

# BMJ Open Protocol for a 30-day randomised, parallel-group, non-inferiority, controlled trial investigating the effects of discontinuing renin-angiotensin system inhibitors in patients with and without COVID-19: the RASCOVID-19 trial

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**To cite:** Kliim-Hansen V, Gasbjerg LS, Ellegaard A-M, *et al.* Protocol for a 30-day randomised, parallel-group, non-inferiority, controlled trial investigating the effects of discontinuing renin-angiotensin system inhibitors in patients with and without COVID-19: the RASCOVID-19 trial. *BMJ Open* 2022;12:e062895. doi:10.1136/bmjopen-2022-062895

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2022-062895>).

Received 24 March 2022  
Accepted 29 September 2022



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## ABSTRACT

**Introduction** The COVID-19 pandemic caused by the virus SARS-CoV has spread rapidly and caused damage worldwide. Data suggest a major overrepresentation of hypertension and diabetes among patients experiencing severe courses of COVID-19 including COVID-19-related deaths. Many of these patients receive renin-angiotensin system (RAS) inhibiting therapy, and evidence suggests that treatment with angiotensin II receptor blockers (ARBs) could attenuate SARS-CoV-induced acute respiratory distress syndrome, and ACE inhibitors and ARBs have been suggested to alleviate COVID-19 pulmonary manifestations. This randomised clinical trial will address whether RAS inhibiting therapy should be continued or discontinued in hospitalised patients with COVID-19.

**Methods and analysis** This trial is a 30-day randomised parallel-group non-inferiority clinical trial with an embedded mechanistic substudy. In the main trial, 215 patients treated with a RAS inhibitor will be included. The participants will be randomly assigned in a 1:1 ratio to either discontinue or continue their RAS inhibiting therapy in addition to standard care. The patients are included during hospitalisation and followed for a period of 30 days. The primary end point is number of days alive and out of hospital within 14 days after recruitment. In a mechanistic substudy, 40 patients treated with RAS inhibition, who are not in hospital and not infected with COVID-19 will be randomly assigned to discontinue or continue their RAS inhibiting therapy with the primary end point of serum ACE2 activity.

**Ethics and dissemination** This trial has been approved by the Scientific-Ethical Committee of the Capital Region of Denmark (identification no. H-20026484), the Danish Medicines Agency (identification no. 2020040883) and by the Danish Data Protection Agency (P-2020-366). The

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Design and outcomes are simple, and the results can be directly applied in clinical practice.
- ⇒ Stratified randomisation will ensure equal distribution of age, trial sites and participation in other COVID-19 randomised clinical trials.
- ⇒ Blinded interim analysis will secure safety.
- ⇒ Renin-angiotensin system (RAS)-specific blood and urine analyses coupled with data on disease progression will provide insight into how ACE inhibitors and angiotensin II receptor blockers affect COVID-19 infection.
- ⇒ Due to the clinical setting of this trial, site investigators, clinical staff and participants will not be blinded; investigators responsible for interim analysis and outcome assessment will be blinded to group allocation.

results of this project will be compiled into one or more manuscripts for publication in international peer-reviewed scientific journals.

**Trial registration number** 2020-001544-26; NCT04351581.

## INTRODUCTION

The COVID-19 pandemic has spread rapidly and caused damage worldwide. Data from some of the earliest and worst affected countries suggest a major overrepresentation of hypertension and diabetes among COVID-19-related deaths and among patients experiencing severe

courses of the disease.<sup>1–3</sup> The majority of patients with hypertension and/or diabetes are taking drugs targeting the renin-angiotensin system (RAS) because of their blood pressure-lowering and/or kidney protective effects. Importantly, the virus causing COVID-19, SARS-CoV-2, as well as SARS-CoV (the virus causing the outbreak of severe acute respiratory syndrome in southern China in 2002/2003) bind to the transmembrane protein ACE2—an important component of RAS—for host cell entry and subsequent viral replication.<sup>4</sup>

ACE2 is a homologue of ACE that regulates RAS by converting angiotensin II to the vasodilatory angiotensin, diminishing and opposing the vasoconstrictive effect of angiotensin II. ACE2 is abundant in the intestines as well as lung alveolar epithelial cells<sup>5</sup> and in rodents, ACE2 expression is shown to decrease with age.<sup>6</sup> ACE2 is normally considered to be an enzyme that limits airway inflammation via effects in RAS,<sup>4</sup> and increased ACE2 activity seems to alleviate acute respiratory distress syndrome (ARDS).<sup>7,8</sup> Importantly, evidence from human<sup>9,10</sup> as well as rodent SARS-CoV studies<sup>11</sup> suggests that the inhibition of RAS by ACE inhibitors (ACEi) or angiotensin II receptor blockers (ARB) leads to upregulation of ACE2, and treatment with ARB leads to attenuation of SARS-CoV-induced ARDS.<sup>12</sup> This is of interest, as the vast majority of deaths from COVID-19 are due to ARDS<sup>3</sup> and ACEi and ARBs have been suggested to alleviate the COVID-19 pulmonary manifestations.<sup>13</sup> Recent observational

studies have reported positive effects on severity<sup>14</sup> and mortality<sup>15</sup> associated with RAS inhibition therapy in patients with COVID-19. In contrast to these notions, concern has been raised that ACE2 upregulation (by RAS inhibitors) will multiply the cellular access points for viral entry and might increase the risk of severe progression of COVID-19<sup>16</sup>—potentially explaining the high morbidity and mortality among patients with COVID-19 who have diabetes and/or hypertension.<sup>1–3</sup> Two recent studies examining the effects of continuation versus discontinuation of RAS inhibitors in patients admitted to hospital with COVID-19 have not found any difference in outcomes between the groups<sup>17,18</sup> and, therefore, mechanistic prospective randomised trials evaluating the effect of continued versus discontinued RAS inhibitory therapy on the course of COVID-19 are needed.<sup>14,15,19,20</sup>

This is a randomised clinical trial with the main objective to investigate the effect of continued versus discontinued RAS inhibiting therapy in hospitalised patients with COVID-19 treated with ACEi or ARB on the number of days alive and out of hospital within 14 days in Denmark.

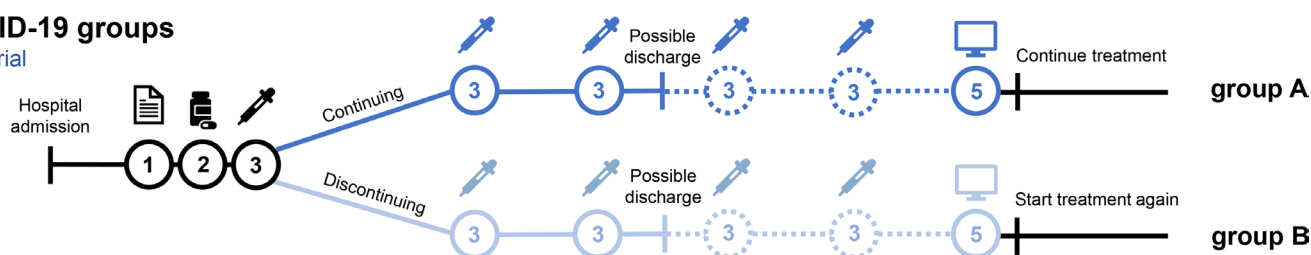
## METHODS AND ANALYSES

### Trial design

Each participant will be randomised to one of four groups: group A, B, C or D (figure 1).

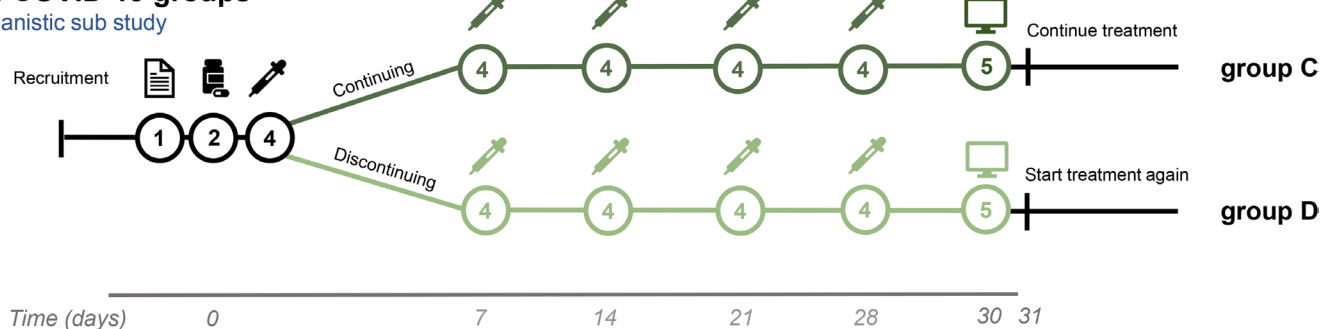
### COVID-19 groups

#### Main trial



### Non-COVID-19 groups

#### Mechanistic sub study



- 1: Informed consent and inclusion
- 2: Randomisation
- 3: Blood and urine samples
- 4: Trial visit with blood and urine samples
- 5: Information from electronic patient chart

**Figure 1** Trial design. COVID-19, coronavirus disease 2019.

COVID-19-infected participants (patients currently infected with COVID-19 and in hospital) will be randomly assigned in a 1:1 ratio to either discontinue or continue their RAS inhibiting therapy in addition to standard care. The group discontinuing RAS inhibition therapy (hereafter termed ‘group B’) will serve as a control group for the group continuing the therapy (hereafter termed ‘group A’).

Participants without COVID-19 will likewise be randomly assigned in a 1:1 ratio to either continue (hereafter termed ‘group C’) or discontinue (hereafter termed ‘group D’) their RAS inhibiting therapy. At inclusion, basic health information regarding the participant will be obtained, including age, gender, weight, height, smoking, alcohol consumption, prior and known diseases and medications. Blood samples as well as urinary samples will be collected at randomisation and every 7 days thereafter during admission for groups A and B, and every 7 days at trial visits for groups C and D (figure 1). Blood and urine will be analysed for relevant components of the RAS with the objective of supporting our clinical findings. Furthermore, messenger RNA expression in peripheral blood cells focusing on the expression of ACE, interferon signatures and T-cell exhaustion markers (which all may have prognostic value for viral infections) will be evaluated.

Supplementary data from routine blood samples including arterial blood gas analyses performed in the clinic on participants in groups A and B will be extracted from the medical charts and thus, causing no trial-related discomfort for the participants. These will

include potassium, sodium, C reactive protein, leucocytes, haemoglobin, haemoglobin A1c, alanine aminotransferase, international normalised ratio, creatinine, triglycerides, ferritin, fibrinogen, beta-2-microglobulin, partial pressure of oxygen and fraction of inspired oxygen. Additional data such as blood pressure, oxygen saturation, heart rate, respiratory frequency and temperature will also be obtained. For groups C and D, at trial visits every 7 days, blood samples for analysis of the above-mentioned parameters will be collected together with the trial samples and data on blood pressure, heart rate, temperature and blood oxygenation.

