DSMB charter for the ProPAC-COVID-trial

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I. Study Identification information

A. Sponsors protocol code: KronLungesyg_COVID_19_protokol_1_4
B. Study Title: Proactive Protection with Azithromycin and hydroxyChloroquine in hospitalized patients with COVID-19 (ProPAC-COVID): A Randomized Clinical Trial
C. Principal Investigator (PI): Jens-Ulrik Jensen MD PhD, Research associate professor
D. Study Coordinator: Pradeesh Sivapalan MD PhD
E. Study centre: a) Department of Internal Medicine, Herlev and Gentofte University Hospital, Hellerup, Denmark. b) Department of Respiratory Medicine, Amager and Hvidovre University Hospital, Copenhagen, Denmark, c) Department of Internal Medicine, Zealand Hospital, University of Copenhagen, Roskilde, Denmark, d) Department of Respiratory Medicine, Bispebjerg University Hospital, Copenhagen, Denmark, e) Department of Respiratory and Infectious Diseases, Nordsjællands Hopsital, Hillerød, f) Department of Respiratory Medicine, Aalborg University Hospital, Aalborg, Denmark; g) Department of Internal Medicine, Odense University Hospital, Odense, Denmark; h) Department of Medicine, Slagelse University hospital, Denmark.

II. Study Overview

A. We are conducting a multicenter, randomized, placebo-controlled, blinded study in hospitalized patients with coronavirus infection (COVID-19). The aim is to determine for patients admitted to hospital with coronavirus infection and symptoms, whether the treatment with virus modifier agent Hydroxychloroquine as well as virus immunomodulatory and antibacterial drug Azithromycin may lead to better outcome (reduce the length of hospitalization, the risk of hospitalization, non-invasive treatment. ventilation and death).

B. The monitoring guideline outlined below for ProBe-COVID-trial will adhere to the protocol approved by the Ethics Committees of all participating sides (H-20022574), Danish Medicines Agency (EudraCT no: 2020-001198-55) and the Danish Data Protection Agency (journal-nr.: P-2020-256)

C. The independent Data and Safety Monitoring Board (DSMB) is established to ensure the safety of research participants and the integrity of the study data. It will periodically monitor progress, efficacy, safety and other confidential data from this trial. It is comprised of experts in relevant biomedical fields and biostatistics who have no direct relationship with the study. Outcome data will be privileged and shared only with members of the DSMB during the conduct of the trial.

III. Data Quality and Safety Review Plan and Monitoring

A. Subject Accrual and Compliance

Review of the rate of subject accrual and compliance with inclusion/exclusion criteria will occur monthly during the first 3-month recruitment phase and then every 3 months to ensure that a sufficient number of participants are being enrolled and that they meet eligibility criteria.

Data on adherence to the treatment protocol will be collected for each patient by research staff and reviewed quarterly by the PI. Adherence of participants will be evaluated by performing pill counts and by monitoring the appropriate measures at each visit.

B. Justification of Sample Size

The probability that the study will detect a treatment difference is 80% at a two-sided 5% significance level. This provides a sample size of 226 subjects. Patients will be randomly assigned in a 1:1 fashion to either:

i) Intervention group: Azithromycin day 1-3: 500 mg x 1, day 4-15: 250 mg x 1
Hydroxychloroquine: Day 1-15: 200 mg x 2

ii) Control group: The control group will always receive the standard treatment and placebo for both types of intervention medication. If part or all the intervention therapy being investigated becomes standard treatment during the study, this may also be offered to the control group.

C. Stopping Rules

This study will be stopped prior to its completion if the intervention is associated with adverse effects that call into question the safety of the intervention.

D. Designation of an Independent Monitor

The Independent Monitor for this study is the GCP unit at Bispebjerg University Hospital, Copenhagen, Denmark (Staff-monitor Kristina Devantier)

E. Safety Review

The DSMB review will be centered in systematic analysis of

1. Days alive and out of hospital within 14 days after recruitment

2. 30-day mortality rate

3. Readmission of all causes within 30 days

F. Membership:

The PI and study staff may opt to attend the meetings for informational purposes but must be excused from portions of the meetings which involve voting and final decision-making. The following members have been requested to be part of DSMB:

- Dr John Hurst PhD FRCP
  Reader in Respiratory Medicine
  Royal Free Campus
  UCL Medical School

- Philipp Schuetz, Professor, Dr.Med. MPH
  Kantonspital Aarau AG |
  KSA · Internal Medicine & Emergency Medicine
  Switzerland

- Bodil Steen Rasmussen
  Clinical Professor, Anaesthesia and Intensive Care Medicine, Aalborg University Hospital and President of EACTA - Aalborg Universitetshospital

These members have previously participated as DSMB members in previous trials, also for our group. They have a very high degree of knowledge on these patients and in-depth experience with trial management. The DSMB will be confirmed in good time before the interim analysis planned at half of full recruitment.

