Statistical analysis plan for the INHALEd nebulised unfractionated HEParin for the treatment of hospitalised patients with COVID-19 (INHALE-HEP) meta-trial

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Abstract

The INHALE-HEP meta-trial is a prospective collaborative individual participant data meta-analysis of randomised controlled trials and early phase studies, to evaluate whether inhaled nebulised UFH in hospitalised patients with COVID-19 who do not require immediate invasive mechanical ventilation, significantly reduces intubation (or death, for patients who died before intubation) at day 28 compared to standard care alone. Objective: In keeping with best practice and with the published protocol, a pre-specified statistical analysis plan has been described and made public before completion of patient recruitment and data collection into the INHALE-HEP meta-trial. Methods: Our statistical analysis plan was designed by the INHALE-HEP executive committee and statisticians and approved by the INHALE-HEP steering committee. We reviewed the data collected as specified in the meta-trial protocol and collected in individual contributing studies. We present information pertaining to data collection, pre-specified subgroups, and study outcomes. Primary and secondary outcomes are defined, and additional subgroup analyses of pre-defined variables are described. Results: We have described our methods for presenting the trial profile and baseline characteristics, as well as our Bayesian approach to monitoring and meta-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considering all participants in the treatment group to which they were assigned, except for cases lost to follow-up or withdrawn. Conclusion: To minimise analytical bias, we have developed a statistical analysis plan and made this available to the public domain before completion of patient recruitment and data collection into the INHALE-HEP meta-trial.

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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 meta-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.

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Competing interests:

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Meta-trial registration: ClinicalTrials.gov ID NCT04635241

Abstract

Background:

The *INHALE* d nebulised unfractionated *HEP* arin for the treatment of hospitalised patients with COVID-19 (INHALE-HEP) meta-trial is a prospective collaborative individual participant data meta-analysis of randomised controlled trials and early phase studies, to evaluate whether inhaled nebulised UFH in hospitalised patients with COVID-19 who do not require immediate invasive mechanical ventilation, significantly reduces intubation (or death, for patients who died before intubation) at day 28 compared to standard care alone.

Objective:

In keeping with best practice and with the published protocol, a pre-specified statistical analysis plan has been described and made public before completion of patient recruitment and data collection into the INHALE-HEP meta-trial.

Methods: Our statistical analysis plan was designed by the INHALE-HEP executive committee and statisticians and approved by the INHALE-HEP steering committee. We reviewed the data collected as specified in the meta-trial protocol and collected in individual contributing studies. We present information pertaining to data collection, pre-specified subgroups, and study outcomes. Primary and secondary outcomes are defined, and additional subgroup analyses of pre-defined variables are described.

Results: We have described our methods for presenting the trial profile and baseline characteristics, as well as our Bayesian approach to monitoring and meta-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.

Conclusion: To minimise analytical bias, we have developed a statistical analysis plan and made this available to the public domain before completion of patient recruitment and data collection into the INHALE-HEP meta-trial.

Introduction

INHALE-HEP is a prospective collaborative individual participant data meta-analysis of randomised controlled trials and early phase studies, to determine whether treatment with nebulised unfractionated heparin (UFH) improves relevant outcomes in hospitalised COVID-19 patients who do not require immediate mechanical ventilation. Individual studies take place in multiple countries.

INHALE-HEP is registered on ClinicalTrials.gov (NCT04545541). The full details of our trial methodology are published in a separate manuscript in this journal. [REFERENCE BJCP]

We previously outlined the scientific rationale and current pre-clinical and clinical evidence for the use of nebulised UFH as a treatment for COVID-19 in a comprehensive review article.[1] In addition to the well-known anti-inflammatory and anticoagulant effects, UFH has proven anti-viral activity against SARS-CoV-2.[2] In a pre-pandemic double-blind randomised study in 256 critically ill ventilated patients, nebulised UFH limited progression of lung injury and accelerated return to home in survivors.[3]

Here we describe the pre-specified statistical analysis plan developed by the study executive committee and trial statisticians before completion of patient recruitment and data collection. Our statistical analysis plan outlines the principles and methods of analysing and reporting the trial results. The use of a pre-specified plan is recommended to reduce the risk of analysis bias arising from knowledge of the trial results emerging during the conduct of the analyses.[4, 5] This statistical analysis plan has been prepared in accordance with published guidelines for the content of statistical analysis plans in clinical trials (Appendix).[5]

Aims and hypotheses

The primary hypothesis of the meta-trial is that 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. We also

hypothesise that treatment with inhaled nebulised UFH of hospitalised patients with COVID-19 reduces the risk of death, reduces the risk of clinical worsening, and improves oxygenation.

The collective aim of the study 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, and therefore with different treatment protocols, control conditions and primary outcomes. [6]

Design

Population

Hospitalised adult patients with confirmed SARS-CoV-2 infection meeting all the inclusion criteria and none of the exclusion criteria (Table 1).