Besides continuing or discontinuing RAS inhibitor therapy, this trial will not interfere with the treatment of COVID-19 or any other conditions during the inclusion period.

### Patient and public involvement

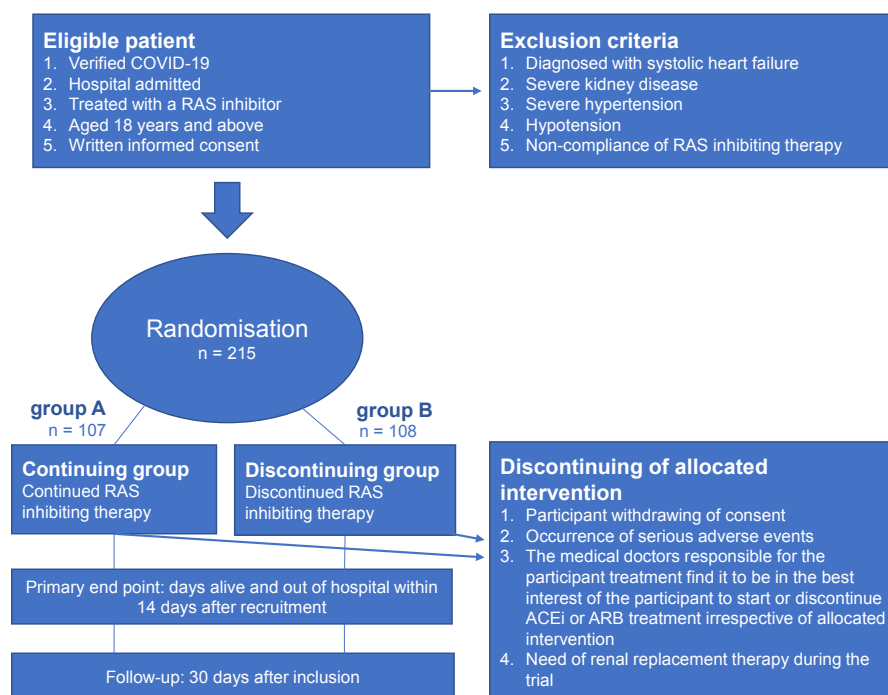
Relevant patients were involved in designing the participants information. No patients and/or the public will be involved in the reporting or dissemination plans of this research.

### Participants and recruitment

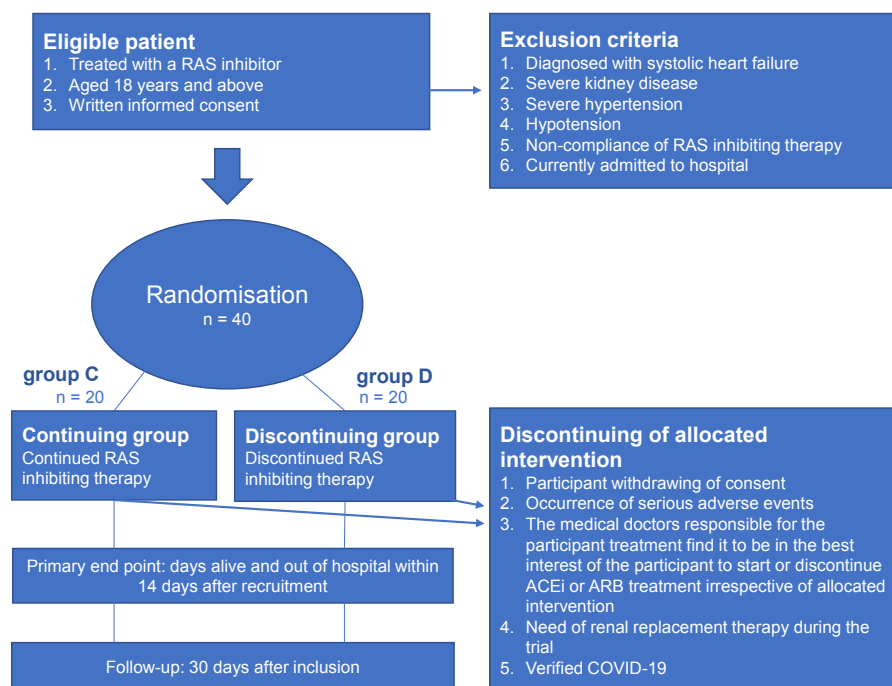
The start date of the study is 18 May 2020 and the estimated completion date for recruitment is 31 October 2022 (see figures 2 and 3).

### Inclusion criteria

1. Verified COVID-19 (only groups A and B).



**Figure 2** Plan for patient inclusion, exclusion and discontinuation for groups A and B. ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blocker; RAS, renin-angiotensin system.



**Figure 3** Plan for patient inclusion, exclusion and discontinuation for groups C and D. ACEi, ACE inhibitors; ARB, angiotensin II receptor blocker; RAS, renin-angiotensin system.

- Hospital admitted (only groups A and B).
- Treated with a RAS inhibitor.
- Aged 18 years and above.
- Written informed consent.

#### Exclusion criteria

- Diagnosed with systolic heart failure; defined by heart failure with reduced ejection fraction (EF) (EF <50%).
- Severe kidney disease; defined by estimated glomerular filtration rate (eGFR)  $\leq 30$  mL/min/1.73 m<sup>2</sup>.
- Severe hypertension; defined by systolic pressure  $\geq 175$  mm Hg and/or diastolic pressure  $\geq 105$  mm Hg.
- Hypotension; defined by systolic pressure  $\leq 100$  mm Hg and/or diastolic pressure  $\leq 60$  mm Hg.
- Non-compliance of RAS inhibition therapy; defined as an estimated adherence <80% assessed by a questionnaire in combination with checking the electronic medication system for redeemed prescriptions in the last 6 months. In borderline cases, the participant is assumed adherent to therapy.
- Contraindications for continued of ACEi or ARB treatment including second and third trimester pregnancy, breast feeding, severe hepatic impairment, hypersensitivity or allergic reactions to the therapy.
- Currently admitted to hospital (only groups C and D).

#### Participant withdrawal criteria

- Participant withdrawing of consent.
- Occurrence of serious adverse events related to continuation or discontinuation of ACEi or ARB treatment.

- In case the medical doctors responsible for the participant treatment find it to be in the best interest of the participant to start or discontinue ACEi or ARB treatment irrespective of allocated intervention.
- Need of renal replacement therapy during the trial.
- A verified COVID-19 diagnosis during the trial (only groups C and D).

In case of withdrawal of consent, follow-up will be discontinued. Otherwise, follow-up will continue for 30 days through medical charts and registers.

#### Sample size

The primary outcome of the RASCOVID-19 trial is days alive and out of hospital within 14 days after recruitment. For groups A and B, using a one-sided  $\alpha$  of 0.025 and a power (1- $\beta$ ) of 0.8 in a group sequential design, 1:1 allocation, with one planned interim analysis at 50% recruited, and with a null hypothesis of 0 days of difference, an SD of 3.8 days in the primary outcome measure, the trial will need to have a sample size of 214 patients to detect a worsening of 1.5 days in the primary outcome. Thus, the non-inferiority limit is 1.5 days.

For groups C and D we looked at a previous study,<sup>21</sup> where serum ACE2 activity levels in healthy individuals were 16.2 $\pm$ 5.4 UF/mL (mean $\pm$ SD) and 24.8 $\pm$ 12.4 UF/mL in hypertensive individuals. Estimating a baseline of 25 UF/mL with an SD of 10 UF/mL and wanting to be able to detect a MIRENIF in serum ACE2 activity of 9 UF/mL between the two COVID-19-negative groups

(ie, continued and discontinued) at trial end and an  $\alpha$  set to 5% and power  $(1-\beta)$  to 80% (corresponding to  $Z_{2\alpha}=1.96$  and  $Z_{\beta}=0.84$ ), then the number of participants needed in each COVID-19-negative group is 19 ( $n=(1.96+0.84)^2 \times (10^2+10^2)/9^2=19$ ). The population size has been set to 20 in each group to ensure power in case of participant dropouts.

### Randomisation

Participants receiving RAS inhibition therapy and complying with trial inclusion and exclusion criteria are randomised by site investigators 1:1 to each arm according to a computer-generated allocation table stratified by age (intervals:  $\leq 65$  years or  $>65$  years), and trial site and participation in other COVID-19 randomised clinical trials for groups A and B. Each participant will be assigned a computer-generated unique allocation number. The allocation table will be kept at a separate research facility and blinded for everyone else than the data analyst responsible for its generation.

### Blinding

The site investigators, clinical staff at trial sites or participants will not be blinded to the intervention. Trial statisticians and investigators responsible for the interim analysis and outcome assessment will be blinded to the group allocation.

### Interventions

The participants will be randomly assigned in a 1:1 ratio to either discontinue or continue their RAS inhibition therapy in addition to standard care, for the trial period of 30 days.

### Adherence

For groups A and B, the administration of medication will be monitored through the electronic patient chart during hospitalisation. Patients discharged before 30 days after enrolment will be followed-up via phone contact to register adherence, deviation and other data. For groups C and D, adherence, deviations and other data will be addressed at every trial visit.

### Outcome measures

#### Primary outcome

The primary end point is days alive and out of hospital within 14 days after recruitment (group A vs group B), on which a patient satisfies categories 0, 1 or 2 on the eight-category ordinal scale (figure 4).<sup>22</sup>

#### Secondary outcomes

The key secondary end point is the occurrence of worsening of COVID-19 (group A vs group B) as assessed by when a patient satisfies category 6, 7 or 8 on the ordinal scale (figure 4) within the trial period.<sup>22</sup>

Other secondary end points include:

- ▶ Time to occurrence of each of the components of the key secondary composite end point (group A vs group B).
- ▶ Kidney function (as assessed by plasma creatinine and eGFR).
- ▶ Duration of index hospitalisation (group A vs group B).
- ▶ 30-day mortality (differences in mortality will be displayed as number of days alive during the intervention period) (group A vs group B).
- ▶ Discharge beyond day 30 (group A vs group B).
- ▶ Number of readmissions after day 30 (group A vs group B).

