequate sample size is reached across several countries, thus potentially speeding up the research process dramatically.[24, 26, 27] Adherence to methodological standards of individual trials represents a guarantee of a high level of overall final quality. Furthermore, by estimating the treatment effect across the various trials upfront, the meta-trial may provide stronger evidence in favour of external validity and replicability of the individual trials. Our meta-trial is designed as a collaborative prospective individual patient data analysis of on-going investigator-initiated, randomised studies of inhaled nebulised UFH in addition to standard care compared to standard care alone in hospitalised patients with confirmed COVID-19.

## Setting

This meta-trial includes studies of inhaled nebulised UFH in hospitalised patients with COVID-19 who do not immediately require invasive mechanical ventilation. A full list of participating institutions is or will be made available in each individual trial record on respective trial registries. New studies from other institutions and countries may be added to this meta-trial after publication of the meta-trial’s protocol and statistical analysis plan, provided the studies meet the eligibility criteria for the meta-trial (patient eligibility criteria, intervention, core set of outcome measures).

## Study eligibility criteria

Individual studies are eligible to be included in this prospective meta-trial if they meet the following requirements:

- Design: Prospective randomised study with an intervention group and a control group
- Patients: Inclusion and exclusion criteria as described in Table 1
- Intervention: Inhaled nebulised unfractionated heparin (the dose, frequency, delivery method and treatment duration are not specified or prescribed by the meta-trial)
- Data collection: Able to collect and provide data required for the meta-trial outcomes: intubation, death, ratio of oxygen saturation by pulse oximetry to the fraction of inspired oxygen (SpO<sub>2</sub>/FiO<sub>2</sub> ratio), modified ordinal clinical scale (Table 2) [28]
- Ethics: Approval of the protocols and related documents obtained from the relevant Human Research Ethics Committee (HREC) or Institutional Review Board (IRB) prior to the commencement of each individual study.

## Recruitment

Due to the rapidly evolving pandemic situation, we have a strong uncertainty about the pace of enrolment. There is likely to be considerable variation in the number of COVID-19 infections requiring hospitalisation in different regions. The pragmatic pre-specified pooled analysis design overcomes recruitment difficulties that could occur in the individual studies given the international dynamics of the COVID-19 pandemic.

Research coordinators and investigators at each site and for each study will work with clinicians to identify potential candidates for enrolment. Logs will be maintained of patients who met the inclusion criteria but were not enrolled, with the reason for exclusion recorded on the log.

## Interventions

Participants assigned to “nebulised UFH” receive nebulised UFH in addition to the standard care required as determined by the treating team. The dose, frequency, duration and delivery method differ between participating studies as follows:

- Brazil, USA, UK and Australia: 25,000 IU UFH every 6 hours using a vibrating mesh nebuliser (Aerogen Solo), for a maximum of 21 days or until the modified ordinal scale is 1 or 2 (Table 2)
- Egypt: 1000 IU/kg predicted body weight UFH every 6 hours for 7 days using a compressed air nebuliser (Beurer IH18)
- Argentina: 5000 IU UFH every 8 hours for 7 days using a Venturi system connected to a full-face mask (Free Breath) fitted with an HMF anti-viral expiratory filter

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.

Nebulised UFH will be withheld if any of the following occurs:

- The treating physician deems that there is a clinically unacceptable increase in APTT
- The treating physician deems that there is excessive bloodstaining of respiratory secretions
- There is pulmonary bleeding, major bleeding or suspected or confirmed heparin-induced thrombocytopenia (HIT)

Nebulised UFH will be recommenced if:

- Having been withheld because the APTT was unacceptably prolonged, the APTT becomes acceptable
- Having been withheld because there was excessive bloodstaining of upper or lower respiratory secretions, the bloodstaining of the respiratory secretions has resolved
- Having been withheld for pulmonary bleeding or major bleeding, the bleeding is definitively controlled
- Having been withheld for suspected HIT, the patient is found not to have this condition

## Relevant concomitant care permitted or prohibited during the trial

Treatment with any or all of the following therapies is permitted during the participating studies and not a reason to withhold study medication: deep vein thrombosis prophylaxis with UFH or low molecular weight heparin (LMWH); ‘full’ therapeutic dose UFH or LMWH for a recognised clinical indication; non-heparin anticoagulants; anti-thrombotic medications; protamine; prone positioning; and inhaled nitric oxide. There are no prohibitions during the trial.

