IntraNasal HEpaRin Trial (INHERIT)

A randomised, placebo-controlled trial to Investigate the efficacy of intranasal heparin treatment to reduce transmission of SARS-CoV-2 infection and COVID disease among household contacts of SARS-CoV-2+ adults and children

Statistical Analysis Plan

Version 1
24 February 2025

Protocol number: NCT05204550

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List of abbreviations

CDC	Centers for Disease Control and Prevention
CCSSSS	COVID-19 Composite Subjective Symptom Severity Score
COVID-19	Coronavirus disease 2019
DASS	Depression, Anxiety, and Stress Scales
GLM	generalized linear mixed models
HIT	Heparin-Induced Thrombocytopenia
ISTH	International Society on Thrombosis and Haemostasis
ITT	Intent-To-Treat
IQR	Interquartile Range
NATA	National Association of Testing Authorities (Australia)
PAOFI	Patient's Assessment of Own Functioning Inventory
PCR	Polymerase chain reaction
PI	Principal Investigator
RAT	Rapid Antigen test
SARS-CoV-2	Severe acute respiratory syndrome Coronavirus 2
SD	Standard Deviation
T-MoCA	Telephone Montreal Cognitive Assessment
UFH	Unfractionated Heparin
WAIS	Wechsler Adult Intelligence Scale

Clarification of terms used:

Day 1 swab: Day 1 swab is defined as the swab taken before starting study drug. This could be on the same day as starting study drug.

Index case: The initial SARS-CoV-2 infected person who reached out for enrolment into the study. In the analysis, the index case is not analysed separately from the other household members. The index case does play a role in the randomisation by determining one of the randomisation strata. Some of the covariates included in multivariate models are also determined at the index case level.

Household contact: A household contact is any household member other than the index case.

Household member: This is a synonym for study participant, and means index cases and household contacts combined. For most analyses, we will include household members, by their SARS-CoV-2 status on day 1.

1. ADMINISTRATIVE INFORMATION

Protocol: Number: NCT05204550; Version: 10; date: 8 Feb 2024
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1.1 Document version history

Version Date	Version	Author	Signature	Change Description	Reason/Comment
24 Feb 2025	1.0		[redacted]	Initial release.	Not applicable.

1.2 Approvals

The undersigned have reviewed this plan and approve it as final. They find it to be consistent with the requirements of the protocol as it applies to their respective areas. They also find it to be compliant with ICH-E9 principles and confirm that this analysis plan was developed in a completely blinded manner (i.e. without knowledge of the effect of the intervention being assessed)

Name	Role on Study	Affiliation	Signature	Date
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2. STUDY SYNOPSIS

The aim of this study is to address the question: Does early treatment of index case and early pre/post exposure prophylaxis of household members with intranasal heparin reduce transmission to household family contacts on Severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) Polymerase chain reaction (PCR) assay by day 10, and subsequently reduce the burden of severe Coronavirus disease 2019 (COVID-19) as

measured by hospitalisation rates in exposed/infected people? A secondary outcome is whether intranasal heparin reduces the duration of transmissibility within the index case.

Multi-centre, prospective, cluster randomised, placebo-controlled two-arm superiority clinical trial.

Individual households with at least one person with PCR or RAT confirmed SARS-CoV-2 infection will be randomised so that all consenting people in that household receive intranasal heparin or placebo. Participants will receive intervention for 10 days and undergo 12 months of follow-up. The primary outcomes are achieved within 10 days. The majority of secondary outcomes related to primary COVID-19 infection are followed for 28 days from randomisation. The secondary outcomes related to "long COVID" are monitored at 6 and 12 months post randomisation.

The target sample size for the primary outcome is 1100 individuals. We planned to enroll 268 households and 1072 individuals.

The rate of subsequent PCR confirmed SARS-CoV-2 infections in exposed households will be measured to determine the effect of intranasal heparin on reducing transmission to close contacts.

The rate of symptom development in all participants will be used to determine effect of treatment in preventing symptomatic disease. The rate of hospitalisation of all participants will be measured to determine the effect of treatment on development of severe disease. The presence of clinical neurological long COVID symptoms will be assessed at 6 and 12 months to determine the effect of treatment on long COVID.

2.1. Primary objective

To test the efficacy of early treatment and post exposure prophylaxis to reduce transmission to household family contacts on SARS-CoV-2 PCR assay by day 10.

Measure: Number of household contacts (swab negative on day 1) testing positive for SARS-CoV-2 by PCR on either of three routine nasopharyngeal swabs on day 3, 5 and 10 after enrolment or on clinically driven swab in the first 10 days. Day 1 swab is defined as the swab taken before starting study drug. This could be on the same day as starting study drug.

2.2. Secondary objectives

1. To test the efficacy of intranasal heparin to reduce SARS-CoV-2 viral shedding over 10 days from day of positive swab (health professional collected swab day 3 and 5, and day 10)

Measure:

1.1. Total number of index cases and household contacts combined (nasopharyngeal swab positive on day 1), who remain swab positive on day 3

1.2. Total number of index cases and household contacts combined (nasopharyngeal swab positive on day 1), who remain swab positive on day 5

1.3. Total number of index cases and household contacts combined (nasopharyngeal swab positive on day 1), who remain swab positive on day 10

1.4. Time to swab negative based on health care provider collected nasal swab for household members (index cases and household contacts) who were swab positive on day 1 by PCR

1.5. Mean Ct values on days 3, 5 and 10

1.6. Lowest Ct value amongst household members who become positive during the first 10 days

2. To test the safety of intranasal heparin for treatment of adult and child outpatients with SARS-CoV-2 infection.

Measure:

2.1 The number of participants who discontinue treatment prior to day 10 from randomisation as a measure of treatment tolerability

2.2: Listing of adverse events and serious adverse events

3. To test whether intranasal heparin administration reduces symptomatic disease in index cases and household contacts.

Measure:

3.1 Number of household contacts (swab negative on day 1 of study) becoming symptomatic of COVID-19 in the next 28 days

Symptomatic COVID-19 is defined as:

- Fever or chills PLUS ≥1 respiratory symptom (sore throat, cough, shortness of breath);
- OR 2 respiratory symptoms (sore throat, cough, shortness of breath);
- OR 1 respiratory symptom (sore throat, cough, shortness of breath) PLUS ≥2 non-respiratory symptoms (chills, nausea, vomiting, diarrhea, headache, conjunctivitis, myalgia, arthralgia, loss of taste or smell, fatigue or general malaise).

3.2 Time to symptom resolution for index case and household contacts who were SARS-CoV-2 positive on day 1, during the study period as measured with daily symptom diary until day 28

Common symptoms included in the symptom diary:

- Fever or chills
- Cough
- Shortness of breath or difficulty breathing
- Fatigue
- Muscle or body aches
- Headache
- New loss of taste or smell
- Sore throat
- Congestion or runny nose
- Nausea or vomiting
- Diarrheoa

4. To test the impact of intranasal heparin on peak severity of illness.

Measure:

4.1. Number of index cases and household contacts swab positive on day 1, hospitalised with COVID-19 by day 28 from randomisation

4.2. Number of household contacts swab negative on day 1, hospitalised with COVID-19 by day 28 from randomisation

4.3 Maximum severity score of participants (index case and household contacts swab positive) during the study period as recorded by daily symptom diary up to day 28.

A COVID-19 Composite Subjective Symptom Severity Score (CCSSSS) will be generated using the 11 common symptoms for COVID-19 infection listed at the Centers for Disease Control and Prevention (CDC) website and a self-rated symptom severity assessment generated for each symptom on a daily basis using a Likert scale for each symptom (Scale 0-3: not present, mild, moderate, severe).

Common symptoms:

- Fever or chills
- Cough
- Shortness of breath or difficulty breathing
- Fatigue
- Muscle or body aches
- Headache
- New loss of taste or smell
- Sore throat
- Congestion or runny nose
- Nausea or vomiting

- Diarrhea

Each symptom will be assigned a score of 0 if not present, 1 if mild, 2 if moderate and 3 if severe. These scores for each symptom will be added together to get the CCSSSS for each day.