### WHO defined Ordinal Scale for Clinical Improvement

1. Not hospitalised, no clinical or virological evidence of infection
2. Not hospitalised, no limitations of activities
3. Not hospitalised, limitation of activities
4. Hospitalised, no oxygen therapy
5. Hospitalised, oxygen by mask or nasal prongs
6. Hospitalised, non-invasive ventilation or high-flow oxygen
7. Hospitalised, intubation and mechanical ventilation
8. Hospitalised, ventilation and additional organ support – pressors, rapid response team (RRT), extracorporeal membrane oxygenation (ECMO)
9. Death

**Figure 4** WHO-defined ordinal scale for clinical improvement.<sup>22</sup> WHO, World Health Organisation.



- Change in circulating levels of RAS components (ACE, ACE2, aldosterone, angiotensin II and renin), expression of ACE, interferon signatures and T-cell exhaustion markers and blood pressure.

## Data management and monitoring

### Data collection

Data will be collected through access to the participant's medical chart as well as through questionnaires, urine and blood samples. Data will be obtained by the site investigators in case report forms stored in the data-managing programme of the Capital Region of Denmark. All participants will be assigned a trial number and will on data sheets and tubes only appear with the trial number. The full name, social security number and trial number will be stored separately. Follow-up will be done at day 30 through electronic patient charts and phone calls.

### Data access

The trial will be conducted in accordance with the applicable rules on clinical trials involving people in respect of quality control and quality management and will follow the Good Clinical Practice (GCP) guidelines.<sup>23</sup> The principal investigator is responsible for managing and achieving data in accordance with current regulations. Trial data will only be made available to third parties in accordance with Danish law.

### Quality control

The trial will be monitored according to Danish law and GCP guidelines by Copenhagen University Hospital's GCP unit.

### Statistical analysis

See online supplemental appendix 1, including figures 1–3 and tables 1–3, and online supplemental appendix 2 for the full statistical analyses plan.

## ETHICS AND DISSEMINATION

This trial has been approved by the Scientific-Ethical Committee of the Capital Region of Denmark (identification no. H-20026484), the Danish Medicines Agency (identification no. 2020040883) and by the Danish Data Protection Agency (P-2020-366) and comply with the international General Data Protection Regulation. The trial will be conducted according to the Declaration of Helsinki. All participants will receive oral and written information and both oral and written consent will be obtained before trial initiation. The participants will be informed by a member of the research group who is not responsible for the treatment of the participant.

The protocol-related procedures are associated with minimal discomfort to the participants, who will either not receive their usual ACEi or ARB or continue their usual therapy during the trial period, depending on assignment to the discontinuation or the continuation group, respectively. Discontinuation of RAS inhibition therapy may result in minimal increases in blood pressure; however,

blood pressure is routinely measured and, thus, closely monitored during their hospital admission. For groups A and B, in case of hospitalisation for <30 days, the participant will be instructed to contact his/her general practitioner at day 30 for blood pressure measurements and re-evaluation of antihypertensive therapy. At discharge, for all participants in groups A and B, the site investigator will also inform the general practitioner of trial participation (via an electronic discharge letter) and at day 30, site investigator will contact each participant to remind them to contact their general practitioner for blood pressure measurement, re-evaluation and recommencement of antihypertensive therapy. Groups C and D will be closely monitored with weekly visits, and a possible rise in blood pressure or other side effects can be quickly addressed.

For groups A and B, discontinuation of RAS inhibition therapy is not expected to improve or worsen the prognosis of patients with COVID-19; therefore, neither the assignment to the continuation nor the discontinuation group can clearly be labelled disadvantageous for the participant. Considering the scope of the COVID-19 pandemic and the number of patients on RAS inhibition treatment, the possible therapeutic insights obtained in this trial may be of profound importance and will hopefully aid healthcare systems in managing COVID-19. Given the precautions made to ensure the safety of all participants, the potential therapeutic benefits of this trial outweigh the relatively small risk of temporarily discontinued use of ACEi or ARBs in the test participants during their participation in the trial.

### Recruitment and informed consent

For groups A and B, participants will be recruited among COVID-19-positive patients admitted to a COVID-19 clinic in the Capital Region of Copenhagen. On admission of patients treated with ACEi and ARBs, site investigators with an employment at the COVID-19 clinic in question will screen the admitted patients for eligibility according to the inclusion and exclusion criteria. A potential participant will be approached during the first days of hospital admission by the site investigator, who will present verbal and written information regarding the trial (see online supplemental appendix 3), and the patient will be invited to participate. The patient will be offered 24 hours for consideration of participation in the trial. If the patient decides to participate, detailed information will be given, and written consent obtained before any protocol-related actions are initiated (see online supplemental appendices 4 and 5). The participants in groups C and D will be recruited through contact to general practitioners and through advertising. A screening visit will be set up over the phone. At this visit, the participant will be screened for eligibility and the patient will, in an undisturbed environment, receive written and verbal information about the trial. If the potential participant decides to participate, written consent will be obtained before any protocol-related actions are initiated. For all groups, the written consent form will include the option of allowing

the investigators to contact the participant again 1 year after randomisation in order to evaluate their medical condition at that point in time. This is completely voluntary and not a part of the trial nor a requirement for inclusion in the trial. Participants will have the opportunity to withdraw at any time.

### Participant confidentiality

Participants will sign a consent form that allows investigators to access hospital records for scientific purposes in order to assess known risk factors for COVID-19 and clinical outcomes during the hospital admission. The signed consent further includes disclosure of health data and other confidential information as part of authorities' control with the trial, as a legal requirement to secure correct completion of the trial. Prior to the written consent, clinical information necessary for identification of eligible patients including verification of COVID-19 will be obtained by site investigators who are employed at the COVID-19 clinic and thus have legal access to this information. The site investigator therefore uses information given by the patients during hospital admission for research purposes. Participant confidentiality is extended to cover any trial information relating to participants. No information concerning the trial or data will be released to any unauthorised third party and will be held in strict confidence. Trial records will be maintained for at least 5 years from the completion date.

### Remuneration for trial participants

The trial is not planned for the benefit of the individual participant. Participants in groups A and B will not receive any remuneration for participation.

The participants in groups C and D will receive 500 Danish kroner per trial visit as remuneration for their time and to cover transportation.

### Assessment of adverse events

There will be daily assessment of the occurrence of serious adverse events with and without a causal relationship to the allocated intervention while the participant is enrolled in the trial and admitted to one of the trial sites. All serious adverse events occurring in the four groups will be registered and included in the final report.

### The Danish Patient Compensation Association

This project is carried out at Herlev-Gentofte Hospital and Hvidovre Hospital; thus, all the participants will be covered by The Danish Patient Compensation Association in the event of a personal injury.

### Protocol modification

In case of protocol modifications, new approvals will be obtained from all relevant authorities.

### Dissemination

The results of this project will be compiled into one or more manuscripts for publication in international peer-reviewed scientific journals. Positive as well as negative

and inconclusive results will all be published, in accordance with the law concerning processing of personal data. Coauthors must fulfil criteria for co-authorship according to the International Committee of Medical Journal Editors.

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**Contributors** LSG, CAH, MBL, DSM, TV, VK-H, A-ME, CL, PS, MBC, J-UJ and FKK designed the trial and wrote the trial protocol. VK-H and HJNL will collect the data. VK-H will perform the data analysis and write the primary publication. All authors will critically review the manuscript and approve the final version.

**Funding** This work was supported by an unrestricted research grant from the Novo Nordisk Foundation (grant number NNF20SA0062873) to Center for Clinical Metabolic Research, Department of Medicine, Copenhagen University Hospital—Herlev and Gentofte, Copenhagen, Denmark to cover remuneration of staff and running costs of the project. The investigators will not receive any personal financial reimbursement from conducting the trial. The funding body has no role in the design of the trial and collection, analysis or interpretation of data or in writing the manuscript.

**Competing interests** None declared.

**Patient and public involvement** Relevant patients were involved in designing the participants information. No patients and/or the public will be involved in the reporting or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Ethics approval** This trial has been approved by the Scientific-Ethical Committee of the Capital Region of Denmark (identification no. H-20026484), the Danish Medicines Agency (identification no. 2020040883) and by the Danish Data Protection Agency (P-2020—366).

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** The data that support the findings of this study are available from the corresponding author, VK-H, upon reasonable request.

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## APPENDIX 1

### DETAILED STATISTICAL ANALYSIS PLAN FOR A 30-DAY RANDOMISED, PARALLEL-GROUP, NON-INFERIORITY, CONTROLLED TRIAL INVESTIGATING THE EFFECTS OF DISCONTINUING RENIN-ANGIOTENSIN SYSTEM INHIBITORS IN PATIENTS WITH AND WITHOUT COVID-19: THE RASCOVID-19 TRIAL

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#### Abstract

**Background:** The coronavirus disease 2019 (COVID-19) pandemic caused by the virus severe acute respiratory syndrome coronavirus 2 has spread rapidly and caused damage worldwide. There has been much discussion about how and if treatment with renin-angiotensin system (RAS) inhibiting therapy of COVID-19 patients could possibly affects the course of the disease. This randomised clinical trial will investigate the effect of continued vs. discontinued RAS inhibiting therapy on the course of COVID-19 in hospitalised patients. To ensure transparency and minimisation of bias, we present this article with a statistical analysis plan, to be published before the last participant is enrolled.

**Methods:** RASCOVID-19 is a 30-day randomised, parallel-group, non-inferiority clinical trial with an embedded mechanistic sub study. The population consist of two arms (one hospitalized with COVID-19 and one not hospitalized and COVID-19 negative), in which participants will be randomly assigned in a 1:1 ratio to either discontinue or continue their RAS-inhibiting therapy in addition to standard care. The intervention is not blinded to site investigators, clinical staff at trial sites or participants. Trial statisticians and investigators responsible for the interim analysis and outcome assessment will be blinded to the group allocation. The primary endpoint is number of days alive and out of hospital within 14 days after recruitment. The key-secondary endpoint is the occurrence of worsening of COVID-19.

**Discussion:** This paper describes the statistical analysis plan for the evaluation of primary and secondary endpoints of the RASCOVID-19 trial. Enrolment of patients to the RASCOVID-19 trial is still on-going. The purpose of this article is to prevent selective reporting of outcomes, data-driven analysis and to increase transparency.