## Provisions for post-trial care

Post-trial care will be standard care through the standard healthcare system from each institution and jurisdiction in each individual study.

## Outcome definitions

### *Primary outcome*

The primary outcome is intubation (or death, for patients who died before intubation) at day 28 after randomisation.

### *Secondary outcomes*

The secondary outcomes are:

- Survival to day 28; Survival to day 60; and Survival to hospital discharge, censored at day 60
- Daily ratio of oxygen saturation by pulse oximetry to the fraction of inspired oxygen (SpO<sub>2</sub>/FiO<sub>2</sub> ratio, highest and lowest levels)
- Daily change in modified ordinal score from baseline to day 14
- Worsening on the modified ordinal scale (see Table 2) at 3, 7 and 14 days

### *Safety outcomes*

The safety outcomes are as follows:

- Number who record major bleeding. 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.
- Number who record pulmonary bleeding. Pulmonary bleeding is frank bleeding in the lungs, trachea or bronchi with repeated haemoptysis or requiring repeated suctioning *and* associated with acute deterioration in respiratory status.
- Number who record epistaxis.
- Number who record HIT. HIT is defined as an unexplained fall in platelet count *and* a positive heparin antibody test.
- Number who record other adverse events and reactions. Adverse events and reactions are those that, in the site Principal Investigator's judgement, are not part of the expected clinical course *and* could be related (at least possibly) to the study *and* were medically significant or had serious sequelae for the patient.

### *Process of care assessments*

Process of care assessments are as follows:

- Time from hospital admission to randomisation
- Total cumulative dose of nebulised heparin
- Days of treatment with nebulised heparin
- Mean daily APTT among all participants, and among those treated with intravenous or subcutaneous unfractionated heparin, and among those not treated with intravenous or subcutaneous unfractionated heparin
- Highest APTT among all participants, and among those treated with intravenous or subcutaneous unfractionated heparin, and among those not treated with intravenous or subcutaneous unfractionated heparin
- Days of treatment with each of the following therapies while in the study: unfractionated heparin, IV and SC; LMWH, IV and SC; lopinavir-ritonavir; remdesivir; hydroxychloroquine; interferon- $\beta$ ; interleukin antagonists; oseltamivir, laninamivir, zaninamivir or peramivir; macrolide; non-macrolide antibacterial; antifungal; corticosteroid; inotrope or vasopressor infusion; and renal replacement.

### *Other Outcomes*

Individual studies may have various other primary and secondary outcomes, which are listed in the individual study protocols.

### **Data Collection**

In each study, data will be collected by trained staff under the supervision of the site principal investigator using a case report form and data dictionary. Data will be collected at baseline, from day 0-14 (blood tests,

SpO<sub>2</sub>/FiO<sub>2</sub> ratio, modified ordinal scale); on day 28 and day 60 (invasive mechanical ventilation status, vital status, discharge status). The detailed list of collected data items and the schedule for data collection are described in the individual study protocols.

De-identified individual patient data from each contributing study will be shared with the meta-trial executive committee under a signed data-sharing agreement and stored in a secure data collection platform, administered by the Australian National University. Electronic information will be kept on password protected computers accessible only to authorised personnel. 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 for a period as required by local laws and regulations. Any paper study material that requires disposal will be shredded using a commercial grade shredder or other means that preserves the confidentiality of participants. Any electronic data requiring disposal will be thoroughly erased from its electronic media. Each participating study will maintain a log of enrolled patients that includes patient identifiers. Patient identifiers are not transferred to the meta-trial coordinating centre, but it must be possible to reidentify patients by each participating study to allow future audit against source documents.

