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

Vivian Kliim-Hansen,[1] Lærke Smidt Gasbjerg,[1,2] Anne-Marie Ellegaard,[1] Hans Johan Niklas Lorentsson,[1,3,4] Mads Bank Lynggaard,[1] Christoffer Andersen Hagemann,[1,5] Christian Legart,[1] David Mathiesen,[1] Pradeesh Sivapalan,[6] Jens Ulrik Stæhr Jensen,[6] Tina Vilsbøll, [1,4] Mikkel Bring Christensen, [1,7] Filip Krag Knop[1]

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

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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).

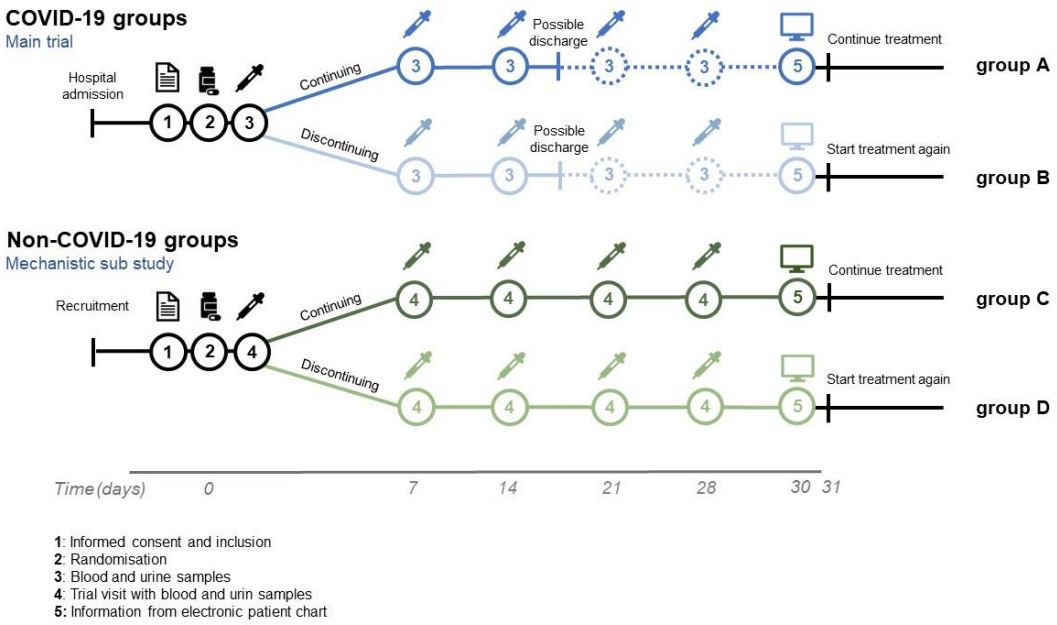

Figure 1: RASCOVID-19 Trial design

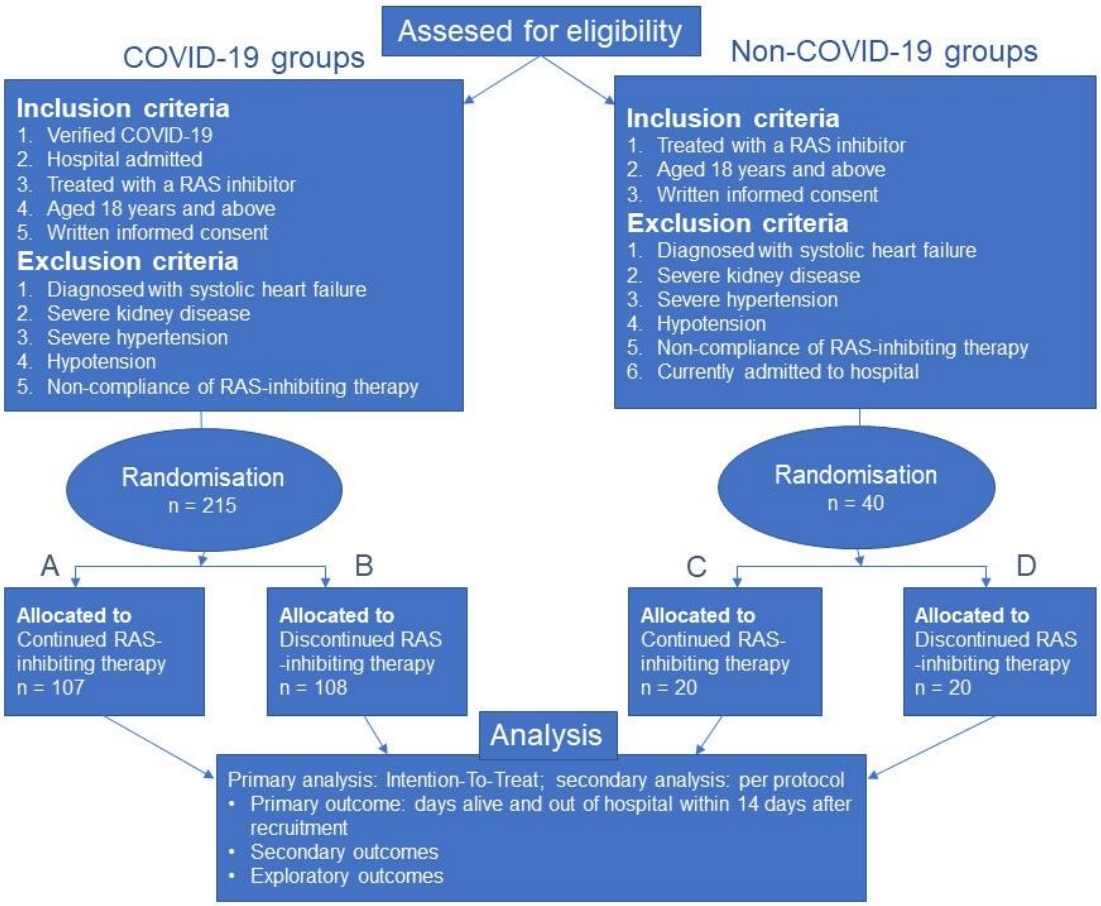

Figure 2: RASCOVID-19 Flowchart. COVID-19: coronavirus disease 2019; RAS: renin–angiotensin system

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 RASCOVID-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.

	TRIAL PERIOD								
	Enrolment	Allocation	Post-allocation						
TIMEPOINT	$-t_1$	0	$t_{day\ 0}$ →						$t_{day\ 30}$
ENROLMENT:									
Eligibility screen	X								
Informed consent	X								
Allocation		X							
INTERVENTIONS:									
Continued RAS-inhibiting therapy			♦—	—	—	—	—	—	—♦
Discontinued RAS-inhibiting therapy			♦—	—	—	—	—	—	—♦
ASSESSMENTS:									
Efficacy variables			♦—	—	—	—	—	—	—♦
Safety variables			♦—	—	—	—	—	—	—♦

Table 1: RASCOVID-19 Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) figure. For a more detailed version, see Appendix 2.
$-t_1$: 0–48 hours before allocation

Sample size

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 alfa 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 group C and group D, the population size (n) has been calculated using the formula:

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