5. To assess the impact of intranasal heparin on long COVID neurological symptoms.

Measure:

5.1 Number of participants with clinical symptoms of neurological long COVID at 6 months post randomisation.

The following symptoms were rated via telehealth or in person using a self-rated symptom assessment using a Likert scale (0-3: absent, mild, moderate, severe) for each symptom:

- Fatigue
- Malaise
- Daytime tiredness
- Impaired concentration
- Brain fog
- Sleep disturbance
- Forgetfulness
- Confusion
- Headache
- Dizziness
- Nausea
- Hypo/anosmia
- Hypo/ageusia
- Impaired walking
- Tingling feet or hands
- Burning feet or hands
- Numb feet or hands
- Impaired fine motor skills
- Muscle pain
- Epilepsy
- Anxiety
- Depression

For participants over 16 years of age, cognition and mood were assessed using the harmonised procedures developed by the Neuro-COVID Neuropsychology International Task force. Included measures were:

- Cognitive screening using Telephone Montreal Cognitive Assessment (T-MoCA)
- Subjective cognitive complaints using Patient's Assessment of Own Functioning Inventory (PAOFI)
- Attention/working memory using the Wechsler Adult Intelligence Scale (WAIS) digit span
- Mood using the Depression, Anxiety and Stress Scales (DASS)

5.2 Number of participants with clinical symptoms of neurological long COVID at 12 months post participation in trial.

2.3 Study population

Adults or children in community setting with RAT or PCR-confirmed SARS-CoV-2 infection and their household contacts. All participants who enter the trial based on a positive RAT will have a confirmatory PCR test taken prior to commencing study medication. This is referred to as the Day 1 swab. Only participants who test PCR negative to SARS-CoV-2 on day 1 swab contribute to the primary outcome measure in addition to relevant secondary aims. Anyone testing PCR positive on day 1 contributes to relevant secondary aims only.

A household contact is defined as anyone living in the same house (street address) regardless of their direct biological relationships.

Children (<5 year old) in households are not treated but monitored only. For households in which the child is the index case, only household contacts >5 years age are randomised to treatment. For households in which the index case is an adult, and the child <5 years old tests PCR negative on day 1, then the child contribute to primary and secondary outcomes even though they themselves are not treated.

Inclusion criteria:

- Any person > 5 years of age who tests positive to SARS-CoV-2 or is a household contact of someone of any age who tests positive is eligible for the trial.
- Index case must be within 72 hours of positive test.
- The positive test can be a RAT or a standard PCR nasal swab performed at a National Association of Testing Authorities (Australia) (NATA) accredited laboratory for the diagnosis of COVID-19 as per the department of health regulations. If initial test is a RAT, then a standard PCR nasal swab performed at a NATA accredited laboratory for the diagnosis of COVID-19 as per the department of health regulations will be collected prior to commencement of study medication but does not delay entry into the study awaiting the confirmatory result.
- All participants must provide a signed and dated consent form and for children < 16 years have a legally acceptable representative capable of understanding the informed consent document and providing consent on the participant's behalf. Consent forms will be developed in multiple languages and provided in a language that the participants are fluent in speaking.
- At least one other person other than the index case in each household must consent to participation to enable the consenting members of the household to be randomised. Household members who do not consent to participate in the randomised trial but who consent to have their COVID-19 status recorded can contribute to outcome measures where relevant.

Exclusion criteria:

- Children age < 5 years are excluded from being randomised to therapy but can contribute to the outcome measures if they are swab negative on day 1.
- Documented Heparin allergy
- Previous documented heparin induced thrombocytopenia (HIT)
- Recurrent epistaxis that has required hospitalisation in last 3 months
- >72 hours since index case tested positive
- Inability to provide participant information and consent form and study instructions in a language in which the patient is competent.

2.4 Intervention

Unfractionated heparin (UFH) 1400u each nostril (as heparin solution 5,000u/ml, 140microL/actuation, TWO actuations each nostril) THREE times daily via a plastic nasal inhalator device (Aptar, UK) for 10 days. This is a maximal dose per day of UFH of 8400u, 700 x 2 actuations per nostril (1400 x2) 3 times per day (1400x2x3 = 8400u).

Comparator 0.9% saline (as saline solution, 140 microlitres/actuation, TWO actuations each nostril) THREE times daily via a plastic nasal inhalator device (Aptar, UK) for 10 days.

2.5 Randomisation and blinding

An independent statistician prepared the randomisation list using block randomisation. This list was provided directly to Northern Health pharmacy. Once a household was enrolled, the pharmacy was notified directly and prepared and dispensed the required study drug based on the randomisation schedule. The randomisation was stratified by randomised within 48 hours of positive test done by the participant for the index case (time of test being collected) versus those who were randomised between 48 and 72 hours, and by whether or not the index case is a child < 5 years.

The randomisation was a 1:1 randomisation by household. If the index case and at least one other person in the household were eligible and consented then all consenting and eligible participants within that household were randomised to the same arm of the study, either active treatment or comparator.

This is a double blind trial and both participants and researchers will be blinded throughout the study. The bottles distributed to the patients were listed as trial medication and the active comparator and placebo are both colourless, odourless and tasteless packaged in similar looking bottles. Both active drug and comparator are stable at room temperature and need no specific storage requirements.

2.6 Sample size

For the primary research outcome, a sample size of 120 index cases per arm will provide 80% power. We anticipate that the attack rate for within household transmission will be approximately 85% in the control arm and 75% in the intervention arm. Under these assumptions, in a cluster randomised trial with a binary outcome, assuming an intracluster correlation coefficient of 0.2, an alpha of 0.05 (two sided), and assuming 3 additional household members (in addition to the index case) we have 80% power to detect a reduction in transmission to household contacts. The requisite sample size is then 120 index cases and 360 household contacts per arm. Allowing for 10% loss to follow-up this is increased to 134 index cases (households) per arm, approximately 536 persons per arm. We plan to enroll 268 households and approximately 1072 individuals.

If the household size is 2 additional people, rather than 3, and with all other assumptions the same, we would require 334 households and approximately 1002 individuals. The target sample size for the primary outcome is 1100 individuals enrolled.

2.7 Study procedures

When a participant is confirmed to be SARS-CoV-2 positive all consenting household members are enrolled and randomised to the same treatment arm. All consenting household members 5 years of age and older will be given the same study treatment. Treatment is 10 days and follow up for primary outcome is 10 days. Follow up for some secondary outcomes are 28 days and outcomes related to long COVID is 6 and 12 months post randomisation.

Daily communication via SMS, online or phone will be conducted by a research team member who will be trained in standard operating procedures as per trial manual. Paediatric or adult swabs (Rhinomed) will be provided to all participants with detailed instructions for self-collection and storage until collected by a research team member. Health care provider collected PCR nasopharyngeal swabs will be collected from all participants prior to commencement of study medication and on day 3, 5 and 10 (+/- 1 day for all time points).

Phone call follow up at day 14 and 28 by a research team member will assess which participants became symptomatic after the initial treatment period and whether participants required hospitalisation during that time. Detailed medical information as to reasons for hospital admission will be sought to confirm if admission was related to COVID-19 infection or for alternative reasons. Research team members will be trained specifically in questions to ask according to trial manual, which will include an escalation process if a research team member believes that additional clinical care is required for the participant or family member.

Telemedicine follow up at day 180 +/- 10 days and day 365 +/- 10 days to ascertain any evidence of long COVID neurological symptoms.

2.8 Deviations from protocol

Secondary measures 1.5 and 1.6 were not specified in the protocol, but were added to the statistical analysis plan.

Reference to consecutive daily swabs were removed, since only the healthcare provider swabs are used and they are not collected daily.

No other large deviations from the protocol occurred. Where the text deviates from the protocol, the changes were made to resolve inconsistencies and ambiguities, without the intention of diverging from the original protocol.

Full details of the background to the trial and its design are presented in the protocol.

3. GENERAL STATISTICAL METHODOLOGY

3.1. Objectives of analysis plan

This statistical analysis plan described the planned analyses of the primary and secondary objectives of the INHERIT trial protocol in detail. Additional post hoc analyses are not included.

3.2. Analysis software

Stata version 18.0 or later will be used to analyse the data.

3.3. Definition of baseline

Baseline is defined as day 1 PCR and pre-Day 1 measures for other measures. Only measures taken prior to dispending study drug will be used as baseline measures.

3.4. Definition of analysis populations

Different study populations are defined to address the different research questions. These are:

- All household members of households where at least one person tested positive and at least one person tested negative for SARS-CoV-2 on day 1 on PCR testing. This includes children < 5years old who test negative to SARS-CoV-2 on day 1.
- All household members who test negative for SARS-CoV-2 on day 1 (including children < 5 years old) on PCR testing.
- All household members (index cases and household contacts) who test positive for SARS-CoV-2 on day 1 on PCR testing. This excludes children < 5 years old who test positive to SARS-CoV-2 on day 1.
- All household members (index cases and household contacts; 5 years and older) prescribed study drug, regardless of SARS-CoV-2 infection status
- All enrolled participants, regardless of SARS-CoV-2 status, who received at least one dose of study drug. This excludes children < 5 years.
- All enrolled participants, regardless of SARS-CoV-2 status.