**Trial registration:** EudraCT number: 2020-001544-26; ClinicalTrials.gov: NCT04351581, registered 17th of April 2020.

#### Background

The coronavirus disease 2019 (COVID-19) pandemic has spread rapidly and caused damage worldwide. Data from some of the earliest and worst affected countries suggest a major overrepresentation of hypertension and diabetes among COVID-19 related deaths and among patients experiencing severe courses of the disease.[1–3] Importantly, evidence from human [4,5] as well as rodent severe acute respiratory syndrome coronavirus (SARS-CoV) studies [6] suggests that the inhibition of RAS by ACE inhibitors (ACEi) or angiotensin II receptor

blockers (ARB) leads to upregulation of ACE2, and treatment with ARB leads to attenuation of SARS-CoV-induced acute respiratory distress syndrome (ARDS).[7] This is of interest, as the vast majority of deaths from COVID-19 are due to ARDS [3] and ACEi and ARBs have been suggested to alleviate the COVID-19 pulmonary manifestations.[8] In contrast to these notions, concern has been raised that ACE2 upregulation (by RAS inhibitors) will multiply the cellular access points for viral entry and might increase the risk of severe progression of COVID-19.[9] Two recent studies examining the effects of continuation vs. discontinuation of RAS inhibitors in patients admitted to hospital with COVID-19 have not found any difference in outcomes between the groups [10,11] and, therefore, mechanistic prospective randomised trials evaluating the effect of continued vs. discontinued RAS inhibitory therapy on the course of COVID-19 are needed.[12–15]

The International Conference on Harmonization of Good Clinical Practice [16] and leading experts [17] recommend that randomised clinical trials should be analysed according to predefined outcomes and a predefined statistical analysis plan. To prevent outcome reporting bias and data driven analysis and to increase transparency, this article will describe the statistical analysis plan for the RASCOVID-19 trial while enrolment of patients and collection of data is still on-going and before the database is accessed for trial end results.

Methods and analysis

Trial overview

RASCOVID-19 is a 30-day, multicentre, randomised, parallel-group, non-inferiority clinical trial, investigating the effect of continued vs. discontinued RAS-inhibiting therapy on the course of COVID-19 in hospitalised patients (figure 1, group A and B). The participants will be randomly assigned in a 1:1 ratio to either discontinue or continue their RAS-inhibiting therapy in addition to standard care for the trial period of 30 days (figure 2).

I addition another group of participants not currently infected with SARS-CoV or in hospital will undergo the same intervention for comparison (figure 1, group C and D).

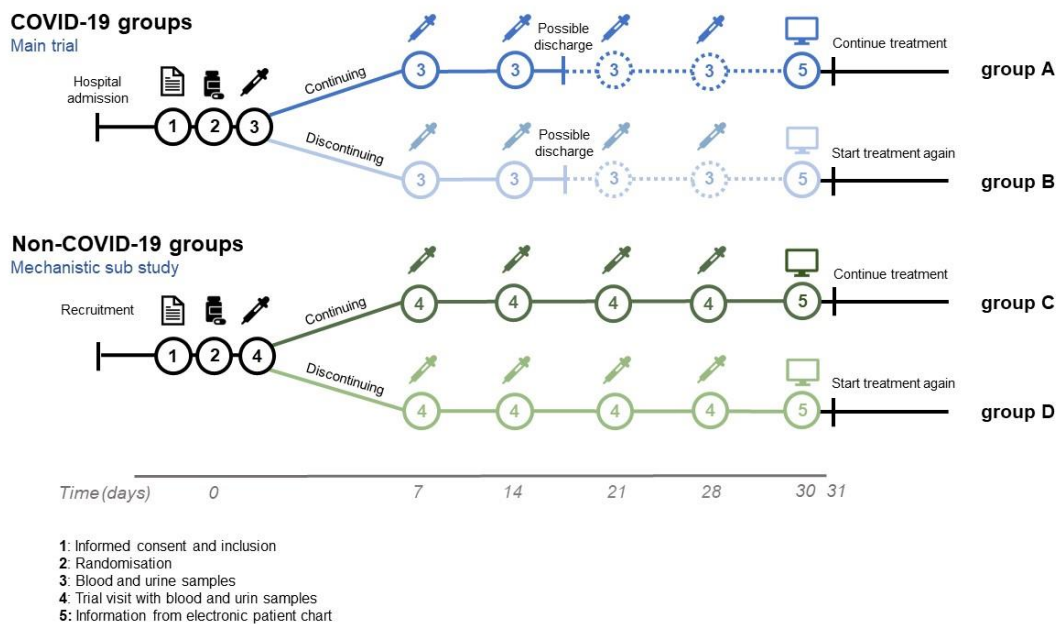


Figure 1: RASCOVID-19 Trial design

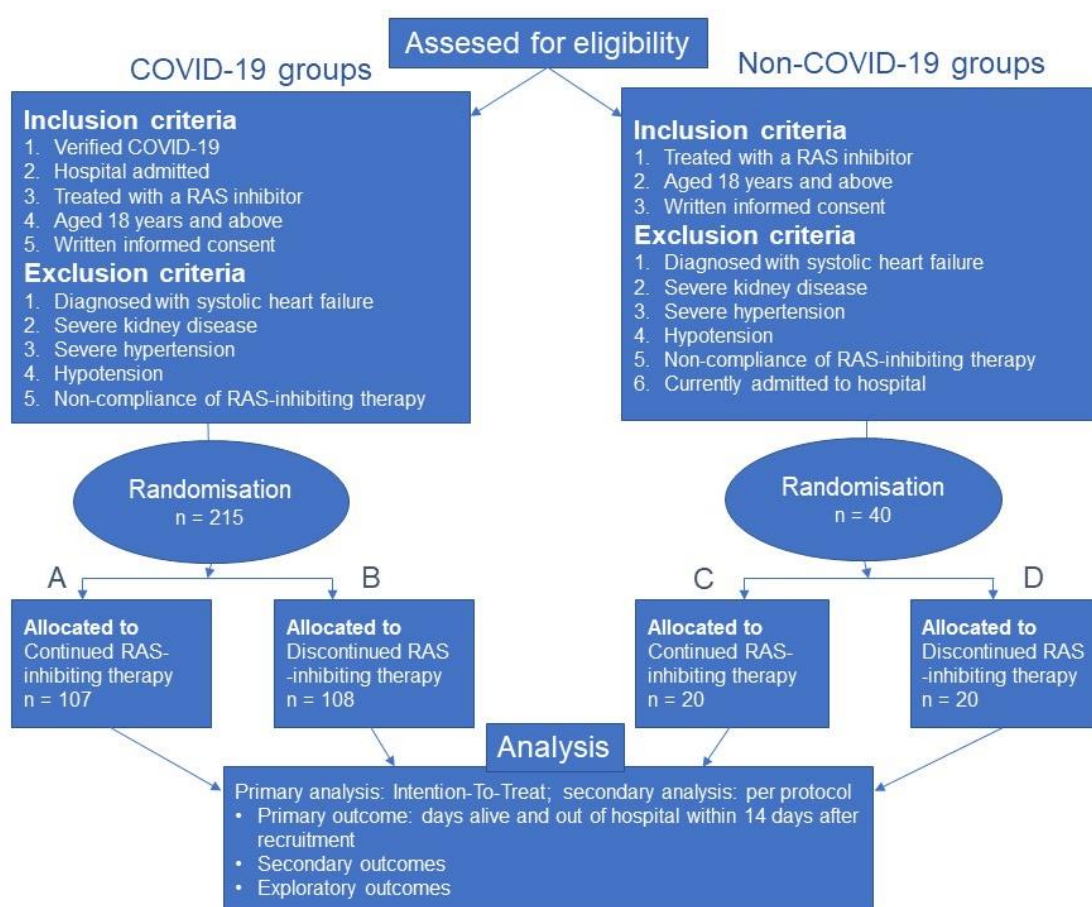


Figure 2: RASCOD-19 Flowchart. COVID-19: coronavirus disease 2019; RAS: renin–angiotensin system

The site investigators, clinical staff at trial sites or participants will not be blinded to the intervention. Trial statisticians and investigators responsible for the interim analysis and outcome assessment will be blinded to the group allocation.

The participants are enrolled in the trial only after obtaining written informed consent.

The trial will be conducted in accordance with the Declaration of Helsinki and is registered at ClinicalTrials.gov (NCT04351581) and EudraCT (2020-001544-26). Before enrolment, the trial was approved by the Scientific-Ethical Committee of the Capital Region of Denmark (identification no. H-20026484), the Danish Medicines Agency (identification no. 2020040883) and by the Danish Data Protection Agency (P-2020-366) and comply with the international General Data Protection Regulation.

Further details can be seen in the protocol. This statistical analysis plan is published while data collection from the RASCOD-19 trial is ongoing. The data analysis of the main publication will follow this plan. The statistical analysis plan has been approved by all authors.

Table 1: RASCOVID-19 Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) figure. For a more detailed version, see Appendix 2.

-t<sub>1</sub>: 0–48 hours before allocation

The primary outcome of the RASCOVID-19 trial is days alive and out of hospital within 14 days after recruitment. For group A and group B, using a 1-sided alpha of 0.025 and a power (1-beta) of 0.8 in a group sequential design, 1:1 allocation, with one planned interim analysis at 50% recruited, and with a null hypothesis of 0 days of difference, an SD of 3.8 days in the primary outcome measure, the trial will need to have a sample size of 214 patients to detect a worsening of 1.5 days in the primary outcome. Thus, the non-inferiority limit is 1.5 days.

$$n = (Z2\alpha + Z\beta)2 \times (SD1^2 SD2^2) / MIRE DIF^2$$

where  $\alpha$  is the significance level,  $\beta$  is the risk of accepting a false hypothesis, MIREdif is the estimated minimum relevant difference, SD is an approximated standard deviation (see below) of the primary endpoint, and  $Z\alpha$  and  $Z\beta$  are standardised deviations corresponding to the selected  $\alpha$  and  $\beta$  (see below). In a previous study,[18] serum ACE2 activity levels in healthy individuals was (mean $\pm$ SD) 16.2 $\pm$ 5.4 one unit of fluorescence (UF)/ml and 24.8 $\pm$ 12.4 UF/ml in hypertensive individuals. If we estimate a baseline of 25 UF/ml with a SD of 10 UF/ml and we want to be able to detect a MIREdif in serum ACE2 activity of 9 UF/ml between the two COVID-19 negative groups (i.e. continued and discontinued) at trial end; and we set  $\alpha = 5\%$  and power  $(1-\beta)$  to 80% (corresponding to  $Z2\alpha = 1.96$  and  $Z\beta = 0.84$ ), then the number of participants needed in each COVID-19 negative group is 19 ( $n = (1.96 + 0.84)^2 \times (10^2 + 10^2)/9^2 = 19$ ). The population size has been set to 20 in each group to ensure power in case of drop out.

### ***Stratification and design variables***

For group A and B, randomisation will be in blocks of unknown size and the final allocation will be stratified for age (intervals:  $\leq 65$  years or  $> 65$  years), trial site and participation in other COVID-19 randomised clinical trials. For group C and D, the allocation will be stratified for age (intervals:  $\leq 65$  years or  $> 65$  years).