## Data management

### *Randomisation, allocation concealment and blinding*

All contributing studies are randomised controlled studies. At randomisation each participant is assigned to nebulised heparin or standard care in a one-to-one allocation ratio. Allocation concealment is performed at the level of each study as specified in the respective study protocols. All contributing studies are open label by design. The meta-trial data analysts are blinded. Unblinding is permissible when pre-specified Bayesian stopping rules for efficacy or safety have been met.

### *Data Safety Monitoring Board*

There is no independent Data Safety Monitoring Board (DSMB) for the meta-trial. DSMBs are recommended for individual studies and will be specified in the protocols of the individual studies if applicable. The INHALE-HEP executive committee and the trial statisticians are responsible for Bayesian monitoring of the meta-trial.

### *Quality Assurance Monitoring*

Conduct and progress of this meta-trial will be monitored on an ongoing basis by the meta-trial executive committee.

## Statistical Analysis

### *Principles*

This prospective analysis will be carried out on studies conducted in multiple countries, which increases effect size estimates across different conditions as well as the external validity of the results. We plan a prospective analysis of individual de-identified patient-level data. Common variables from all datasets will be combined to conduct the analysis.

If consent for participation is withdrawn or consent to continue is not given, the data will not be used unless consent to do so is obtained, including for all mortality time points. Analyses will be performed by intention-to-treat according to the participants' randomly allocated group, regardless of treatment compliance. These analyses will include participants for whom consent to continue is refused but the use of data already collected is allowed, including the primary outcome, and will exclude patients who do not fulfil the study entry criteria.[29]

Missing data will not be imputed. The multilevel models described in the analysis are able to handle missing data due to loss to follow-up. Where there are missing observations, the number of observations used will be reported. Two-sided hypothesis testing at a significance level of 0.05 will be used. No adjustment for multiple tests will be made, with the interpretation of the significance of the tests being appropriate for the

primary or secondary nature of the outcome. Analyses will be conducted using the Statistical Package for the Social Sciences (SPSS) Research Engine, Version 24.0 IBM SPSS Statistics or later, and “R” version 3.5.0 or later.

### *Sample Size*

To demonstrate a clinically important reduction in the primary outcome, a sample size of 712 is required, assuming a decrease in the proportion of patients receiving invasive mechanical ventilation from 12% to 6%, with power 80% and a two-sided significance level of 0.05.

Each individual contributing study may have a different sample size based on their primary outcome, which will have been reported on the individual trial registrations.

### *Monitoring and Interim analyses*

We plan to perform monthly monitoring and analysis of the primary outcome in the accumulating data, with use of Bayesian monitoring rules that allow timely decisions without the penalties for multiple data looks and alpha spending associated with the classic randomised controlled trial monitoring approach. [21, 30, 31] At the first interim analysis, the prior distribution of the proportion of patients intubated will be multiplied by the likelihood of the observed data to give a posterior distribution of the proportion of patients intubated. At each subsequent interim analysis, the previous posterior distribution becomes the new prior, and a new posterior distribution of the proportion of patients who were intubated will be reported. The pooling of data into the prior distributions and the Bayesian updating of posterior distributions prevent the stopping rule from being overly influenced by potential bias from differential recruitment rates in different trials. Prespecified monitoring criteria will guide the recommendations of the meta-trial’s executive committee. If the probability of a difference in proportions of intubated patients in the two groups of 6% or more rises above 0.90, then the executive committee can recommend that interim analyses be conducted following the methods in the analyses section, to support a decision to stop the meta-trial for efficacy. If the probability of a difference in proportions of 6% or more falls below 0.10, then the executive committee can recommend that interim analyses be conducted following the methods in the analyses section, to support a decision to stop the meta-trial for futility.[31, 32]

### *Trial profile*

Patient flow through the meta-trial will be presented in a Consolidated Standards of Reporting Trials diagram (Figure 1).[33] We will report the number of patients who meet the trial eligibility criteria, the number of patients randomised, and the number of patients in the intention-to-treat dataset for whom data are available for evaluation of the primary outcome.