In Sections 5 and 6 we specify which population is used to assess each of the study objectives. Despite the specific analysis populations described, all analyses will follow the Intention to treat (ITT) principle where participants will be analysed in the arms they were randomised to, regardless of whether they received or used study drug.

3.5. Adjustment for multiplicity

No adjustment for multiplicity will be made.

3.6. Interim analyses

No interim analyses were done or planned.

3.7. Handling of missing data

If less than 10% of data is missing, the primary analysis will be conducted using the participants with available data for each outcome. However, if there are >10% missing data in the primary or secondary outcomes, we will conduct the analysis under a plausible assumption regarding the missingness mechanism that will be guided using expert clinical knowledge prior to observing the data, which will be determined by generating directed acyclic graphs. We suspect that the data will be recoverable (that is able to be estimated without bias from the observed data alone), and multiple imputation will be used to handle the missing data in all

outcomes. Imputations will be generated using chained equations, also known as fully conditional specification, with 50 imputed datasets and 10 iterations between each imputation. Ideally this would be conducted using a single regression model for all outcomes, although it may be necessary to impute incomplete outcomes using separate models. Imputation will be carried out separately by arm, to ensure that any treatment effects are maintained. Baseline characteristics as well as any variables that are predictors of missingness and/or associated with the incomplete outcomes will be included as auxiliary variables in the imputation model. Estimates of interest will be obtained using Rubin's rules, and will be reported with 95% confidence intervals and *p*-values.

3.8. Assigning SARS CoV-2 infection status at day 1 and for all outcomes

The following algorithm will be used to determine whether a participant is regarded as positive or negative for SARS CoV-2. In general, only the health care provider collected PCR result will be used to determine infection status. The exception would be when the result was inconclusive.

SARS CoV-2 infection at the time point will be positive if the health care provider collected PCR result is "Detected" and negative if the PCR result is "Not detected".

If the result of the healthcare provider collected swab was inconclusive the following algorithm will be followed:

The result of the self-collected Rhinomed swab collected on the same date as the inconclusive healthcare provider collected swab will determine the final result. If the result of the self-collected Rhinomed swab is "Detected" the result will be positive and if the result is "Not detected" the result will be negative.

If the self-collected Rhinomed swab was also inconclusive, or was missing, the following algorithm will be followed (using the healthcare provider collected swab):

- If the inconclusive result was followed later by a "Detected" result (for example, Inconclusive on Day 3 and Detected on Day 5) then the inconclusive result will be deemed to be positive.
- If the inconclusive result was followed later by a "Not detected" result, then the inconclusive result will be deemed to be negative.
- If the inconclusive result was the last available result, then the inconclusive result will be deemed to be negative.

This algorithm will be used to determine both the primary endpoint (positive on any of Day 3, 5 or 10) and all secondary endpoints related to SARS-CoV-2 positivity.

For the primary objective only, the following two sensitivity analyses will also be done:
Sensitivity analysis 1: Only healthcare provider collected swabs will be used. If the result is inconclusive, it will be regarded as positive.
Sensitivity analysis 2: Only healthcare provider collected swabs will be used. If the result is inconclusive, it will be regarded as negative.

3.9. Baseline covariate set

A set of covariates which will be included in models for all primary and secondary outcomes (unless specified otherwise) are: stratification factors (time from positive test to randomisation (binary)) and whether the index case is a child < 5 years(binary), participant age (continuous), inhaled steroid use at baseline (binary), days since symptom onset for index case at randomisation (continuous), whether there are children in the household (binary) and household size (continuous). This is referred to as the baseline covariate set.

Some of these covariates are correlated with each other and may also have sparse data in some of the cells, which may lead to convergence problems with the models. If that is the case, we will exclude some of the baseline covariate set until we can get a model that converges. We will first exclude the sparsest variables, and secondly exclude the variables most correlated with other variables.

We will also repeat each analysis with a model including only the two stratification variables.

4. DESCRIPTIVE STATISTICS

4.1. Recruitment and follow-up

We will summarise the number of households and participants enrolled. We will also detail how many index cases, household members, SARS-CoV-2 positive and negative household members were enrolled. We will also show how many households were enrolled and were eligible for the primary analysis. This will be summarised in a CONSORT flowchart.

4.2. Baseline characteristics

The following variables will be summarised at baseline by treatment arm. Categorical variables will be summarised as the number and percentage, and continuous variables as mean, standard deviation (SD) and range (minimum and maximum) or median and interquartile range (IQR) when continuous data is skewed.

Household information: Household size, number of children in household, household type, number of bathrooms, number of bedrooms, number of household members enrolled.
Index case information: Time of positive test collection, index case <5 years old, age, interpreter required, sex, COVID-19 vaccine history (number of doses received), had COVID-19 before (number of infections), COVID-19 symptoms present (yes/no and fever or chills, cough, shortness of breath, fatigue, muscle or body aches, headache, loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, diarrhea), number of days with symptoms, nasal spray use
Household member information: Age, interpreter required, SARS-CoV-2 status at screening, sex, COVID-19 vaccine history (number of doses received), had COVID-19 before (number of infections), COVID-19 symptoms present (fever or chills, cough, shortness of breath, fatigue, muscle or body aches, headache, loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, diarrhea)

Demographic data at baseline will be provided for the household, index case and household members. For household members, the demographics will be provided overall, as well as by SARS-CoV-2 status.

4.3. Protocol deviations

Protocol deviations will be listed.

4.4. Compliance

Participants will be asked about compliance and symptoms daily. Parents will act as a proxy for children <16 years old. They will be asked how many doses they have used in the previous day. We will provide the number of participants who took 0, 1, 2 or 3 doses per day for 10 days.

We will also calculate the percentage of prescribed study dose that was taken. Each participant should take 3 doses per day, 30 doses over the 10 days. Participants could start the study late on the first day, in which case one would expect them to only have used 1 or 2 doses, instead of 3. Starting late on the first day would also distort reporting of study compliance on Day 2, since we ask “how many doses of study drug have you taken in the last 24 hours”. We do not have the time of day when the study was started and thus cannot determine how many doses a participant should have used on the first or second day. For this reason, we will exclude Days 1 and 2 from the calculation of compliance. Thus, the percentage compliance will be calculated as (number of doses taken from days 3 to 10/24) multiplied by 100. If compliance data is missing for a day, the denominator will be reduced by 3. The mean percentage compliance will be summarised. All compliance summaries will be provided in each treatment arm as well as for participants who were positive and negative for COVID-19 at baseline by treatment arm.

4.5. Concomitant therapies

Concomitant therapies will be listed per treatment arm. Both the medication and the indication will be listed. Concomitant therapies administered nasally and anti-virals used will also be summarised.

5. ANALYSIS OF THE PRIMARY OUTCOME(S)

5.1. Main analysis

The primary outcome will be the number (and proportion) of household members swab negative on day 1 (study timepoint called baseline) testing positive for SARS-CoV-2 by PCR on either of three routine nasopharyngeal swabs on day 3, 5 and 10 after enrolment.

Primary estimand

Population: Household members (including children < 5 years) who test negative for SARS CoV-2 on day 1 (baseline) PCR testing using the health care provider swabs

Treatment: Initially randomised intervention to unfractionated intranasal heparin 1400u each nostril (as heparin solution 5,000u/ml, 140microL/actuation, TWO actuations each nostril) THREE times daily via a plastic nasal inhalator device or saline control and any subsequent deviations to the per protocol use of the intervention over 10 days

Outcome: Testing positive for SARS-CoV-2 by PCR on any of three health care provider collected swabs at days 3, 5 and 10. The algorithm to determine SARS-CoV-2 positivity is described in detail in Section 3.8. If one of the post-baseline swabs is missing, but all observed swabs were negative, the participant will be regarded to be negative. If more than one post-baseline swab is missing and the observed swabs were all negative, the outcome will be regarded to be missing.

Summary measure: Both relative (risk ratio) and absolute differences (risk difference) in proportions will be reported with 95% confidence intervals

Potential intercurrent events:

Index case in the household not taking study drug. This is defined as compliance <90%
Participant (this household member) not taking study drug. This is defined as compliance <90%
Either participant (this household member) or index case stop treatment due to adverse event
Participant hospitalisation during first 10 days (removed from household)
Participant received an anti-viral

Strategy for handling intercurrent event:

In the primary analysis all intercurrent events will be handled through the treatment policy strategy, which means that the intercurrent events will be ignored.