IV. Analyses

The analyses described in this document will be performed by investigator, Josefin Eklöf MD Ph.d.-student, with guidance from the Principal investigator Jens Ulrik Jensen, Section of Respiratory Medicine, Department of Medicine, Herlev and Gentofte Hospital, University of Copenhagen, Hellerup, Denmark, once the data have been entered, cleaned and released for use.

This document provides a description of the statistical analyses that will be performed for the evaluation of the primary and secondary endpoints of the ProBe-COVID-trial.

The analyses described in this document are compatible with the recommendations of the CONSORT 2010 statement (www.consort-statement.org)[1].

A. Analysis population

Data will be analyzed using intention-to-treat (ITT) principles. All randomized patients will be analyzed in the groups to which they were originally allocated to, regardless of whether they actually received the intended treatment or whether a protocol violation or protocol deviation occurred[1].

Patients who withdrew consent for use of their data will not be included in any analysis. Only the facts that they were enrolled into the trial and withdrew consent, and the original study group to which they were allocated, will be reported.

Two-sided 5% significance levels will be used to identify statistically significant results. All confidence intervals reported will be 95% confidence intervals.

A secondary analysis of the primary efficacy outcome will use a per protocol (PP) population.

B. Definitions

Baseline (during admission)

Follow-up is done on days 14, 29, 90 and 365 days. This is obtained via the journal system.

C. Analysis Software

All analyses will be performed using SAS software version 9.4.

D. Descriptive analyses

The following baseline characteristics of the study population will be summarized separately within each randomized group:

- Age, years (mean ± SD)
- Male, n (%) / Female, n (%)
- Baseline, body mass index, kg/m^2 (mean 95% CI)
- Current smoker, n (%)
- Ex-smoker, n (%)
- Nonsmoker, n (%)
- Alcohol use, n (%)
- Pack-years history (mean 95% CI)
- GOLD classification 1-4 og A-D
- Baseline Arterial blood gas
- Systemic screening for comorbidities
- LTOT use and dosage
- Home NIV
- Baseline, systolic blood pressure, mm Hg, median (quartiles)
- Baseline, diastolic blood pressure, mm Hg, median (quartiles)
- Baseline, heart rate, beats/min, median(quartiles)
- Baseline, oxygen saturation, %
- Baseline, temperature (°C), median (quartiles)
- Baseline, Dyspnea mMRC, n (%)
- Baseline, leukocyte count, $x10^9$ cells/L (mean 95%CI)
- Baseline, CRP, mg/L

- Chest X-ray infiltrate, n (%)

For continuous variables, means and standard deviations will be presented, unless the variable has highly skewed distribution, in which case the median and interquartile range (IQR) will be presented. For categorical variables, the number and percentage of participants within each category will be presented. For each variable, the percent of missing values will be reported.

E. Primary objective and outcome

The primary outcome is days alive and out of hospital within 14 days after recruitment. This is a very sensitive and specific outcome. Among other advantages, lead-time bias due to death was avoided using this endpoint measure (i.e., patients who died early would not be counted as a short length of stay). We will use student's t-test or Wilcoxon-Mann-Whitney test depending on the data distribution,

F. Secondary objective and outcomes

The following endpoints will be included when assessing the clinical outcome:

1. Ordinary outcome.
   The patient is categorized into one of the following 8 categories on day 15:
   a. Death
   b. Inpatient and mechanical ventilation or ExtraCorporalMembraneOxygenation (ECMO)
   c. Inpatient and Non-invasive ventilation or high-flow oxygen device
   d. Hospitalized and given oxygen supplements that do not live up to oxygen supplements in (2) or (3) - e.g. oxygen on "nostrils"
   e. Hospitalized and do not receive oxygen supplementation but need treatment (COVID-19 related or other)
   f. Hospitalized and do not receive oxygen supplements and do not need treatment (just observed)
   g. Discharged with restriction on activities, may be free of oxygen depletion or use LTOT ("home oxygen")
   h. Discharged, no restrictions on activities
   i. Number of readmissions for all causes within 30 days
2. 30-day mortality
3. Readmission of all causes within 30 days

G. COPD related hospital readmission within 30 days

30-day hospital readmission rates will be analyzed by chi-squared tests or Fisher exact test.

H. All-cause mortality and time to next exacerbation

Time to readmission of all causes or time to death will be calculated using the Kaplan-Meier method in combination with the log-rank test and Cox proportional hazards models.

I. Interim analysis

We have planned the interim analysis when all the data from the first 113 patients have been entered into the database (half of the patients recruited (half of the patients recruited). The DSMB may, apart from this planned interim analysis, decide to request an extra-ordinary interim analysis at any time point. This will be blinded to the investigators.

J. References

1. **CONSORT STATEMENT** [http://www.consort-statement.org]

Extra ordinary interim analysis:

Proactive Protection with Azithromycin and hydroxyChloroquine in hospitalized patients with COVID-19 (ProPAC-COVID):

A Randomised, Good-Practice-monitored, Placebo-controlled, double-blind trial to clarify hospital length and risk of intensive care may reduce in hospitalized patients who have COVID-19 treated with azithromycin and hydroxychloroquine for 15 days after inclusion.