### *Participant characteristics and baseline comparisons*

Patient characteristics at baseline will be tabulated by treatment group (Table 3). The categorical variables will be presented as frequency counts (n) and as a proportion of the number of patients with available data (%). Continuous variables will be presented as summary statistics for location (mean or median) and variability (standard deviation or interquartile range). The total counts for variables with missing data will be indicated.

### *Analyses*

#### *Primary outcome*

The primary outcome is intubation (or death, for patients who died before intubation) after randomisation. This will be assessed in a time to event analysis and a regression analysis of the proportion of patients receiving intubation by day 28 after randomisation.

Because of the meta-trial design, we use multilevel modelling (patients nested in sites nested in trials), with site as a random effect and trial as a fixed effect, along with testing the effect of other covariates as collected in the common variable set. The fixed effect of dose and device will also be estimated across the sites which

use different combinations. The fixed effect of country can also be assessed amongst the trials which use the same dose-device combination.

We analyse binomial outcomes using multilevel logistic regression, reported as odds ratios and 95% confidence intervals. We analyse time to death using multilevel Cox proportional-hazards regression, reported as hazard ratios and 95% confidence intervals. For time to intubation, death will be treated as a competing risk. The analysis will compare the cause-specific hazard in the treatment groups using the same multilevel Cox proportional hazards model.[34] Continuous outcomes will be analysed using multilevel linear regression, reported as differences in means and 95% confidence intervals. We will present intubation to 28 days using a Kaplan–Meier survival curve and compare groups using a stratified log-rank test.

### *Secondary outcomes*

Secondary outcomes will be analysed with the same analyses as described for the primary outcome.

### *Subgroup analyses*

We plan to undertake subgroup analyses of the following variables: severity of COVID-19 (according to the PaO<sub>2</sub>/FiO<sub>2</sub> ratio and the modified ordinal scale), duration of intervention, time from admission to start of intervention, time from development of symptoms to start of intervention, administration of other therapies, age and sex of the patients.

### *Safety outcomes and adverse events*

Adverse events are categorised as “not related”, “unlikely”, “possibly”, “probably” or “definitely related” to treatment, as determined by site investigators. Events will be tabulated by treatment group and reported as frequency counts (n) and proportions (%).

### *Future analyses*

Individual studies contributing to the meta-trial may be analysed and published separately as per the original protocols of these studies. We will consider conducting hypothesis-generating exploratory analyses other than those pre-specified above to further evaluate the impact of nebulised heparin on outcomes in this dataset. Any such analyses conducted after knowing the main results of the INHALE-HEP meta-trial will be cautiously interpreted and clearly indicated in any subsequent publications.

## **Ethics and dissemination**

All contributing studies and the meta-trial will be performed in accordance with the ethical principles of the Declaration of Helsinki. Approval of the protocols and related documents will be obtained from the relevant Human Research Ethics Committee (HREC) or Institutional Review Board (IRB) prior to the commencement of each individual study. These authorisations will include data inclusion in the pooled analysis. The investigators of the individual studies will ensure that all HREC/IRB conditions for the conduct of each study are met and that all requisite information is submitted to the responsible HREC/IRB. Any protocol modifications will be communicated timely to relevant parties, including investigators and HREC/IRBs.

The individual study protocols outline the process and requirements for obtaining patients’ consent to participate in their study and as required by local laws and regulations.

The results of this study will be provided to the WHO, published in peer-reviewed medical journals and presented to the medical community and other stakeholders.

## **Study status**

At the time of submitting for publication, the studies in Argentina, Egypt and Brazil are recruiting patients. Preparations for the studies in the USA, UK and Australia are underway.

## **Conclusion**

Nebulised UFH has a strong scientific and biological rationale, and warrants urgent investigation of its therapeutic potential, for COVID-19. This investigator-initiated international individual patient data meta-trial of randomised controlled trials and early phase studies investigates the efficacy and safety of nebulised UFH, on relevant outcomes in patients who are hospitalised for COVID-19. Our pre-specified meta-trial protocol and statistical analysis plan was prepared before completion of patient recruitment and data collection. The protocol provides a detailed description of the principles and methods for analysing and reporting the trial results and is in keeping with best research practice.