The analysis will follow the intention to treat principle, but only some households will be eligible for this objective. A household will be eligible if there is at least one participant in the household who tested positive to SARS-CoV-2 by PCR on Day 1 and one participant who tested negative to SARS-CoV-2 by PCR on Day 1, using the health care provider collected swab. It does not matter whether it was the index case or another household member who tested positive. Households where all participants test positive or where all participants test negative will not be eligible for this analysis.

Treatment arms will be compared using generalised linear mixed models (GLM) with infection status as the binary outcome, adjusting for stratification factors (time from positive test to randomisation, whether the index case is a child < 5 years), participant age, inhaled steroid use at baseline, days since symptom onset at randomisation, whether there are children in the household and household size (referred to as the defined baseline covariate set, see Section 3.9), with household as random effect to take the clustering by household into account. Both relative and absolute differences in proportions will be reported with 95% confidence intervals.

Relative differences (risk ratios) between the treatment arms will be calculated using a Poisson regression with robust standard errors in Stata as follows:

```
xtpoisson outcome i.arm baseline_covariates, re vce(robust) irr
```

Absolute differences (risk difference) between the treatment arms will be calculated in Stata as follows using a mixed effects GLM with random intercepts:
meglm outcome i.arm baseline_covariates || household:, family(bin) link(logit)

The margins statement will be used to compute the risk difference by subtracting the probability of the outcome in the control arm from the probability in the treatment arm
margins i.arm, atmeans post
lincom _b[1.arm] - _b[0.arm]

Both these models are fairly complicated models to fit and might not converge if sparse data is encountered, given all the baseline covariates included. If the models do not converge, the following strategies will be tried:

- Exclude some of the baseline covariates – especially binary covariates, covariates with sparse categories, or covariates with little variability
- Or, fit the following simpler models

Relative differences (risk ratios) between the treatment arms will be calculated in Stata as follows using robust standard errors:

glm outcome i.arm baseline_covariates, fam(bin) link(log) nolog eform vce(cluster household)

Absolute differences (risk difference) between the treatment arms will be calculated in Stata as follows using robust standard errors:

glm outcome i.arm baseline_covariates, fam(bin) link(identity) nolog vce(cluster household)

5.2. Sensitivity analyses

Four sensitivity analyses are planned:

1. The analysis described above will be repeated using multiple imputation, if more than 10% of outcome data is missing.
2. The analysis described above willbe repeated without the covariates participant age, inhaled steroid use at baseline, days since symptom onset at randomisation, whether there are children in the household and household size.
3. The algorithm to determine SARS-CoV-2 infection will be changed by deeming all inconclusive results (including on Day 0) to be positive, using only healthcare provider collected swabs.
4. The algorithm to determine SARS-CoV-2 infection will be changed by deeming all inconclusive results (including on Day 0) to be negative, using only healthcare provider collected swabs.

5.3. Supplementary analyses

We define a supplementary estimand, through handing the intercurrent event of not taking study drug differently.

Supplementary estimand
Population: Household contacts who test negative for SARS CoV-2 on day 1 (baseline) PCR testing using the health care provider swabs
Treatment: Unfractionated intranasal heparin 1400u each nostril (as heparin solution 5,000u/ml, 140microL/actuation, TWO actuations each nostril) THREE times daily via a plastic nasal inhalator device or saline control
Outcome: Testing positive for SARS-CoV-2 by PCR on any of three health care provider collected swabs at days 3, 5 and 10 while participant and index case do not discontinue treatment due to adverse events. The algorithm to determine SARS-CoV-2 positivity is described in detail in Section 3.8. If one of the post-baseline swabs is missing, but all observed swabs were negative, the participant will be regarded to be negative. If more than one post-baseline swab is missing and the observed swabs were all negative, the outcome will be regarded to be missing.

Summary measure: Both relative (risk ratio) and absolute differences (risk difference) in proportions will be reported with 95% confidence intervals

Potential intercurrent events:

Index case in the household not taking study drug. This is defined as compliance <90%
Participant (this household member) not taking study drug. This is defined as compliance <90%
Either participant (this household member) or index case stop treatment due to adverse event
Participant hospitalisation during first 10 days (removed from household)
Participant received an anti-viral

Strategy for handling intercurrent event:

Index case in the household not taking study drug. This is defined as compliance <90%: This intercurrent event will be handled following the hypothetical strategy. For index cases who used <90% of study drugs we will set all SARS-CoV2 infections observed in the household to missing. We will use multiple imputation to impute these outcomes.
Participant (this household member) not taking study drug. This is defined as compliance <90%: This intercurrent event will be handled following the hypothetical strategy. We will set all SARS-CoV2 infections observed to missing. We will use multiple imputation to impute these outcomes.
Either participant (this household member) or index case stop treatment due to adverse event: We will handle this intercurrent event using the while on treatment strategy. We will do this by excluding outcomes after participants stop study treatment due to adverse events from the analysis.
All other intercurrent events will be handled by using the treatment policy strategy, which means that those intercurrent events will be ignored.

This analysis will only be done if more than 7% of participants had the intercurrent events.

5.4. Subgroup analyses

The following subgroup analyses will be done:
Age: <5, 5-<18, 18-65, >65 years
Anti-viral treatment: Use of anti-viral treatment by the index case at randomisation. These include Paxlovid, Molnupiravir, Remdesivir and Favipiravir.
Number of SARS-CoV-2 exposures (vaccinations and infections) prior to the trial: 4 or less, vs > 4
Use any nasal treatment prior to coming into trial (Carrageenan or inhaled steroid, variables cm_flonasalspray_yn and cm_inhaledsteroids_yn)
Number of people in house: 2-3 vs > 3
Ratio of people to bedrooms: < 1, 1, > 1

The subgroup analysis will be done by including an interaction term between the treatment arm and the subgroup in the model described in Section 5.1. For example,
xtpoisson outcome i.arm##i.subgroup baseline_covariates, re vce(robust) irr

The p-value of the subgroup by arm interaction term will be assessed to determine whether there could be a subgroup effect, with the understanding that the analysis is probably underpowered.

6. SECONDARY OUTCOMES

For all secondary outcomes referring to SARS-CoV-2 status we will use the algorithm as discussed in Section 3.8 and used for the primary outcome to determine SARS-CoV-2 infection status at any time point.

6.1 Secondary outcome 1. Efficacy of intranasal heparin to reduce SARS-CoV-2 viral shedding

To test the efficacy of intranasal heparin to reduce SARS-CoV-2 viral shedding over 10 days from day of positive swab (health professional collected swab day 3 and 5, and day 10)

Measure

1.1. Total number of index cases and household contacts combined (nasopharyngeal swab positive on day 1) who remain swab positive on day 3 according to health care provider collected swab

1.2. Total number of index cases and household contacts combined (nasopharyngeal swab positive on day 1) who remain swab positive on day 5 according to health care provider collected swab

1.3. Total number of index cases and household contacts combined (nasopharyngeal swab positive on day 1) who remain swab positive on day 10 according to health care provider collected swab

Estimand

Population: Household members who tested positive for SARS CoV-2 on day 1 on a nasopharyngeal swab PCR testing (health care provider collected swab)

Treatment: Initially randomised intervention to unfractionated intranasal heparin 1400u each nostril (as heparin solution 5,000u/ml, 140microL/actuation, TWO actuations each nostril) THREE times daily via a plastic nasal inhalator device or saline control and any subsequent deviations to the per protocol use of the intervention over 10 days

Outcome: Three different analyses will be done with 3 different outcomes

a) Testing positive for SARS-CoV-2 by PCR on day 3 (using health care provider collected swab)
b) Testing positive for SARS-CoV-2 by PCR on day 5 (using a health care provider collected swab)
c) Testing positive for SARS-CoV-2 by PCR on day 10 (using a health care provider collected swab)

Summary measure: Both relative (risk ratio) and absolute differences (risk difference) in proportions will be reported with 95% confidence intervals

Potential intercurrent events:

Index case in the household not taking study drug. This is defined as compliance <90%
Participant (this household member) not taking study drug. This is defined as compliance <90%
Either participant (this household member) or index case stop treatment due to adverse event
Participant hospitalisation during first 10 days (removed from household)
Participant received an anti-viral

Strategy for handling intercurrent event:

All intercurrent events will be handled through the treatment policy strategy, which means that the intercurrent events will be ignored.

The same analysis as described in Section 5.1 for the primary outcome will be done. We will do the same sensitivity and supplementary analysis, but no subgroup analyses are planned.