### ***Outcomes***

#### ***Primary outcome***

The primary endpoint is days alive and out of hospital within 14 days after recruitment (group A vs. group B), on which a patient satisfies categories 0, 1 or 2 on the eight-category ordinal scale (figure 3).[19]

#### **WHO defined Ordinal Scale for Clinical Improvement**

1. Not hospitalised, no clinical or virological evidence of infection
2. Not hospitalised, no limitations of activities
3. Not hospitalised, limitation of activities
4. Hospitalised, no oxygen therapy
5. Hospitalised, oxygen by mask or nasal prongs
6. Hospitalised, non-invasive ventilation or high-flow oxygen
7. Hospitalised, intubation and mechanical ventilation
8. Hospitalised, ventilation and additional organ support – pressors, rapid response team (RRT), extracorporeal membrane oxygenation (ECMO)
9. Death

*Figure 3: WHO defined Ordinal Scale for Clinical Improvement.[19] WHO: World Health Organisation*

#### ***Secondary outcomes***

The key-secondary endpoint is the occurrence of worsening of COVID-19 (group A vs. group B) as assessed by when a patient satisfies category 6,7 or 8 on the ordinal scale (figure 3) within the trial period.[19]

Other secondary endpoints include:

- Time to occurrence of each of the components of the key-secondary composite endpoint (group A vs. group B)
- Kidney function (as assessed by plasma creatinine and eGFR)
- Duration of index hospitalisation (group A vs. group B)
- 30-day mortality (differences in mortality will be displayed as number of days alive during the intervention period) (group A vs. group B)
- Discharge beyond day 30 (group A vs. group B)
- Number of readmissions after day 30 (group A vs. group B)
- Change in circulating levels of RAS components (ACE, ACE2, aldosterone, angiotensin II and renin), expression of ACE, interferon signatures, T cell exhaustion markers and blood pressure

#### ***Measurement of outcome variables***

Data will be collected through access to the participants medical chart as well as through questionnaires, urine and blood samples during the full trial period of 30 days, and at trial visits. Data will be obtained by the site investigators in case report forms stored in the data-managing program of the Capital Region of Denmark. All participants will be assigned a trial number and will on data sheets and tubes only appear with the trial number.

The full name, social security number and trial number will be stored separately. For patients in group A and B, who are discharged before 30 days follow up will be done through electronic patient charts and phone calls.

### Baseline characteristics

The baseline characteristics of the participants will be obtained from the patient, and from the patients' medical chart after randomisation. The baseline characteristics can be seen in Table 2.

|                              | Factor                                                 | Unit                          | Data          |
|------------------------------|--------------------------------------------------------|-------------------------------|---------------|
| Demographic characteristics  |                                                        |                               |               |
|                              | Age                                                    | years                         | mean $\pm$ SD |
|                              | Sex (Male / female)                                    | %                             | n/total       |
|                              | White race                                             | %                             | n/total       |
|                              | Current smoker                                         | %                             | n/total       |
|                              | Ex-smoker                                              | %                             | n/total       |
|                              | Non-smoker                                             | %                             | n/total       |
|                              | Smoking history, pack-years history                    | years                         | mean, 95% CI  |
|                              | Alcohol use                                            | units per week                | mean, 95% CI  |
|                              | Manifest atherosclerotic cardiovascular disease        | %                             | n/total       |
|                              | Active non-melanoma skin cancer                        | %                             | n/total       |
|                              | Dementia                                               | %                             | n/total       |
|                              | Diabetes type 2                                        | %                             | n/total       |
|                              | Diabetes type 1                                        | %                             | n/total       |
|                              | If diabetes, baseline or recent HbA1c, mmol/mol        | %                             | median, IQR   |
|                              | Chronic obstructive pulmonary disease                  | %                             | n/total       |
|                              | Asthma                                                 | %                             | n/total       |
|                              | If pulmonary disease, baseline or recent FEV1/FVC      | % of expected value           | median, IQR   |
|                              | Severe chronic kidney disease, stage 4-5               | %                             | n/total       |
|                              | Hypertension                                           | %                             | n/total       |
|                              | If hypertension, duration of hypertension              | years                         | median, IQR   |
|                              | Type of RAS targeting treatment (ACE inhibitor or ARB) | %                             | n/total       |
|                              | Duration of RAS targeting treatment                    | months                        | median, IQR   |
|                              | Medical treatments other than RAS targeting treatment  | number of drugs; drug name(s) | n/total       |
| Paraclinical characteristics |                                                        |                               |               |
|                              | Baseline body mass index                               | kg/m <sup>2</sup>             | mean, 95% CI  |
|                              | Baseline systolic blood pressure                       | mm Hg                         | median, IQR   |
|                              | Baseline diastolic blood pressure, mm Hg (median, IQR) | mm Hg                         | median, IQR   |
|                              | Baseline heart rate                                    | beats/minute                  | median, IQR   |
|                              | Use of oxygen therapy                                  | %                             | median, IQR   |
|                              | Respiratory rate                                       | breaths per minute            | median, IQR   |
|                              | Baseline oxygen saturation, %                          | %                             | median, IQR   |
|                              | Baseline temperature                                   | °C                            | median, IQR   |
|                              | Baseline leukocyte count                               | $\times 10^9$ cells/L         | mean, 95% CI  |
|                              | Baseline CRP                                           | mg/L                          | median, IQR   |
|                              | Baseline D-dimer                                       | mg/L                          | median, IQR   |
|                              | Baseline ferritin                                      | $\mu$ g/L                     | median, IQR   |
|                              | Baseline troponin T                                    | ng/L                          | median, IQR   |

|  |                                    |        |             |
|--|------------------------------------|--------|-------------|
|  | Baseline eGFR                      | mL/min | median, IQR |
|  | Baseline arterial blood gas values |        |             |
|  | pCO <sub>2</sub>                   | kPa    | median, IQR |
|  | pO <sub>2</sub>                    | kPa    | median, IQR |
|  | HCO <sub>3</sub>                   | mmol/L | median, IQR |
|  | pH                                 |        | median, IQR |
|  | Chest X-ray infiltrate             | %      | n/total     |

Table 2: RASCOVID-19 Baseline characteristics

*General analysis principles*

The analysis principles are as follows:

- All analyses will be conducted on an intention-to-treat basis. All randomised participants will be analysed in the group to which they were assigned
- Statistical hypothesis tests will be evaluated at a nominal two-sided 5% level of significance
- Intervention effect estimates (i.e. difference in means, hazard ratio) and their 95% confidence interval (CI) will be reported for all outcomes
- P values will not be adjusted for multiple comparisons
- P values will be reported to two decimal places unless the P value is less than 0.001, in which case it will be reported as '< 0.001'
- Analyses will be conducted primarily using SAS version 9.4

*Level of significance*

All the statistical tests will be performed using a 5% significance level, and we will report the 95% confidence interval. No adjustment for multiplicity is needed for the primary hypothesis.

*Missing data*

It is not anticipated that there will be a lot of missing data. However, in the unlikely event that there is more than 10% of data values missing, missing values will be imputed, if possible, using a suitable imputation method.

*Statistical analysis*

Table of statistical analysis:

|  | Factor                                                          | Unit   | Data         | Analysis                              |
|--|-----------------------------------------------------------------|--------|--------------|---------------------------------------|
|  | Primary Outcome                                                 |        |              |                                       |
|  | Days alive and out of hospital within 14 days after recruitment | days   | mean, 95% CI | t-test or a non-parametric test       |
|  | Secondary outcomes                                              |        |              |                                       |
|  | Intubation and mechanical ventilation                           | %      | n/total      | Chi-square test or fishers exact test |
|  | Ventilation and additional organ support                        | %      | n/total      | Chi-square test or fishers exact test |
|  | Death                                                           | %      | n/total      | Chi-square test or fishers exact test |
|  | Referral to treatment in an intensive care unit                 | %      | n/total      | Chi-square test or fishers exact test |
|  | Kidney function                                                 | mL/min | median, IQR  | t-test or Mann-Whitney test           |

|  |                                                     |      |             |                                                                  |
|--|-----------------------------------------------------|------|-------------|------------------------------------------------------------------|
|  | Duration of index hospitalisation                   | days | median, IQR | t-test or Mann-Whitney test                                      |
|  | 30-day mortality                                    | days | median, IQR | Kaplan-Meier plots method in combination with the log-rank test. |
|  | Discharge beyond day 30                             | %    | n/total     | Chi-square test or fishers exact test                            |
|  | Number of readmissions after day 30 days            | n    | n/total     | Chi-square test or fishers exact test                            |
|  | Number of days alive during the intervention period | days | median, IQR | t-test or Mann-Whitney test                                      |

Table 3: RASCOVID-19 Statistical analysis. CI: confidence interval; IQR: interquartile range; n: number

### Statistical analysis of the primary outcome

The primary outcome is the number of days alive and out of hospital within 14 days after recruitment in the continuing group compared to the discontinuing group (group A vs. group B). Data for the primary outcome analysis will be presented as mean with 95% CI and corresponding t-test or a non-parametric test if the data is not normally distributed (table 3).

In general, data will be processed and presented with the use of standard descriptive statistics. Normally distributed data will be compared using standard parametric statistical methods. Repeated measurement analysis of variance will be used for statistical analysis of repeated measurements in the same subject. Data that are not normally distributed will be compared using the Mann-Whitney U-test or the Wilcoxon test for data pairs. 95% confidence intervals will be calculated. Two-sided 5% significance levels will be used to identify statistically significant results. The primary endpoint will be analysed according to the intention-to-treat analysis set with appropriate support provided by the per-protocol analysis set. In the intention-to-treat analysis, every randomised subject will be analysed according to their original assignment. Per-protocol analysis denotes the comparison of treatment groups including only those patients who completed the treatment originally allocated. Data will be presented both with and without adjustment for participation in other clinical trials and for drug class (ACEi or ARBs). Excluded participants and missing, unused or false data will be described.

### Statistical analyses of secondary and explorative outcomes

Analyses of the composite key secondary as well as other secondary endpoints outlined in the protocol from baseline to follow-up will be included when assessing the clinical outcome. Appropriate statistical tests will be used for each dataset (table 3). Assessment of secondary endpoints will be performed by intention-to-treat (ITT) analysis according to the number of participants adhering to the allocated intervention.

### Interim analysis

A Data and Safety Monitoring Board (DSMB) will be appointed and act according to a charter agreed by the investigators and approved by the sponsor. When half of the total population has been randomised (i.e. 108 participants), a blinded interim analysis based on the ITT population will be performed to evaluate the continuation of the trial. The sample size will be evaluated and if needed, a higher number of participants will be applied for to relevant authorities. As main statistical measures, an O'Brien-Fleming plot of the primary endpoint and mortality (calculating Z-scores) will be performed. Moreover, the DSMB will assess the primary outcome measure and can, based on admission duration data (days), recommend to adjust the number of days alive and out of hospital to 21 instead of 14 days. In this case, there is no new sample size calculation since the standard deviation of the primary outcome does not change substantially, which we do not anticipate. The

interim analysis will be performed and presented by a sub-investigator not otherwise involved in the data collection or analyses. The data will be presented in a blinded fashion.