## Legend

Figure 1: Consolidated Standards of Reporting Trials (CONSORT) diagram of participants in the INHALE-HEP meta-trial

Table 1: Patient eligibility criteria for enrolment in studies contributing to the INHALE-HEP meta-trial

Table 2: Modified Ordinal Clinical Scale for COVID-19

Table 3: Presentation of Baseline Characteristics of the Patients

Appendix 1: Reporting checklist for a protocol, based on the SPIRIT guidelines

Appendix 2: Statistical analysis plan checklist

## References

1. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA* 2020.
2. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, Cereda D, Coluccello A, Foti G, Fumagalli R, Iotti G, Latronico N, Lorini L, Merler S, Natalini G, Piatti A, Ranieri MV, Scandroglio AM, Storti E, Cecconi M, Pesenti A, Network C-LI, Nailescu A, Corona A, Zangrillo A, Protti A, Albertin A, Forastieri Molinari A, Lombardo A, Pezzi A, Benini A, Scandroglio AM, Malara A, Castelli A, Coluccello A, Micucci A, Pesenti A, Sala A, Alborghetti A, Antonini B, Capra C, Troiano C, Roscitano C, Radrizzani D, Chiumello D, Coppini D, Guzzon D, Costantini E, Malpetti E, Zoia E, Catena E, Agosteo E, Barbara E, Beretta E, Boselli E, Storti E, Harizay F, Della Mura F, Lorini FL, Donato Sigurta F, Marino F, Mojoli F, Rasulo F, Grasselli G, Casella G, De Filippi G, Castelli G, Aldegheri G, Gallioli G, Lotti G, Albano G, Landoni G, Marino G, Vitale G, Battista Perego G, Evasi G, Citerio G, Foti G, Natalini G, Merli G, Sforzini I, Bianciardi L, Carnevale L, Grazioli L, Cabrini L, Guatteri L, Salvi L, Dei Poli M, Galletti M, Gemma M, Ranucci M, Riccio M, Borelli M, Zambon M, Subert M, Cecconi M, Mazzoni MG, Raimondi M, Panigada M, Belliato M, Bronzini N, Latronico N, Petrucci N, Belgiorio N, Tagliabue P, Cortellazzi P, Gnesin P, Grosso P, Gritti P, Perazzo P, Severgnini P, Ruggeri P, Sebastiano P, Covello RD, Fernandez-Olmos R, Fumagalli R, Keim R, Rona R, Valsecchi R, Cattaneo S, Colombo S, Cirri S, Bonazzi S, Greco S, Muttini S, Langer T, Alaimo V, Viola U. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. *JAMA* 2020.
3. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, Huang H, Zhang L, Zhou X, Du C, Zhang Y, Song J, Wang S, Chao Y, Yang Z, Xu J, Zhou X, Chen D, Xiong W, Xu L, Zhou F, Jiang J, Bai C, Zheng J, Song Y. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med* 2020.
4. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* 2020.
5. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, the Northwell C-RC, Barnaby DP, Becker LB, Chelico JD, Cohen SL, Cookingham J, Coppa K, Diefenbach MA, Dominello AJ, Duer-Hefele J, Falzon L, Gitlin J, Hajizadeh N, Harvin TG, Hirschwerk DA, Kim EJ, Kozel ZM, Marrast