Measure

1.4. Time to swab negative based on health care provider collected nasal swab for household members index cases and household contacts) who were swab positive on day 1 by PCR

Estimand

Population: Household members who tested positive for SARS CoV-2 on day 1 on a nasopharyngeal swab PCR

Treatment: Initially randomised intervention to unfractionated intranasal heparin 1400u each nostril (as heparin solution 5,000u/ml, 140microL/actuation, TWO actuations each nostril) THREE times daily via a plastic nasal inhalator device or saline control and any subsequent deviations to the per protocol use of the intervention over 10 days

Outcome: Days from randomisation to the date of the first negative nasal swab. Participants who still test positive on day 10 will be censored on day 10 and regarded as not testing negative.

Summary measure: Median time to first negative test in each treatment arm. Hazard ratio.

Potential intercurrent events:

Index case in the household not taking study drug. This is defined as compliance <90%
Participant (this household member) not taking study drug. This is defined as compliance <90%
Either participant (this household member) or index case stop treatment due to adverse event
Participant hospitalisation during first 10 days (removed from household)
Participant received an anti-viral

Strategy for handling intercurrent event:

All intercurrent events will be handled through the treatment policy strategy, which means that the intercurrent events will be ignored.

Days to first negative test will be calculated from baseline to the first negative PCR tests within the first 10 days after randomisation. Participants who still test positive at the last time point will be censored at the time

of last test. Participants who are lost to follow-up without testing negative, will be censored at the time of the last positive test. The days to negative test will be compared between the two treatment arms using a proportional hazards models with clustered standard errors [using vce(cluster) in Stata]. The model will be adjusted for the same set of defined baseline covariates (Section 5.1). Days to negative test will be summarised by reporting the median, with 95% confidence interval.

Measure

1.5 Mean Ct values on days 3, 5 and 10

Estimand

Population: Household members who tested positive for SARS CoV-2 on day 1 on a nasopharyngeal swab PCR
Treatment: Initially randomised intervention to unfractionated intranasal heparin 1400u each nostril (as heparin solution 5,000u/ml, 140microL/actuation, TWO actuations each nostril) THREE times daily via a plastic nasal inhalator device or saline control and any subsequent deviations to the per protocol use of the intervention over 10 days
Outcome: The mean Ct value at each time point on all genes (E, N, RdRp/S gene). Ct value for the virus that was not detected will be set at the maximum number of cycles performed in the lab (40).
Summary measure: The mean difference between arms will be reported with 95% confidence interval
Potential intercurrent events:

Index case in the household not taking study drug. This is defined as compliance <90%
Participant (this household member) not taking study drug. This is defined as compliance <90%
Either participant (this household member) or index case stop treatment due to adverse event
Participant hospitalisation during first 10 days (removed from household)
Participant received an anti-viral

Strategy for handling intercurrent event:

All intercurrent events will be handled through the treatment policy strategy, which means that the intercurrent events will be ignored.

Treatment arms will be compared using mixed effects linear regression with Ct value as the outcome, adjusting for stratification factors (time from positive test to randomisation, whether the index case is a child < 5 years), participant age, inhaled steroid use at baseline, days since symptom onset at randomisation, whether there are children in the household and household size (referred to as the defined baseline covariate set), with household as random effect to take the clustering by household into account.

Measure

1.6 Lowest Ct value amongst household members who become positive during the first 10 days

Estimand

Population: Household members who tested negative for SARS CoV-2 on day 1 on a nasopharyngeal swab PCR and subsequently become SARS CoV-2 positive during the first 10 days
Treatment: Initially randomised intervention to unfractionated intranasal heparin 1400u each nostril (as heparin solution 5,000u/ml, 140microL/actuation, TWO actuations each nostril) THREE times daily via a plastic nasal inhalator device or saline control and any subsequent deviations to the per protocol use of the intervention over 10 days
Outcome: The mean Ct value at each time point at or after the first positive SARS-CoV-2 test on all genes (E, N, RdRp/S gene). Ct value for the virus that was not detected will be set at the maximum number of cycles performed in the lab (40). For each participant the lowest Ct value detected at or after the first positive test will be used.
Summary measure: The mean difference between arms will be reported with 95% confidence interval

Treatment arms will be compared using mixed effects linear regression with lowest Ct value as the outcome, adjusting for the defined baseline covariate set, with household as random effect to take the clustering by household into account.

The mean difference between the treatment arms will be calculated in Stata as follows using a mixed effects GLM:

mixed outcome i.arm baseline_covariates || household:

6.2 Secondary outcome 2. Safety of intranasal heparin

To test the safety of intranasal heparin for treatment of adult and child outpatients with SARS-CoV-2 infection

Measure
2.1 The number of participants who discontinue treatment prior to day 10 from randomisation as a measure of treatment tolerability

Estimand
Population: Household members (older than 5 years) prescribed study drug, regardless of SARS-CoV-2 infection status (all enrolled participants)
Treatment: Unfractionated intranasal heparin 1400u each nostril (as heparin solution 5,000u/ml, 140microL/ actuation, TWO actuations each nostril) THREE times daily via a plastic nasal inhalator device or saline control
Outcome: The number of participants who discontinue treatment prior to day 10
Summary measure: Proportion in each arm, with 95% confidence interval.
Potential intercurrent events: None identified

No statistical comparison will be made between the treatment arms. We will simply provide the proportion, with a 95% confidence interval, adjusted for clustering by household.

6.3 Secondary outcome 3. Reduction of symptomatic disease

To test whether intranasal heparin administration reduces symptomatic disease in household members

Measure 3.1
Number of household contacts (swab negative on day 1 by PCR) becoming symptomatic of COVID-19 in next 28 days.

Symptomatic COVID-19 is defined as:
- Fever or chills PLUS ≥1 respiratory symptom (sore throat, cough, shortness of breath);
- OR 2 respiratory symptoms (sore throat, cough, shortness of breath);
- OR 1 respiratory symptom (sore throat, cough, shortness of breath) PLUS ≥2 non-respiratory symptoms (nausea or vomiting, diarrhea, headache, congestion or runny nose, sore throat, loss of taste or smell, myalgia, fatigue).

Symptoms are recorded as not present, mild, moderate or severe. A symptom will be regarded as being present if it is any of mild, moderate or severe.

Estimand
Population: Household contacts who test negative for SARS CoV-2 on day 1 by PCR
Treatment: Initially randomised intervention to unfractionated intranasal heparin 1400u each nostril (as heparin solution 5,000u/ml, 140microL/actuation, TWO actuations each nostril) THREE times daily via a plastic nasal inhalator device or saline control and any subsequent deviations to the per protocol use of the intervention over 10 days
Outcome: Becoming symptomatic of COVID-19 as defined above in the first 28 days.
Summary measure: Both relative (risk ratio) and absolute differences (risk difference) in proportions will be reported with 95% confidence intervals
Potential intercurrent events:

Index case in the household not taking study drug. This is defined as compliance <90%
Participant (this household member) not taking study drug. This is defined as compliance <90%
Either participant (this household member) or index case stop treatment due to adverse event
Participant hospitalisation during first 10 days (removed from household)
Participant received an anti-viral

Strategy for handling intercurrent event:

All intercurrent events will be handled through the treatment policy strategy, which means that the intercurrent events will be ignored.

The same analysis as described in Section 5.1 for the primary analysis will be done.

Measure 3.2

Days to symptom resolution for household members who were swab positive on day 1 by PCR, during the study period as measured with daily symptom diary until day 28.
Common symptoms included in the symptom diary are: Fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, diarrhea. The symptoms are measured as not present, mild, moderate or severe. Symptom resolution is defined as a symptom improving by at least 2 categories from its first measurement (on Day 1) or being not present. For example, a symptom measured as severe on Day 1 would be resolved if it measured mild, all other symptoms would be resolved if it changed from moderate to not present or from mild to not present. Symptom resolution had to be maintained for 2 consecutive days.