Study concept and design

The meta-trial employs prospective pooling of individual patient data from ongoing individual clinical trials and early phase studies.[6] The term "meta-trial" has been previously referenced by Li et al,[7] referring to a prospective meta-analysis planned to streamline data collection from multiple individual trials, allowing for faster accumulation of data for major clinical endpoints during the pandemic. This meta-trial is designed as a collaborative prospective individual patient data meta-analysis of investigator-initiated, randomised studies of nebulised UFH in addition to standard care, compared to standard care alone, in hospitalised patients with confirmed COVID-19 infection. The primary outcome of the meta-trial is intubation (or death, for patients who died before intubation) at day 28 after randomisation. Primary outcomes for individual studies may be clinical or biochemical endpoints and are listed in the individual trial protocols.

Study setting

This meta-trial will include hospitalised patients with COVID-19 who do not immediately require invasive mechanical ventilation from participating studies. A full list of participating institutions is available in each individual trial record on respective trial registries. 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 criteria for the meta-trial (patient eligibility criteria, intervention, core set of outcome measures).

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 hospital admission in different countries and regions. The pragmatic pre-specified prospective meta-analysis design essentially deals with recruitment difficulties that could occur in the individual trials given the international dynamics of the COVID-19 pandemic.

Randomisation

Each individual study is randomised employing a one-to-one allocation ratio. At randomisation each participant is assigned to nebulised unfractionated heparin or standard care. For analysis, randomisation will be stratified at the individual study level.

Interventions

Participants assigned to "nebulised UFH" will receive nebulised UFH 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.

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 include:

- 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 (SpO2/FiO2 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

Other Outcomes

Safety outcomes and process of care assessments are described in our methodology article published in this journal. [REFERENCE BJCP] We will also collect information regarding protocol adherence and deviations from the protocol. Individual studies in the meta-trial may have various other additional outcomes, which are listed in the individual study protocols.

Data Collection

Data will be collected by trained staff at each site 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, SpO2/FiO2 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 provided in the individual study protocols.

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 intubation from 12% to 6%, with power 80% and a two-sided significance level of 0.05.

Statistical Analysis

Principles

This prospective meta-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 meta-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.[8]

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.

Monitoring and Interim analyses

We plan to perform monthly monitoring and analysis of the accumulating data, with use of Bayesian stopping rules that allow timely decisions without the penalties for multiple data looks and alpha spending associated with the classic randomised controlled trial monitoring approach. [18, 21, 22]. 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. The prespecified stopping criteria will guide the recommendations of the meta-trial's executive committee. For example, if the probability of a difference in proportions of 6% or more falls below 0.10, then the steering committee can recommend that the meta-trial can be stopped for futility.[9, 10]

Trial profile

Patient flow through the meta-trial will be presented in a Consolidated Standards of Reporting Trials diagram (Figure 1).[11] 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 regression 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.[12] 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.

Prior distributions will be placed on all parameters in the regression models described. Three types of priors will be employed: sceptical, neutral and enthusiastic.[9] For example, the neutral prior will be centred at 0, the enthusiastic prior at the clinically important effect mentioned in the sample size calculation and the sceptical priors at the negative of that clinically important effect.

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 PaO2/FiO2 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.

Conclusion

This investigator-initiated international prospective meta-trial of randomised controlled trials and early phase studies will investigate the efficacy and safety of nebulised UFH, on relevant outcomes in hospitalised COVID-19 patients. Our pre-specified statistical analysis plan was prepared before completion of patient recruitment and data collection of the INHALE-HEP meta-trial. The plan 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: Eligibility criteria for enrolment in the INHALE-HEP meta-trial

Table 2: Modified Ordinal Clinical Scale for COVID-19

Table 3: Presentation of Baseline Characteristics of the Patients

Appendix: Statistical analysis plan checklist

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`Table 2 SAP Ordinal Scale.docx` available at https://authorea.com/users/381121/articles/561966-statistical-analysis-plan-for-the-inhaled-nebulised-unfractionated-heparin-for-the-treatment-of-hospitalised-patients-with-covid-19-inhale-hep-meta-trial

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`Table 3 INHALE-HEP baseline characteristics.docx` available at https://authorea.com/users/381121/articles/561966-statistical-analysis-plan-for-the-inhaled-nebulised-unfractionated-heparin-for-the-treatment-of-hospitalised-patients-with-covid-19-inhale-hep-meta-trial

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CONSORT Flow Diagram INHALE-HEP SAP.docx available at https://authorea.com/users/381121/articles/561966-statistical-analysis-plan-for-the-inhaled-nebulised-unfractionated-heparin-for-the-treatment-of-hospitalised-patients-with-covid-19-inhale-hep-meta-trial