### *Outline of figures and tables in the primary manuscript*

The manuscript will include a consolidated standard of reporting of randomised trials (CONSORT) flow chart, a Kaplan-Meier plot to describe the rate of death by treatment groups (for group A and B), a table with baseline characteristics of the ITT population and a table including the primary and secondary outcomes according to the two allocation and pairwise comparisons.

### *Blinding of statisticians*

The interim and final analyses will be performed by MD PhD Pradeesh Sivapalan and Professor Jens-Ulrik Jensen (who are not investigators of this trial) from Section of Respiratory Medicine, Department of Medicine, Copenhagen University Hospital - Herlev and Gentofte, Copenhagen, Denmark.

### **Trial status**

Currently 78 participants have been enrolled in the trial; 40 in group A and B, and 38 in group C and D. Recruitment is expected to finish 1<sup>st</sup> July 2022.

### **Abbreviations**

ACE: angiotensin-converting enzyme

ACE2: angiotensin-converting enzyme 2

ARB: angiotensin II receptor blocker

CI: confidence interval

CONSORT: consolidated standards of reporting of randomised trials

COVID-19: coronavirus disease 2019

CRP: c-reactive protein

DSMB: data safety monitoring board

eGFR: estimated glomerular filtration rate

FEV1: forced expired volume

FiO<sub>2</sub>: fraction of inspired oxygen

FVC: forced vital capacity

HbA1c: haemoglobin A1c

HCO<sub>3</sub>: bicarbonate

IQR: interquartile range

ITT: intention to treat

pCO<sub>2</sub>: partial pressure of carbon dioxide

pO<sub>2</sub>: partial pressure of oxygen

RAS: renin–angiotensin system

SARS-CoV: severe acute respiratory syndrome coronavirus

SD: standard deviation

UF: one unit of fluorescence

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### Authors contributions

LSG, CAH, MBL, TV, VKH, AME, MBC, JUSJ and FKK designed the trial and wrote the trial protocol. VKH and HJNL are collecting the data. VKH, will perform the data analysis and write the primary publication. All authors have critically edited the manuscript and approved the final version.

### Funding

This work was supported by an unrestricted grant from the Novo Nordisk Foundation (grant number NNF20SA0062873) to Center for Clinical Metabolic Research, Copenhagen University Hospital – Herlev and Gentofte, Copenhagen, Denmark. The investigators will not receive any personal financial reimbursement from conducting the trial. The funding body has no role in the design of the trial and collection, analysis or interpretation of data or in writing the manuscripts.

### Conflict of interest

The authors declare that they have no competing interests in relation to this trial.

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## APPENDIX 2

### Schedule of enrolment, interventions and assessments, Group A + B

|                                     | STUDY PERIOD    |            |                 |                |                |                |                |                |                |
|-------------------------------------|-----------------|------------|-----------------|----------------|----------------|----------------|----------------|----------------|----------------|
|                                     | Enrolment       | Allocation | Post-allocation |                |                |                |                |                |                |
| TIMEPOINT                           | -t <sub>1</sub> | 0          | t <sub>1</sub>  | t <sub>2</sub> | t <sub>3</sub> | t <sub>4</sub> | t <sub>5</sub> | t <sub>6</sub> | t <sub>7</sub> |
| <b>ENROLMENT:</b>                   |                 |            |                 |                |                |                |                |                |                |
| Eligibility screen                  | X               |            |                 |                |                |                |                |                |                |
| Informed consent                    | X               |            |                 |                |                |                |                |                |                |
| Questionnaire                       | X               |            |                 |                |                |                |                |                |                |
| Allocation                          |                 | X          |                 |                |                |                |                |                |                |
| <b>INTERVENTIONS:</b>               |                 |            |                 |                |                |                |                |                |                |
| Continued RAS-inhibiting therapy    |                 |            | ↔               |                |                |                |                |                |                |
| Discontinued RAS-inhibiting therapy |                 |            | ↔               |                |                |                |                |                |                |
| <b>ASSESSMENTS:</b>                 |                 |            |                 |                |                |                |                |                |                |
| Basic Health Information            |                 |            | X               |                |                |                |                |                |                |
| Biochemistry Standard               |                 |            | X               | X              |                |                |                |                |                |
| A-gas                               |                 |            | X               | X              |                |                |                |                |                |
| EWS                                 |                 |            | X               | X              |                |                |                |                |                |
| Radiology                           |                 |            | X               |                | X              |                |                |                |                |
| Study Specific bio-samples          |                 |            | X               |                |                | X              |                |                |                |
| Primary endpoint day 14             |                 |            |                 |                |                |                | X              |                |                |
| Primary endpoint day 21             |                 |            |                 |                |                |                |                | X              |                |
| Key Secondary endpoints             |                 |            |                 |                | X              |                |                |                |                |
| Discharge                           |                 |            |                 |                | X              |                |                |                |                |
| 30 days follow-up                   |                 |            |                 |                |                |                |                |                | X              |
| AE                                  |                 |            |                 |                | X              |                |                |                |                |
| Drop out                            |                 |            |                 |                | X              |                |                |                |                |

- t<sub>1</sub> 0-48 hours before allocation
- t<sub>1</sub> first 24 hours after allocation
- t<sub>2</sub> thrice daily during admission
- t<sub>3</sub> all available data during admission
- t<sub>4</sub> weekly during admission
- t<sub>5</sub> day 14
- t<sub>6</sub> day 21
- t<sub>7</sub> day 30

## Schedule of enrolment, interventions and assessments, Group C + D

|                                            | STUDY PERIOD    |            |                 |                |                |                |                |                |
|--------------------------------------------|-----------------|------------|-----------------|----------------|----------------|----------------|----------------|----------------|
|                                            | Enrolment       | Allocation | Post-allocation |                |                |                |                |                |
| TIMEPOINT                                  | -t <sub>1</sub> | 0          | t <sub>1</sub>  | t <sub>2</sub> | t <sub>3</sub> | t <sub>4</sub> | t <sub>5</sub> | t <sub>6</sub> |
| <b>ENROLMENT:</b>                          |                 |            |                 |                |                |                |                |                |
| Eligibility screen                         | X               |            |                 |                |                |                |                |                |
| Informed consent                           | X               |            |                 |                |                |                |                |                |
| Questionnaire                              | X               |            |                 |                |                |                |                |                |
| <b>Allocation</b>                          |                 | X          |                 |                |                |                |                |                |
| <b>INTERVENTIONS:</b>                      |                 |            |                 |                |                |                |                |                |
| <i>Continued RAS-inhibiting therapy</i>    |                 |            | ↔               |                |                |                |                |                |
| <i>Discontinued RAS-inhibiting therapy</i> |                 |            | ↔               |                |                |                |                |                |
| <b>ASSESSMENTS:</b>                        |                 |            |                 |                |                |                |                |                |
| <i>Basic Health Information</i>            |                 |            | X               |                |                |                |                |                |
| <i>Biochemistry Standard</i>               |                 |            | X               | X              | X              | X              | X              |                |
| <i>EWS</i>                                 |                 |            | X               | X              | X              | X              | X              |                |
| <i>Study Specific bio-samples</i>          |                 |            | X               | X              | X              | X              | X              |                |
| <i>Primary endpoint day 14</i>             |                 |            |                 |                | X              |                |                |                |
| <i>Primary endpoint day 21</i>             |                 |            |                 |                |                | X              |                |                |
| <i>Key Secondary endpoints</i>             |                 |            |                 | X              | X              | X              | X              | X              |
| <i>30 days follow-up</i>                   |                 |            |                 |                |                |                |                | X              |
| <i>AE</i>                                  |                 |            |                 | X              | X              | X              | X              | X              |
| <i>Drop out</i>                            |                 |            |                 | X              | X              | X              | X              | X              |

- t<sub>1</sub> before allocation  
t<sub>1</sub> first study visit, day 0  
t<sub>2</sub> second study visit, day 7  
t<sub>3</sub> third study visit, day 14  
t<sub>4</sub> fourth study visit, day 21  
t<sub>5</sub> fifth study visit, day 28  
t<sub>6</sub> day 30



Deltagerinformation angående deltagelse i et videnskabeligt forsøg

## Effekten af seponering af hæmmere af renin-angiotensin systemet hos patienter med COVID-19

Original titel: *Effects of discontinuing renin-angiotensin system inhibitors in patients with COVID-19*

**Dette videnskabelige forsøg henvender sig til patienter med sygdommen COVID-19, der tager én af to bestemte typer blodtrykssænkende medicin. Vi vil undersøge om disse typer af blodtrykssænkende medicin påvirker sygdomsforløbet med COVID-19.**

Vi vil spørge, om du vil deltage i et sundhedsvidenskabeligt forskningsprojekt, der udføres på Herlev-Gentofte Hospital under ledelse af overlæge og professor Filip Krag Knop.

På de næste sider beskriver vi, hvad forsøget går ud på, og hvordan det udføres. Det er naturligvis helt frivilligt at deltage i forsøget, og du kan trække dig ud undervejs – også selv om du har skrevet under på at ville deltage. Du behøver ikke begrunde, hvorfor du alligevel ikke ønsker at deltage, og det vil selvfølgelig ikke have betydning for din videre behandling.

Tag dig god tid til at læse denne information, før du beslutter dig. Hvis du beslutter dig for at deltage i forskningsprojektet, vil vi bede dig om at underskrive en samtykkeerklæring. Før du bestemmer dig for, om du vil deltage, vil du have mulighed for betænkningstid, og du har ret til at drøfte din deltagelse med en pårørende eller anden bisidder samt have vedkommende med pr. telefon eller videosamtale, når vi informerer dig nærmere om projektet.

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## Formål med forsøget

COVID-19 er en sygdom, der skyldes smitte med den nye coronavirus (som hedder SARS-Cov-2). Renin-angiotensin-systemet bliver i daglig tale kaldt RAS og er et vigtigt hormonsystem, som er med til at regulere blodtrykket. Hvis man har forhøjet blodtryk, kan to forskellige typer blodtrykssænkende medicin påvirke RAS, hhv. *angiotensin converting enzyme*-hæmmere (ACE-hæmmere) og angiotensin II-receptorblokkere (ARB). ACE-hæmmere er medicin, der typisk slutter på ”-pril” fx enalapril. ARB er medicin, der typisk slutter på ”-tan” fx losartan. Din læge kan have udskrevet disse to typer medicin af andre grunde end for at behandle blodtrykket. Formålet med dette forsøg er at undersøge, hvordan behandling med ACE-hæmmere eller ARB og dermed en ændring af et af kroppens naturlige hormonsystemer (RAS) kan påvirke udviklingen af sygdommen COVID-19. I dette forsøg indgår derfor kun godkendte lægemidler i en mængde (dosis), som du allerede tager.