Estimand

Population: Household members who test positive for SARS CoV-2 on day 1 by PCR
Treatment: Initially randomised intervention to unfractionated intranasal heparin 1400u each nostril (as heparin solution 5,000u/ml, 140microL/actuation, TWO actuations each nostril) THREE times daily via a plastic nasal inhalator device or saline control and any subsequent deviations to the per protocol use of the intervention over 10 days
Outcome: Days from randomisation to the first day with symptom resolution. Participants who still have symptoms on day 28 will be censored on day 28 and regarded as not having symptom resolution. Participants who had no symptoms at randomisation, will be regarded as having 0 days to symptom resolution.
Summary measure: Median days to symptom resolution in each treatment arm. Hazard ratio. If all participants are symptom free at the end of follow-up, we will be able to estimate the difference in mean days to resolution of symptoms between the arms
Potential intercurrent events:

Index case in the household not taking study drug. This is defined as compliance <90%
Participant (this household member) not taking study drug. This is defined as compliance <90%
Either participant (this household member) or index case stop treatment due to adverse event
Participant received an anti-viral

Strategy for handling intercurrent event:

All intercurrent events will be handled through the treatment policy strategy, which means that the intercurrent events will be ignored.

Days to symptom resolution will be calculated from baseline to the first (of 2 consecutive days) day with symptom resolution (as defined above) for each of the symptoms individually. Participants who still have symptoms at the last time point will be censored at the time of last symptom checklist completed. Participants who are lost to follow-up will be censored at the last time a checklist was completed. The same analysis as described in Section 6.1 for endpoint 1.4 will be done.

In addition, an analysis for resolution of all symptoms will be done. This will be defined as the first day with all symptoms either mild or not present, maintained for 2 consecutive days. The analysis will be done in the same manner as for each individual symptom.

6.4 Secondary outcome 4. Impact on peak severity of illness

Measure 4.1

Number of household members swab positive on day 1 by PCR, hospitalised with COVID-19 by day 28 from randomisation

Estimand

Population: Household members who test positive for SARS CoV-2 on day 1 by PCR

Treatment: Initially randomised intervention to unfractionated intranasal heparin 1400u each nostril (as heparin solution 5,000u/ml, 140microL/actuation, TWO actuations each nostril) THREE times daily via a plastic nasal inhalator device or saline control and any subsequent deviations to the per protocol use of the intervention over 10 days
Outcome: Participants reported being hospitalised in first 28 days
Summary measure: Both relative (risk ratio) and absolute differences (risk difference) in proportions will be reported with 95% confidence intervals
Potential intercurrent events:

Index case in the household not taking study drug. This is defined as compliance <90%
Participant (this household member) not taking study drug. This is defined as compliance <90%
Either participant (this household member) or index case stop treatment due to adverse event
Participant received an anti-viral

Strategy for handling intercurrent event:

All intercurrent events will be handled through the treatment policy strategy, which means that the intercurrent events will be ignored.

The same analysis as described in Section 5.1 for the primary analysis will be done.

Measure 4.2

Number of household contacts swab negative on day 1 by PCR, hospitalised with COVID-19 by day 28 from randomisation

Estimand

Population: Household contacts who test negative for SARS CoV-2 on day 1 by PCR
Treatment: Initially randomised intervention to unfractionated intranasal heparin 1400u each nostril (as heparin solution 5,000u/ml, 140microL/actuation, TWO actuations each nostril) THREE times daily via a plastic nasal inhalator device or saline control and any subsequent deviations to the per protocol use of the intervention over 10 days
Outcome: Participants reported being hospitalised in first 28 days
Summary measure: Both relative (risk ratio) and absolute differences (risk difference) in proportions will be reported with 95% confidence intervals
Potential intercurrent events:

Index case in the household not taking study drug. This is defined as compliance <90%
Participant (this household member) not taking study drug. This is defined as compliance <90%
Either participant (this household member) or index case stop treatment due to adverse event
Participant received an anti-viral

Strategy for handling intercurrent event:

All intercurrent events will be handled through the treatment policy strategy, which means that the intercurrent events will be ignored.

The same analysis as described in Section 5.1 for the primary analysis will be done.

Measure 4.3

Maximum severity score of participants (household members swab positive) during the study period as recorded by daily symptom diary up to day 28.

A CCSSSS will be calculated using the 11 common symptoms for COVID-19 infection listed at the CDC website (fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, diarrhea) and a self-rated symptom severity assessment generated for each symptom on a daily basis using a Likert scale for each symptom (Scale 0-3: not present, mild, moderate, severe).

Each symptom will be assigned a score of 0 if not present, 1 if mild, 2 if moderate and 3 if severe. These scores for each symptom will be added together to get the CCSSSS for each day. This highest score during the 28 days after randomisation will be the maximum severity score. Scores on Day 1 and Day 2 will be excluded from this calculation.

Estimand

Population: Household members who test positive for SARS CoV-2 on day 1 by PCR
Treatment: Initially randomised intervention to unfractionated intranasal heparin 1400u each nostril (as heparin solution 5,000u/ml, 140microL/actuation, TWO actuations each nostril) THREE times daily via a plastic nasal inhalator device or saline control and any subsequent deviations to the per protocol use of the intervention over 10 days
Outcome: Maximum severity score calculated as the highest daily score on the CCSSSS during the 28 days after randomisation
Summary measure: The mean difference between arms will be reported with 95% confidence interval
Potential intercurrent events:

Index case in the household not taking study drug. This is defined as compliance <90%
Participant (this household member) not taking study drug. This is defined as compliance <90%
Either participant (this household member) or index case stop treatment due to adverse event
Participant received an anti-viral

Strategy for handling intercurrent event:

All intercurrent events will be handled through the treatment policy strategy, which means that the intercurrent events will be ignored.

Treatment arms will be compared using mixed effects linear regression with maximum symptom severity as the outcome, adjusting for stratification factors (time from positive test to randomisation, whether the index case is a child < 5 years), participant age, inhaled steroid use at baseline, days since symptom onset at randomisation, whether there are children in the household and household size (referred to as the defined baseline covariate set), with household as random effect to take the clustering by household into account.

The mean difference between the treatment arms will be calculated in Stata as follows using a mixed effects GLM with random intercepts:
mixed outcome i.arm baseline_covariates || household:

6.5 Secondary outcome 5. Clinical symptoms of neurological long COVID

Measure 5.1

Number of participants with clinical symptoms of neurological long COVID at 6 months post participation in trial.

We have several measures of neurological long COVID

Measure 5.1.1

The following symptoms were rated via telehealth or in person using a self-rated symptom assessment using a Likert scale (0-3: absent, mild, moderate, severe) for each symptom:

- Fatigue
- Malaise
- Daytime tiredness
- Impaired concentration
- Brain fog
- Sleep disturbance
- Forgetfulness
- Confusion
- Headache
- Dizziness
- Nausea
- Hypo/anosmia
- Hypo/ageusia
- Impaired walking
- Tingling feet or hands
- Burning feet or hands

- Numb feet or hands
- Impaired fine motor skills
- Muscle pain
- Epilepsy
- Anxiety
- Depression

In the first instance, an estimate will be calculated to compare the two randomised treatment arms, on each of the reported symptoms individually. The research question is: In individuals randomised to using heparin or placebo (both SARS-CoV-2 positive and negative at baseline) does heparin use vs placebo over 10 days reduce long covid symptoms at 6 months?

Estimand

Population: Household members (older than 5 years) enrolled in the study, regardless of SARS-CoV-2 infection status (all enrolled participants)
Treatment: Initially randomised intervention to unfractionated intranasal heparin 1400u each nostril (as heparin solution 5,000u/ml, 140microL/actuation, TWO actuations each nostril) THREE times daily via a plastic nasal inhalator device or saline control and any subsequent deviations to the per protocol use of the intervention over 10 days
Outcome: Ordinal Likert scale measurement of severity of each of the above symptoms at 6 months, with a 2 month window (i.e. including outcomes measured between 4 and 8 months)
Summary measure: The overall odds ratio will be reported with 95% confidence interval
Potential intercurrent events:

Index case in the household not taking study drug. This is defined as compliance <90%
Participant (this household member) not taking study drug. This is defined as compliance <90%
Either participant (this household member) or index case stop treatment due to adverse event
Participant received an anti-viral

Strategy for handling intercurrent event:

All intercurrent events will be handled through the treatment policy strategy, which means that the intercurrent events will be ignored.

We will summarise the number of participants in each of the 4 categories of the Likert scale in each treatment arm. A mixed effects proportional odds logistic regression will be used to calculate the overall odds ratio, adjusted for the stratification variables and clustered on household. The assumption of proportional odds will be investigated. If it is violated, we will fit a multinomial regression and calculate an odds ratio for each category.

This analysis will also be repeated in the subgroup of participants who tested positive to SARS-CoV-2 infection at baseline.

The following subgroup analyses will be done with the symptom of fatigue as the outcome:
Age: Younger than 65 vs 65 and older
Pre-existing mental health problems: This will be measured by self-reported current comorbidities as mental health disorder (variable mhcat___18).
Previous SARS-CoV-2 infections: Any vs none

These subgroup analyses will be done by including an interaction term between the treatment arm and the subgroup in the mixed effects proportional odds logistic regression model described above. The p-value of the subgroup by arm interaction term will be assessed to determine whether there could be a subgroup effect, with the understanding that the analysis is probably underpowered.