- LM, Mogavero JN, Osorio GA, Qiu M, Zanos TP. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA* 2020; 323: 2052-59.
6. Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, Tobin KA, Cerfolio RJ, Francois F, Horwitz LI. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. *BMJ* 2020; 369: m1966.
  7. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, Vanstapel A, Werlein C, Stark H, Tzankov A, Li WW, Li VW, Mentzer SJ, Jonigk D. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. *N Engl J Med* 2020.
  8. van Haren FMP, Page C, Laffey JG, Artigas A, Camprubi-Rimblas M, Nunes Q, Smith R, Shute J, Carroll M, Tree J, Carroll M, Singh D, Wilkinson T, Dixon B. Nebulised heparin as a treatment for COVID-19: scientific rationale and a call for randomised evidence. *Crit Care* 2020; 24: 454.
  9. Conzelmann C, Muller JA, Perkhofer L, Sparrer KM, Zelikin AN, Munch J, Kleger A. Inhaled and systemic heparin as a repurposed direct antiviral drug for prevention and treatment of COVID-19. *Clin Med (Lond)* 2020.
  10. Baker EH, Gnjjidic D, Kirkpatrick CMJ, Pirmohamed M, Wright DFB, Zecharia AY. A call for the appropriate application of clinical pharmacological principles in the search for safe and efficacious COVID-19 (SARS-CoV-2) treatments. *Br J Clin Pharmacol* 2020.
  11. Mycroft-West C, Su D, Elli S, Guimond S, Miller G, Turnbull J, Yates E, Guerrini M, Fernig D, Lima M, Skidmore M. The 2019 coronavirus (SARS-CoV-2) surface protein (Spike) S1 Receptor Binding Domain undergoes conformational change upon heparin binding. *bioRxiv* 2020.
  12. Kwon PS, Oh H, Kwon SJ, Jin W, Zhang F, Fraser K, Hong JJ, Linhardt RJ, Dordick JS. Sulfated polysaccharides effectively inhibit SARS-CoV-2 in vitro. *Cell Discov* 2020; 6: 50.
  13. Clausen TM, Sandoval DR, Spliid CB, Pihl J, Perrett HR, Painter CD, Narayanan A, Majowicz SA, Kwong EM, McVicar RN, Thacker BE, Glass CA, Yang Z, Torres JL, Golden GJ, Bartels PL, Porell RN, Garretson AF, Laubach L, Feldman J, Yin X, Pu Y, Hauser BM, Caradonna TM, Kellman BP, Martino C, Gordts P, Chanda SK, Schmidt AG, Godula K, Leibel SL, Jose J, Corbett KD, Ward AB, Carlin AF, Esko JD. SARS-CoV-2 Infection Depends on Cellular Heparan Sulfate and ACE2. *Cell* 2020; 183: 1043-57 e15.
  14. Tree JA, Turnbull JE, Buttigieg KR, Elmore MJ, Coombes N, Hogwood J, Mycroft-West CJ, Lima MA, Skidmore MA, Karlsson R, Chen YH, Zhang Y, Spalluto CM, Staples KJ, Yates EA, Gray E, Singh D, Wilkinson T, Page CP, Carroll MW. Unfractionated heparin inhibits live wild-type SARS-CoV-2 cell infectivity at therapeutically relevant concentrations. *Br J Pharmacol* 2020.
  15. Dixon B, Schultz MJ, Hofstra JJ, Campbell DJ, Santamaria JD. Nebulized heparin reduces levels of pulmonary coagulation activation in acute lung injury. *Crit Care* 2010; 14: 445.
  16. Dixon B, Campbell DJ, Santamaria JD. Elevated pulmonary dead space and coagulation abnormalities suggest lung microvascular thrombosis in patients undergoing cardiac surgery. *Intensive Care Medicine* 2008; 34: 1216-23.
  17. Dixon B, Schultz MJ, Smith R, Fink JB, Santamaria JD, Campbell DJ. Nebulized heparin is associated with fewer days of mechanical ventilation in critically ill patients: a randomized controlled trial. *Crit care* 2010; 14: R180.
  18. Dixon B, Smith R, Santamaria JD, Orford NR, Wakefield BJ, Ives K, McKenzie R, Zhang B, Yap CH. A trial of nebulised heparin to limit lung injury following cardiac surgery. *Anaesth Intensive Care* 2016; 44: 28-33.
  19. Dixon B, Smith R. Nebulised Heparin for Lung Injury - Clinical Protocol V1. In: St.Vincent's Hospital Melbourne Australia, 2011.