Coronavirus bruger et protein uden på kroppens celler til at komme ind i cellerne. Dette protein er en del af RAS og er bl.a. til stede uden på celler i lungerne. Det er én af grundene til, at coronavirus angriber lungerne. Virus skal ind i cellerne for at kunne gøre sin skadelige effekt, og proteinet har derfor en nøglerolle i kampen mod ny coronavirus.

De to typer af blodtrykssænkende medicin (ACE-hæmmere og ARB) påvirker muligvis proteinet, men vi ved på nuværende tidspunkt ikke, om dette har en betydning på kroppens reaktion på COVID-19. Da det er to meget almindelige former for blodtrykssænkende medicin, er det vigtigt at undersøge, hvordan det påvirker forløbet af COVID-19, så vi hurtigst muligt kan få etableret retningslinjer omkring brugen af disse hos patienter med COVID-19 – både i Danmark og i resten af verden. Det er det, vi gerne vil undersøge i dette forsøg.

Din deltagelse i forsøget omfatter din indlæggelse med COVID-19 og varer i alt 30 dage. Halvdelen af deltagerne skal fortsætte deres vanlige behandling med ACE-hæmmere eller ARB, men den anden halvdel skal holde pause i 30 dage. Vores hypotese er, at der ikke vil være en forskel i sygdomsforløbet mellem de to grupper, men dette er vigtigt at få bekræftet. Vi vil indhente oplysninger om dig fra din elektroniske journal i Sundhedsplatformen i 30 dage, fra du accepterer deltagelsen. Dette sker derfor mens, du er indlagt, men også efter din udskrivelse, hvis du er indlagt i færre end 30 dage.

## Forsøgets opbygning

Inden du kommer med i forsøget, vil vi gennemgå kravene for deltagelse med dig og sikre, at disse er opfyldt samt besvare de spørgsmål til denne deltagerinformation, som du evt. måtte have.

Hvis du ønsker at deltage, vil vi læse information om dig (køn, alder, højde, vægt, aktuelle sygdomme), din aktuelle helbredssituation og dit forløb med COVID-19 i din elektroniske journal i Sundhedsplatformen.

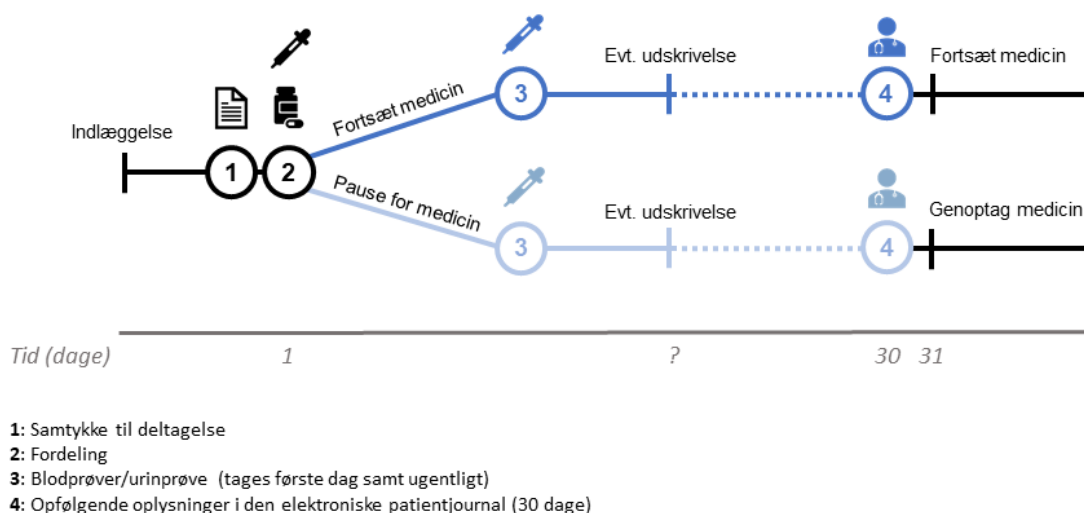
Du finder en oversigt over forsøget på figur 1 på næste side. Når du deltager i forsøget, vil det den første dag blive tilfældigt bestemt, om du er blandt dem, der skal fortsætte eller stoppe med at tage den blodtrykssænkende medicin, som påvirker RAS. Hvis du får flere typer blodtrykssænkende medicin, vil du fortsat skulle tage den resterende medicin, og mens du er indlagt, vil dit blodtryk blive

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målt dagligt for at sikre, at det ikke bliver for højt eller for lavt. Den læge, der er ansvarlig for din behandling, vil være klar over, hvorvidt du fortsat tager medicinen eller ej, og hvis du er interesseret, vil du således også kunne få det at vide.



**Figur 1.** Oversigt over forsøget

I tillæg til de blodprøver som rutinemæssigt tages, mens du er indlagt, vil der blive taget enkelte blodprøver samt en urinprøve til undersøgelse af RAS den første dag, du er med i forsøget. Disse ekstra blodprøver og urinprøven vil herefter blive taget en gang om ugen, mens du er indlagt på hospitalet. Når du bliver udskrevet, tages disse prøver ikke længere.

30 dage efter din indtrædelse i dette forsøg, vil vi læse i din elektroniske journal i Sundhedsplatformen for at følge op på din helbredsmæssige situation.

Det vil ikke påvirke din øvrige behandling for COVID-19, at du deltager i dette forsøg.

Hvis du beslutter at være med i dette forsøg, vil vi bede om tilladelse til at kontakte dig et år efter din udskrivelse for at spørge ind til dit helbred på det tidspunkt. Dette er helt frivilligt, og er således ikke en del af aktuelle forsøg eller et krav for at deltage i forsøget. Selv om du nu siger ja til, at vi må kontakte dig om et år, har du stadig lov til at fortryde og sige nej til at deltage, når vi kontakter dig.

### Forsøgsdeltagere

Der skal indgå 215 hospitalsindlagte patienter med COVID-19 i forsøget. For at deltage skal du:

1. være diagnosticeret med COVID-19
2. være hospitalsindlagt
3. være i daglig behandling med blodtrykssænkende medicin: enten en ACE-hæmmer eller ARB
4. være 18 år eller derover
5. have underskrevet informeret samtykke

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For at deltage i forsøget må du ikke:

1. være diagnosticeret med systolisk hjertesvigt (hjertesvigt med nedsat uddrivningsfraktion)
2. have svær nyresygdom
3. have svært forhøjet blodtryk
4. have for lavt blodtryk
5. have et uregelmæssigt forbrug af RAS-hæmmende medicin
6. være i situationer hvor de RAS-hæmmende midler ikke bør anvendes (kontraindikationer) inkl. graviditet i andet eller tredje trimester, være ammende, have svært nedsat leverfunktion, overfølsomhed eller allergi over for lægemidlerne.

Når du giver dit samtykke til forsøget, giver du os samtidig tilladelse til at indhente information om alle ovenstående punkter. For at vurdere om du har et uregelmæssigt forbrug af blodtrykssænkende medicin, vil vi stille dig nogle spørgsmål om dette (eller besvare samme spørgsmål på et spørgeskema) samt indhente informationer om dine recepter fra ”Det Fælles Medicinkort”.

### Efter forsøget

Hvis du fortsat er indlagt på hospitalet, når der er gået 30 dage, vil vi sørge for at informere dig om, at du fra dette tidspunkt af skal fortsætte eller genoptage din vanlige medicin.

Hvis du er udskrevet fra hospitalet, når der er gået 30 dage, og du har holdt pause med din medicin, ringer vi til dig for at minde dig om at genoptage din vanlige medicin derhjemme. Vi anbefaler, at du kontakter din egen læge for at få målt dit blodtryk i den forbindelse.

Hvis du har skulle fortsætte med din medicin under indlæggelsen, og er udskrevet fra hospitalet, før der er gået 30 dage, vil du få udleveret medicin fra os til de restende dage af forsøget. Vi ringer til dig efter 30 dage for at minde dig om, at du nu skal fortsætte med din egen medicin.

Efter din udskrivelse kan du altid kontakte os ved spørgsmål.

### Bivirkninger, risici, komplikationer og ulemper

Det er ukendt, hvorvidt det at stoppe med blodtrykssænkende medicin er skadeligt eller gavnligt for forløbet af COVID-19, og det er således uvist, hvorvidt det vil have en effekt for dig at indgå i forsøget.

Dit blodtryk bliver normalt målt flere gange dagligt på hospitalet, og lægerne vil således tydeligt kunne følge med i, hvordan dit blodtryk udvikler sig og behandle dig på baggrund af dette, så du får den bedste behandling. Stopper du med at tage din blodtrykssænkende medicin, vil dit blodtryk formentlig stige, og hvis du skulle få forhøjet blodtryk, kan lægen enten beslutte at give dig en anden type blodtrykssænkende medicin eller genoptage din vanlige medicin. Hvis lægen vælger at give dig en ny type blodtrykssænkende medicin, vil denne naturligvis kunne have bivirkninger. Det vil være lægens ansvar at informere dig om disse, før du begynder at tage medicinen, og de vil derfor ikke blive gennemgået her. Selvom lægen vælger at genoptage din vanlige behandling, vil du stadig kunne være med i forsøget. Din behandling vil altså til enhver tid være vigtigere end forsøget.

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Deltagelse i forsøget inkluderer ekstra blodprøvetagninger samt urinprøver. Én gang ved indtrædelse i forsøget og derefter en gang om ugen under hele din indlæggelse. Blodprøvetagning er forbundet med let ubehag. I sjældne tilfælde kan det ske, at der opstår overfladisk betændelse i den blodåre, blodprøven er taget fra. Tilstanden er ufarlig og går oftest over af sig selv. Der er minimal risiko for komplikationer ved denne tilstand, og svære tilfælde af infektion kan behandles med antibiotika eller antiinflammatorisk creme. Risikoen minimeres ved, at vi følger almindelige kliniske standarder. Der kan være risici ved forsøget, som vi endnu ikke kender. Vi beder dig derfor om at fortælle, hvis du oplever problemer med dit helbred, mens forsøget står på.

### **Behandling af personlige oplysninger herunder journaloplysninger**

Når du siger ja til at deltage i forsøget, omfatter samtykket adgang til dine personlige oplysninger fra din elektroniske journal i Sundhedsplatformen. Disse oplysninger bruges til at sikre at kriterierne for deltagelse i projektet er opfyldt. Vi vil desuden i løbet af forsøget indhente oplysninger om, hvordan dit COVID-19 sygdomsforløb udvikler sig, da det netop er dette, vi er interesseret i at undersøge. Derudover giver du os lov at se i Det Fælles Medicinkort, hvorvidt du regelmæssigt har fået udleveret medicin af typerne ACE-hæmmer eller ARB. Desuden indebærer dit samtykke, at vi får adgang til din elektroniske journal i Sundhedsplatformen, hvor vi vil indhente oplysninger om din helbredsstatus efter 30 dage. Vi vil også bede om tilladelse til at kontakte dig et år efter din udskrivelse for at undersøge din helbredsmæssige situation på det tidspunkt.