Measure 5.1.2

Each symptom will be assigned a score of 0 if not present, 1 if mild, 2 if moderate and 3 if severe. These scores for each symptom will be added together to get the total neurological long COVID score, ranging from 0 to 66.

Estimand

Population: Household members (older than 5 years) enrolled in the study, regardless of SARS-CoV-2 infection status (all enrolled participants)
Treatment: Initially randomised intervention to unfractionated intranasal heparin 1400u each nostril (as heparin solution 5,000u/ml, 140microL/actuation, TWO actuations each nostril) THREE times daily via a plastic nasal inhalator device or saline control and any subsequent deviations to the per protocol use of the intervention over 10 days
Outcome: Continuous neurological long COVID score (described above) at 6 months, with a 2 month window (i.e. including outcomes measured between 4 and 8 months)
Summary measure: The mean difference between arms will be reported with 95% confidence interval
Potential intercurrent events:

Index case in the household not taking study drug. This is defined as compliance <90%
Participant (this household member) not taking study drug. This is defined as compliance <90%
Either participant (this household member) or index case stop treatment due to adverse event
Participant received an anti-viral

Strategy for handling intercurrent event:

All intercurrent events will be handled through the treatment policy strategy, which means that the intercurrent events will be ignored.

The same analysis as described for Measure 4.3 will be done.

This analysis will also be repeated in the subgroup of participants who had SARS-CoV-2 infection.

The following subgroup analyses will be done:
Age: Younger than 65 vs 65 and older
Pre-existing mental health problems: This will be measured by self-reported current comorbidities as mental health disorder (variable mhcat___18).
Previous SARS-CoV-2 infections: Any vs none

These subgroup analyses will be done by including an interaction term between the treatment arm and the subgroup in the model described for Measure 4.3. For example, using the Stata code
mixed outcome i.arm##i.subgroup baseline_covariates || household:

The p-value of the subgroup by arm interaction term will be assessed to determine whether there could be a subgroup effect, with the understanding that the analysis is probably underpowered.

Measure 5.1.3

In addition to assessing whether treatment assignment was associated with neurological long COVID we want to investigate whether neurological long COVID outcomes were different for participants who tested positive for SARS-CoV-2 vs those who tested negative.

Estimand

Population: Household members (older than 5 years) enrolled in the study, regardless of SARS-CoV-2 infection status (all enrolled participants)
Exposures compared: Tested positive for SARS-CoV-2 any time during the study (baseline positive or positive during the trial) vs tested negative for SARS-CoV-2 at all time points
Outcome: Ordinal Likert scale measurement of severity of each of the symptoms listed in Measure 5.1.1. at 6 months, with a 2 month window (i.e. including outcomes measured between 4 and 8 months)
Summary measure: The overall odds ratio will be reported with 95% confidence interval
Potential intercurrent events: None
Strategy for handling intercurrent event: Not applicable

We will summarise the number of participants in each of the 4 categories of the Likert scale in each exposure group. A proportional odds logistic regression will be used to calculate the overall odds ratio, adjusted for the stratification variables and randomised arm and clustered on household. The assumption of proportional odds

will be investigated. If it is violated, we will fit a multinomial regression and calculate an odds ratio for each category.

Measure 5.1.4

In addition to assessing whether treatment assignment was associated with neurological long COVID we want to investigate whether neurological long COVID outcomes were different for participants who tested positive for SARS-CoV-2 vs those who tested negative. The research question is: Does testing positive for SARS-CoV-2 at baseline or during the 10 days of active treatment increase the severity of long COVID symptoms at 6 months?

Estimand

Population: Household members (older than 5 years) enrolled in the study, regardless of SARS-CoV-2 infection status (all enrolled participants)
Exposures compared: Tested positive for SARS-CoV-2 any time during the study (baseline positive or positive during the trial) vs tested negative for SARS-CoV-2 at all time points
Outcome: Continuous neurological long COVID score (described above) at 6 months, with a 2 month window (i.e. including outcomes measured between 4 and 8 months)
Summary measure: The mean difference between SARS-CoV-2 infected and uninfected participants will be reported with 95% confidence interval
Potential intercurrent events: None
Strategy for handling intercurrent event: Not applicable

The two exposures will be compared using mixed effects linear regression with neurological long COVID score as the outcome, adjusting for stratification factors (time from positive test to randomisation, whether the index case is a child < 5 years) randomised treatment arm and the defined baseline covariate set, with household as random effect to take the clustering by household into account.

The mean difference between the exposures will be calculated in Stata as follows using a mixed effects GLM with random intercepts:
mixed outcome i.infection_status i.arm baseline_covariates || household:

Measure 5.1.5

For participants over 16 years of age, cognition and mood were assessed using the harmonised procedures developed by the Neuro-COVID Neuropsychology International Task force. Included measures were:

- Cognitive screening using Telephone Montreal Cognitive Assessment (T-MoCA) Total Score
- Subjective cognitive complaints using Patient's assessment of Own Functioning Inventory (PAOFI)
  - Total
  - Memory
  - Language and communication
  - Use of hands
  - Sensory-perception
  - Higher-level cognitive and intellectual functions
  - Work/recreation
- Attention/working memory using the Wechsler Adult Intelligence Scale (WAIS) digit span
  - Digit Span Forward
  - Digit Span Backward
- Mood using the Depression, Anxiety and Stress Scales (DASS)
  - Depression
  - Anxiety
  - Stress

For each of the tests and scales listed above we will calculate the following estimand:

Estimand

Population: Household members (older than 16 years) enrolled in the study, regardless of SARS-CoV-2 infection status (all enrolled participants)

Treatment: Initially randomised intervention to unfractionated intranasal heparin 1400u each nostril (as heparin solution 5,000u/ml, 140microL/actuation, TWO actuations each nostril) THREE times daily via a plastic nasal inhalator device or saline control and any subsequent deviations to the per protocol use of the intervention over 10 days
Outcome: Each continuous scale measuring cognition or mood as listed above at 6 months, with a 2 month window (i.e. including outcomes measured between 4 and 8 months)
Summary measure: The mean difference between arms will be reported with 95% confidence interval
Potential intercurrent events:

Index case in the household not taking study drug. This is defined as compliance <90%
Participant (this household member) not taking study drug. This is defined as compliance <90%
Either participant (this household member) or index case stop treatment due to adverse event
Participant received an anti-viral

Strategy for handling intercurrent event:

All intercurrent events will be handled through the treatment policy strategy, which means that the intercurrent events will be ignored.

The same analysis as described for Measure 4.3 will be done.

This analysis will also be repeated in the subgroup of participants who had SARS-CoV-2 infection.

Measure 5.1.6
In addition to assessing whether treatment assignment was associated with neurological long COVID we want to investigate whether neurological long COVID outcomes were different for participants who tested positive for SARS-CoC-2 vs those who tested negative.

For each of the scales listed in Measure 5.1.5 we will also calculate the following estimand:

Estimand
Population: Household members (older than 16 years) enrolled in the study, regardless of SARS-CoV-2 infection status (all enrolled participants)
Exposures compared: Tested positive for SARS-CoV-2 any time during the study (baseline positive or positive during the trial) vs tested negative for SARS-CoV-2 at all time points
Outcome: Each continuous scale measuring cognition or mood as listed in Section 5.1.5 at 6 months, with a 2 month window (i.e. including outcomes measured between 4 and 8 months)
Summary measure: The mean difference between SARS-CoV-2 infected and uninfected participants will be reported with 95% confidence interval
Potential intercurrent events: None
Strategy for handling intercurrent event: Not applicable

The same analysis as described in Measure 5.1.5 will be done.

Measure 5.2
Number of participants with clinical symptoms of neurological long COVID at 12 months post participation in trial.

The measures done at 6 months will be repeated at 12 months. The same analyses as described for 6 months (Measures 5.1.1 to 5.1.6) will be repeated at 12 months.

7. SAFETY OUTCOMES

Adverse events and serious adverse events will be summarised by treatment arm.

The following adverse events and reactions were reported:

- Major bleeding or clinically relevant non major bleeding as defined by The International Society on Thrombosis and Haemostasis (ISTH) for clinical trials involving anticoagulant drugs (Kaatz S, Ahmad D,

Spyropoulos AC, Schulman S; Subcommittee on Control of Anticoagulation. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. J Thromb Haemost. 2015 Nov;13(11):2119-26. doi: 10.1111/jth.13140. PMID: 26764429).