where α is the significance level, β 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 Zα and Zβ are standardised deviations corresponding to the selected α and β (see below). In a previous study,[18] serum ACE2 activity levels in healthy individuals was (mean±SD) 16.2±5.4 one unit of fluorescence (UF)/ml and 24.8±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 α = 5% and power (1-β) 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: ≤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: ≤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 ± 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^2	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	µg/L	median, IQR
	Baseline troponin T	ng/L	median, IQR

	Baseline eGFR	mL/min	median, IQR
	Baseline arterial blood gas values		
	pCO_2	kPa	median, IQR
	pO_2	kPa	median, IQR
	HCO_3	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 1st 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_2: fraction of inspired oxygen

FVC: forced vital capacity

HbA1c: haemoglobin A1c

HCO_3: bicarbonate

IQR: interquartile range

ITT: intention to treat

pCO_2: partial pressure of carbon dioxide

pO_2: partial pressure of oxygen

RAS: renin–angiotensin system

SARS-CoV: severe acute respiratory syndrome coronavirus

SD: standard deviation

UF: one unit of fluorescence

Authors affiliations

[1]Center for Clinical Metabolic Research, Department of Medicine, Copenhagen University Hospital - Herlev and Gentofte, Copenhagen, Denmark

[2]Department of Biomedical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

[3]Section of Infectious Medicine, Department of Medicine, Copenhagen University Hospital - Herlev and Gentofte, Copenhagen, Denmark

[4]Steno Diabetes Center Copenhagen, Hellerup, Denmark

[5]Gubra ApS, Hørsholm, Denmark

[6]Section of Respiratory Medicine, Department of Medicine, Copenhagen University Hospital - Herlev and Gentofte, Copenhagen, Denmark

[7]Department of Clinical Pharmacology, Copenhagen University Hospital - Bispebjerg and Frederiksberg, Copenhagen, Denmark

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.

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Conflict of interest

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

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