Når du indvilger i at deltage i forskningsprojektet, omfatter samtykket adgang til videregivelse og behandling af nødvendige oplysninger om dit helbred, øvrige private forhold og andre fortrolige oplysninger, som led i relevante myndigheders kontrol og tilsyn (f.eks. Lægemiddelstyrelsen). Derudover kan Lægemiddelstyrelsen, samt forsøgets sponsor, investigatore og *good clinical practice* monitor få direkte adgang til at indhente oplysninger i patientjournalen herunder elektroniske journaler med henblik på kontrol og inspektion af forsøgets udførelse. Alle involverede parter har fuld tavshedspligt, og der er ingen oplysninger, der vil påvirke dine nuværende eller fremtidige rettigheder til behandling eller andre rettigheder i øvrigt. Forskningsprojektet er godkendt af Lægemiddelstyrelsen, Videnskabsetisk Komite og Videnscenter for Dataanmeldelse. Dine oplysninger bliver behandlet i overensstemmelse med databeskyttelsesloven og databeskyttelsesforordningen.

### **Biologisk materiale**

I forbindelse med forsøget udtages en urinprøve (6 ml) samt 30 ml blod ved starten af forsøget og derefter én gang hver uge, mens du er indlagt. Den samlede mængde vil således variere alt efter, hvor længe du er indlagt. Blodet opbevares forsvarligt på Center for Klinisk Metabolisk Forskning, Gentofte Hospital (som en forskningsbiobank) og vil blive analyseret for stoffer, som viser aktiviteten i RAS eller virussygdommen. Noget materiale opbevares også med henblik på eventuel gentagelse af analyser, hvis det bliver nødvendigt, og det resterende materiale bliver destrueret senest 31. marts 2028. Hver forsøgsdeltager tildeles et forsøgsnummer, og det er kun dette nummer, som vil stå på prøveglassene.

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Du kan til hver en tid kontakte Center for Klinisk Metabolisk Forskning og få dit materiale destrueret uden begrundelse og uden at det vil påvirke dine fremtidige rettigheder. Forskningsbiobanken er godkendt af Videnskabsetisk Komité og Datastilsynet.

### Forsøgets nytte

Dette forsøg undersøger, om to meget almindelige former for blodtrykssænkende medicin (ACE-hæmmere og ARB) påvirker RAS og forløbet af COVID-19. Alene i Danmark er der flere hundredetusinde mennesker, der dagligt tager disse to typer medicin. COVID-19 er en alvorlig sygdom, og det er derfor vigtigt at undersøge om ACE-hæmmere og ARB påvirker forløbet af sygdommen. Forsøget vil således ikke direkte komme dig til gavn, men vil give os viden om disse vigtige problemstillinger, der kan hjælpe til hurtigst muligt at få etableret retningslinjer omkring brugen af disse i relation til sygdommen COVID-19 – både i Danmark og i resten af verden.

### Afbrydelse af forsøget

Forsøget afbrydes for dig:

- Hvis du ønsker at udgå
- Hvis resultaterne fra 108 deltagere (*statistisk midtvejsanalyse*), viser, at en af grupperne klarer sig væsentlig bedre end den anden
- Hvis ekstraordinære omstændigheder umuliggør fuldførelse af forsøget. Hvis der opstår ekstraordinære hændelser, der medfører at projektet ikke kan fuldføres helt eller delvist, vil forsøget blive afbrudt for alle igangværende forsøgsdeltagere og du informeres om årsagen.

### Vederlag

Der ydes ingen økonomisk kompensation for deltagelse i forsøget.

### Økonomi

Forsøgsansvarlig er professor, overlæge, ph.d. Filip Krag Knop. Initiativtagere til forsøget er en forskningsgruppe med stor erfaring med hormonsystemer, lægemidler og kliniske forsøg som ledes af professor, overlæge, ph.d. Filip Krag Knop.

Projektets driftsudgifter er dækket af Novo Nordisk Fonden med en samlet støtte på 3.335.000 kr. Støtten dækker udgifterne i forbindelse med forsøget herunder løn. Novo Nordisk Fonden vil ikke få indflydelse på forsøgsdesignet, og vil ikke få indflydelse på tolkning eller offentliggørelse af data. Fondsmidlerne er indsat på fondskonti under Center for Klinisk Metabolisk Forskning, Gentofte Hospital, som er under hospitalets revision. Hverken den forsøgsansvarlige eller andre i forskningsgruppen har økonomiske interesser i udførelsen eller resultaterne af projektet.

### Adgang til forsøgsresultater

Resultaterne af forsøget vil blive sammenskrevet til en eller flere artikler og vil blive offentliggjort hurtigst muligt, fagligt forsvarligt og i overensstemmelse med Databeskyttelsesloven. Såfremt du

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ønsker det, vil du blive skriftligt informeret om resultaterne efter forsøgets afslutning, dvs. efter at forsøg for alle inkluderede forsøgspersoner er afsluttet, og data er gjort op.

**Forsøgspersoners generelle rettigheder og kontaktperson for forsøget**

Vi håber, at du med denne information har fået tilstrækkeligt indblik i, hvad det vil sige at deltage i forsøget, og at du føler dig rustet til at beslutte, om du vil deltage. Vi beder dig også læse det vedlagte materiale "Forsøgspersonens rettigheder i et sundhedsvidenskabeligt forskningsprojekt".

Hvis du vil vide mere om forsøget, er du meget velkommen til at kontakte os på Center for Klinisk Metabolisk Forskning, Gentofte Hospital:

Professor og overlæge Filip Krag Knop, ph.d.  
Gentofte Hospitalsvej 7, 2900 Hellerup  
Mailadresse: [filip.krag.knop.01@regionh.dk](mailto:filip.krag.knop.01@regionh.dk)  
Telefon: +45 3867 4266

Kontaktoplysninger til den ansvarlige læge på Herlev Hospital:

Hans Johan Niklas Lorentsson  
Borgmester Ib Juuls Vej 1, 2730 Herlev  
Mailadresse: FØLGER  
Telefon: FØLGER

Kontaktoplysninger til den ansvarlige læge på Gentofte Hospital:

Vivian Kliim-Hansen  
Gentofte Hospitalsvej 2, 2900 Hellerup  
Mailadresse: FØLGER  
Telefon: FØLGER

Med venlig hilsen

Filip Krag Knop  
Professor og overlæge, ph.d.  
Forsøgsansvarlig

## DET VIDENSKABSETISKE KOMITÆSYSTEM

**Informeret samtykke til deltagelse i et sundhedsvidenskabeligt forskningsprojekt****Titel:** Effects of discontinuing renin-angiotensin system inhibitors in patients with COVID-19**Dansk titel:** Effekten af seponering af hæmmere af renin-angiotensin systemet hos patienter med COVID-19**Erklæring fra forsøgspartageren:**

Jeg har fået skriftlig og mundtlig information, og jeg ved nok om formål, metode, fordele og ulemper til at sige ja til at deltage.

Jeg ved, at det er frivilligt at deltage, og at jeg altid kan trække mit samtykke tilbage uden at miste mine nuværende eller fremtidige rettigheder til behandling.

Jeg giver samtykke til at deltage i forskningsprojektet og til, at mine blodprøver opbevares i forbindelse med forskningsprojektet, som beskrevet i deltagerinformationen (v4, 25-mar-2021). Jeg har fået en kopi af dette samtykkeark samt en kopi af den skriftlige information om projektet til eget brug.

Forsøgspartagerens navn (blokbogstaver): \_\_\_\_\_

Dato/Tid: \_\_\_\_\_ |\_\_|\_\_|:|\_\_|\_\_| Underskrift: \_\_\_\_\_

Hvis der kommer nye væsentlige helbredsoplysninger frem om dig i forskningsprojektet vil du blive informeret. Vil du **frabede** dig information om nye væsentlige helbredsoplysninger, som kommer frem i forskningsprojektet, bedes du markere her: \_\_\_\_\_ (sæt X)

Ønsker du at blive informeret om forskningsprojektets resultat samt eventuelle konsekvenser for dig?:

Ja \_\_\_\_\_ (sæt X)      Nej \_\_\_\_\_ (sæt X)

**Erklæring fra den, der afgiver information:**

Jeg erklærer, at forsøgspartageren har modtaget mundtlig og skriftlig information om forskningsprojektet.

Efter min overbevisning er der givet tilstrækkelig information til, at der kan træffes beslutning om deltagelse i projektet.

Navnet på den, der har afgivet information: \_\_\_\_\_

Dato/Tid: \_\_\_\_\_ |\_\_|\_\_|:|\_\_|\_\_| Underskrift: \_\_\_\_\_

## DET VIDENSKABSETISKE KOMITÈSYSTEM

**Informeret samtykke til deltagelse i et sundhedsvidenskabeligt forskningsprojekt**  
*Opfølgning***Titel:** Effects of discontinuing renin-angiotensin system inhibitors in patients with COVID-19**Dansk titel:** Effekten af seponering af hæmmere af renin-angiotensin systemet hos patienter med COVID-19**Erklæring fra forsøgspartageren:**

Jeg har fået skriftlig og mundtlig information, og jeg ved nok om formål, metode, fordele og ulemper til at sige ja til at deltage.

Jeg ved, at det er frivilligt at deltage, og at jeg altid kan trække mit samtykke tilbage uden at miste mine nuværende eller fremtidige rettigheder til behandling.

Jeg giver samtykke til, at sundhedspersoner nævnt i deltagerinformationen (v4, 25-mar-2021) må kontakte mig 12 måneder efter min deltagelse i forskningsprojektet med henblik på at få oplysninger om mit helbred og eventuelle sygdomme. Jeg har fået en kopi af dette samtykkeark samt en kopi af den skriftlige information om projektet til eget brug.

Forsøgspartagerens navn (blokbogstaver): \_\_\_\_\_

Dato/Tid: \_\_\_\_\_ |\_\_|\_\_|:|\_\_|\_\_| Underskrift: \_\_\_\_\_

**Erklæring fra den, der afgiver information:**

Jeg erklærer, at forsøgspartageren har modtaget mundtlig og skriftlig information om forskningsprojektet.

Efter min overbevisning er der givet tilstrækkelig information til, at der kan træffes beslutning om deltagelse i projektet.

Navnet på den, der har afgivet information: \_\_\_\_\_

Dato/Tid: \_\_\_\_\_ |\_\_|\_\_|:|\_\_|\_\_| Underskrift: \_\_\_\_\_