- Nasal itching
- Any nose bleeding (free flowing blood vs not)
- HIT, which is an unexplained fall in platelet count and a positive heparin antibody test
- Local nasal irritation
- Local or generalised oedema
- Thrombosis
- Sneezing
- Other adverse events and reactions that, in the site Principal Investigator's (PI) judgement, are not part of the expected clinical course and could be related (at least possibly) to the study and are medically significant or had serious sequelae

Nose bleeds will be further described by providing the mean duration of nose bleeds.

All adverse events and serious adverse events will be listed by treatment arm using the population of household members (older than 5 years) prescribed study drug, regardless of SARS-CoV-2 infection status (all enrolled participants)

8. LISTINGS, TABLES AND FIGURES

Listing 1: Protocol deviations
Listing 2: Concomitant therapies
Arm PID Therapy Indication route Dose Frequency

Figure 1: CONSORT flow chart

Table 1: Participant recruitment and follow-up

	Total	**Heparin**	**Placebo**
	n (%)	**n (%)**	**n (%)**
Number of index participants screened			
Reasons screened households not enrolled			
Number of households randomised			
Reasons screened participants not enrolled			
Number of positive household members			
Number of negative household members			
Number completed 10 days of treatment			
Number attended 28 day visit			
Number attended 6 month visit			
Number attended 12 month visit			

Table 2: **Baseline characteristics: Mean or number and proportion**

	Heparin N =	**Placebo N =**	**Overall N =**
All variables listed in Section 4.2			

Table 3: **Baseline characteristics of household members by SARS-CoV-2 status: Mean or number and proportion**

	Heparin N =		**Placebo N =**	
	SARS-CoV-2 positive	**SARS-CoV-2 negative**	**SARS-CoV-2 positive**	**SARS-CoV-2 negative**
All household member variables listed in Section 4.2				

Table 4: Compliance

Number of doses received	**Day 1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Heparin										
0										
1										
2										
3										
Placebo										
0										
1										
2										
3										

Table 5: Compliance

	Heparin	**Placebo**
Mean percentage compliance		

Table 6: Concomitant therapy (Number of participants used)

Therapy	**Heparin**	**Placebo**
Therapy name	x	x
Etc		

Table 7: Nasal concomitant therapies

Therapy	**Heparin**	**Placebo**
Therapy	x	x
Etc		

Table 8: Primary outcome: Percentage (95% CI) testing positive for SARS-CoV-2

	Percentage testing positive N (%) 95% CI		**Comparison between arms (95% CI)**
	Heparin	**Placebo**	
Treatment policy estimand			
Complete case analysis with covariates			
Risk difference			
Risk ratio			
Complete case analysis without covariates			
Risk difference			
Risk ratio			
Analysis using multiple imputation			
Risk difference			
Risk ratio			
Hypothetical estimand			
Risk difference			

Risk ratio			

Table 9: Subgroup analyses for primary outcome

	Percentage testing positive N (%) 95% CI		**Comparison between arms (95% CI)**
	Heparin	**Placebo**	
Subgroup 1			**p-value**
Cat 1 n =			
Cat 2 n =			
Subgroup 2			
Cat 1 n =			
Cat 2 n =			
Etc			

Table 10: Secondary outcome 1: Efficacy of intransal heparin to reduce SARS-CoV-2 viral shedding

Day		**Percentage testing positive N (%) 95% CI**		**Comparison between arms (95% CI)**
	Treatment policy estimand	**Heparin**	**Placebo**	
	Complete case analysis with covariates			
Day 3	Risk difference			
	Risk ratio			
Day 5	Risk difference			
	Risk ratio			
Day 10	Risk difference			
	Risk ratio			
	Repeat for **Complete case analysis without covariates** **Analysis using multiple imputation** **Hypothetical estimand**			

Table 11: Secondary outcome 1: Time to swab negative

	Heparin	**Placebo**	**Hazard ratio (95% CI)**
Median (95% CI)			-

Table 12: Secondary outcome 2: Safety of intranasal heparin

	Heparin	**Placebo**
Number discontinued treatment prior to day 10	N (%) 95% CI	

Table 13: Secondary outcome 3.1: Reduction of symptomatic disease

	Percentage testing positive N (%) 95% CI		Comparison between arms (95% CI)
	Heparin	**Placebo**	
Treatment policy estimand			
Complete case analysis with covariates			
Risk difference			
Risk ratio			
Complete case analysis without covariates			
Risk difference			
Risk ratio			
Analysis using multiple imputation			
Risk difference			
Risk ratio			

Table 14: Secondary outcome 3.2: Reduction of symptomatic disease
Repeat Table 11

Table 15: Secondary outcomes 4.1 and 4.2: Hospitalisations

		Percentage hospitalised N (%) 95% CI		Comparison between arms (95% CI)
		Heparin	**Placebo**	
Household members				-
	Risk difference	-	-	
	Risk ratio	-	-	
Household members				-
	Risk difference	-	-	
	Risk ratio	-	-	

Table 16: Secondary outcome 4.1: Impact on peak severity of illness (maximum severity score) mean (95% CI)

Heparin	Placebo	Mean difference (95% CI)

Table 17: Secondary outcome 5.1.1. Neurological long COVID at 6 months. Presence of symptoms

	Heparin N (%)				Placebo N (%)				Overall odds ratio
Symptom	**Not present**	**Mild**	**Moderate**	**Severe**	**Not present**	**Mild**	**Moderate**	**Severe**	
Fatigue									
Malaise									
Daytime tiredness									
etc									

Table 18: Secondary outcome 5.1.1. Neurological long COVID at 6 months. Presence of symptoms in subgroup of participants who had SARS-CoV-2 infection
Repeat Table 17

Table 19: Secondary outcome 5.1.2. Neurological long COVID at 6 months. Continuous neurological long COVID score

	Heparin	Placebo	Mean difference (95% CI)
All participants			
Subgroup of participants who had SARS-CoV-2 infection			

Table 20: Secondary outcome 5.1.3. Neurological long COVID at 6 months. Presence of symptoms

	SARS-CoV-2 positive				SARS-CoV-2 negative				Overall odds ratio
Symptom	**Not present**	**Mild**	**Moderate**	**Severe**	**Not present**	**Mild**	**Moderate**	**Severe**	
Fatigue									
Malaise									
Daytime tiredness									
etc									

Table 21: Secondary outcome 5.1.4. Neurological long COVID at 6 months. Continuous neurological long COVID score

Heparin	Placebo	Mean difference (95% CI)

Table 22: Secondary outcome 5.1.5. Neurological long COVID at 6 months

Scale	Mean (95% CI)		Mean difference between arms (95% CI)	p-value
	Heparin	Placebo		
e.g. WAIS digit span				
DASS etc				
Repeat for subgroup of participants SARS-CoV--2 positive				

Table 23: Secondary outcome 5.1.6. Neurological long COVID at 6 months.

Scale	Mean (95% CI)		Mean difference (95% CI)	p-value
	SARS-CoV-2 positive	SARS-CoV-2 negative		
e.g. WAIS digit span				
DASS etc				
Repeat for subgroup of participants SARS-CoV--2 positive				

Table 24: Secondary outcome 5.1.6. Neurological long COVID at 6 months. Subgroup analyses
Repeat Table 22 for each subgroup, also include p-value for subgroup

Table 25: Secondary outcome 5.2.1. Neurological long COVID at 6 months. Presence of symptoms
Repeat Table 17

Table 26: Secondary outcome 5.2.1. Neurological long COVID at 6 months. Presence of symptoms in subgroup of participants who had SARS-CoV-2 infection
Repeat Table 18

Table 27: Secondary outcome 5.2.2. Neurological long COVID at 6 months. Continuous neurological long COVID score
Repeat Table 19

Table 28: Secondary outcome 5.2.3. Neurological long COVID at 6 months. Presence of symptoms
Repeat Table 20

Table 29: Secondary outcome 5.2.4. Neurological long COVID at 6 months. Continuous neurological long COVID score
Repeat Table 21

Table 30: Secondary outcome 5.2.5. Neurological long COVID at 6 months.
Repeat Table 22

Table 31: Adverse events

	Heparin n (%)	**Placebo n (%)**
Major bleed		
Nasal itching		
Nose bleed		
HIT		
Local nasal irritation		
Loal or generalized oedema		
Thrombosis		
Sneezing		
Other		
Serious adverse events		
Mean duration of nose bleeds		