20. Dixon B, Smith R, Campbell D, Moran J, Doig G, Rechnitzer T, MacIsaac C, Simpson N, van Haren F, Ghosh A, Gupta S, Broadfield E, Crozier T, French C, Santamaria J. Nebulised heparin for patients with or at risk of acute respiratory distress syndrome: a multicentre, randomised, double-blind, placebo-controlled phase 3 trial. *Lancet Respir Med* [accepted for publication 05 October 2020; in-press].
21. Petkova E, Antman EM, Troxel AB. Pooling Data From Individual Clinical Trials in the COVID-19 Era. *JAMA* 2020.
22. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gotzsche PC, Krleza-Jeric K, Hrobjartsson A, Mann H, Dickersin K, Berlin JA, Dore CJ, Parulekar WR, Summerskill WS, Groves T, Schulz KF, Sox HC, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013; 158: 200-7.
23. Gamble C, Krishan A, Stocken D, Lewis S, Juszcak E, Dore C, Williamson PR, Altman DG, Montgomery A, Lim P, Berlin J, Senn S, Day S, Barbachano Y, Loder E. Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. *JAMA* 2017; 318: 2337-43.
24. Li J, Pavlov I, Laffey JG, Roca O, Mirza S, Perez Y, McNicholas B, Cosgrave D, Vines D, Tavernier E, Ehrmann S. Meta-trial of awake prone positioning with nasal high flow therapy: Invitation to join a pandemic collaborative research effort. *J Crit Care* 2020; 60: 140-42.
25. Tavernier E, Trinquart L, Giraudeau B. Finding Alternatives to the Dogma of Power Based Sample Size Calculation: Is a Fixed Sample Size Prospective Meta-Experiment a Potential Alternative? *PLoS One* 2016; 11: e0158604.
26. Simonsen L, Higgs E, Taylor RJ. Clinical research networks are key to accurate and timely assessment of pandemic clinical severity. *Lancet Glob Health* 2018; 6: e956-e57.
27. Memoli MJ. Pandemic research in the ICU: always be prepared. *Crit Care Med* 2013; 41: 1147-8.
28. Characterisation WHOvGOTC, Management of C-i. A minimal common outcome measure set for COVID-19 clinical research. *Lancet Infect Dis* 2020; 20: e192-e97.
29. Fergusson D, Aaron SD, Guyatt G, Hebert P. Post-randomisation exclusions: the intention to treat principle and excluding patients from analysis. *BMJ* 2002; 325: 652-4.
30. Lewis RJ, Angus DC. Time for Clinicians to Embrace Their Inner Bayesian?: Reanalysis of Results of a Clinical Trial of Extracorporeal Membrane Oxygenation. *JAMA* 2018; 320: 2208-10.
31. Saville BR, Connor JT, Ayers GD, Alvarez J. The utility of Bayesian predictive probabilities for interim monitoring of clinical trials. *Clin Trials* 2014; 11: 485-93.
32. Pedroza C, Tyson JE, Das A, Laptook A, Bell EF, Shankaran S, for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Advantages of Bayesian monitoring methods in deciding whether and when to stop a clinical trial: an example of a neonatal cooling trial. *Trials* 2016; 17: 335.
33. Schulz KF, Altman DG, Moher D, Group C. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010; 340: c332.
34. Stone JH, Frigault MJ, Serling-Boyd NJ, Fernandes AD, Harvey L, Foulkes AS, Horick NK, Healy BC, Shah R, Bensaci AM, Woolley AE, Nikiforow S, Lin N, Sagar M, Schrage H, Huckins DS, Axelrod M, Pincus MD, Fleisher J, Sacks CA, Dougan M, North CM, Halvorsen YD, Thurber TK, Dagher Z, Scherer A, Wallwork RS, Kim AY, Schoenfeld S, Sen P, Neilan TG, Perugino CA, Unizony SH, Collier DS, Matza MA, Vinh JM, Bowman KA, Meyerowitz E, Zafar A, Drobni ZD, Bolster MB, Kohler M, D'Silva KM, Dau J, Lockwood MM, Cubbison C, Weber BN, Mansour MK, Investigators BBTT. Efficacy of Tocilizumab in Patients Hospitalized with Covid-19. *N Engl J Med* 2020.

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