Report date: May 31, 2020

Conducted and reported by:

Alexander Svorre Jordan, Bach.Med, Respiratory Research Unit, Section of Pumonary Medicine, Herlev and Gentofte Hospital, University of Copenhagen, Herlev, Denmark.

Josefin Eklöf, MD, PhD, Respiratory Research Unit, Section of Pumonary Medicine, Herlev and Gentofte Hospital, University of Copenhagen, Herlev, Denmark.

Principal investigator / Study director and scientific sponsor:

Jens-Ulrik Stæhr Jensen, MD, PhD, Research Associate Professor: Respiratory Research Unit, Section of Pumonary Medicine, Herlev and Gentofte Hospital, University of Copenhagen, Herlev, Denmark.

Recruiting study centers:

1. Pulmonary medicine section, Gentofte hospital, Kildegårdsvej 28, 2900 Hellerup, Denmark.
2. Pulmonary Medicine Department, Hvidovre Hospital, Kettegaard alle 30, Hvidovre, Denmark.
3. Pulmonary Medicine Section, Herlev Hospital, Herlev Ringvej, Herlev, Denmark.
4. Pulmonary and infectious medicine department, North Zealand Hospital, Dyrehavevej 29, 3400 Hillerød, Denmark.
5. Pulmonary Medicine Department, Aalborg Hospital, Hobrovej 18 -22, 9000 Aalborg, Denmark.
6. Pulmonary Medicine Section, Medical Department, Roskilde Hospital, Roskilde, Denmark.
7. Pulmonary Medicine Department, Bispebjerg Hospital, Bispebjerg Bakke 23, 2400 Copenhagen, Denmark.
8. Medical Department, Slagelse Hospital, Denmark.

Aim of the study:
The aim of this randomised GCP-controlled trial is to clarify whether combination therapy with macrolide azithromycin and hydroxychloroquine via anti-inflammation/immune modulation, antiviral efficacy and pre-emptive treatment of supra-infections can shorten hospitalisation duration (measured as "days alive and out of hospital"; primary outcome), reduce the risk of non-invasive ventilation, intensive care and death.

Analyses:
Data is analyzed using intention-to-treat (ITT) principles, as stated in the trial protocol. All randomized patients were analyzed in the groups, to which they were originally allocated, regardless of whether they actually received the intended treatment or whether a protocol violation or protocol deviation occurred.

Total number of patients that are planned to be recruited to the trial: 226
First patient in: April 2020
Total number of patients recruited: 75 (33% of the planned patients. Treatment group A, n=41; Treatment group B, n=34)

Following outcomes are included in the interim analyses:

- Days alive and out of hospital (DAOH) within 14 days after recruitment (primary outcome)
- All-cause mortality rate 30 days after recruitment
- Readmission (any cause) or all-cause mortality within 30 days after recruitment
- ECG at baseline or day 2-5 with QTc (F) > 500 ms

Completed 14 days follow-up:
n=65 (treatment group A: 37/37, treatment group B: 28/28 patients)

Completed 30 days follow-up:
n=44 (treatment group A: 25/25, treatment group B: 19/19 patients)

1. Descriptive analyses:

Baseline characteristics of the population is described below (Table 1). The baseline characteristics are determined based on the population that completed 14 day follow-up (n=65), which is the same population for which the primary outcome was analyzed. The number of patients in each treatment group are noted in the first row of the table. In case of missing values, the total of number of patients are noted in the same row as the corresponding variable.

Table 1. Baseline characteristics of trial participants in both treatment groups (n=65).

Variables:	**Treatment group A: (n=37)**	**Treatment group B: (n=28)**
Age, years, median (IQR)	60 (51-82)	62 (52-78)
Male, n (%)	23 (62,2)	14 (50,0)
Pack-years tobacco, median (IQR)	5 (0-27)	0 (0-25)
Oxygen consumption, L/min, median (IQR) (Treatment group 1 n=36, Treatment group 2 n=27)	0,5 (0-2)	1 (0-2)
CRP, mg/L, median (IQR) (Treatment group 1 n=35, Treatment group 2 n=27)	59 (36-145)	57 (33-118)
Diabetes mellitus, n (%)	9 (24,3)	6 (21,4)
Heart failure, n (%)	4 (10,8)	2 (7,1)
Atrial fibrillation, n (%)	8 (22,2)	2 (7,1)

2. Outcomes analysed in the interim analyses:

2.1 Days alive and out of hospital (DAOH) within 14 days after recruitment

	Treatment group A (n=37)	Treatment group B (n=28)	P-value
DAOH, mean (95% CI)	7.8 (6.4-9.3)	7.6 (5.9-9.3)	0.81
DAOH, median (IQR)	9 (3-11)	9.5 (5-10)	0.62

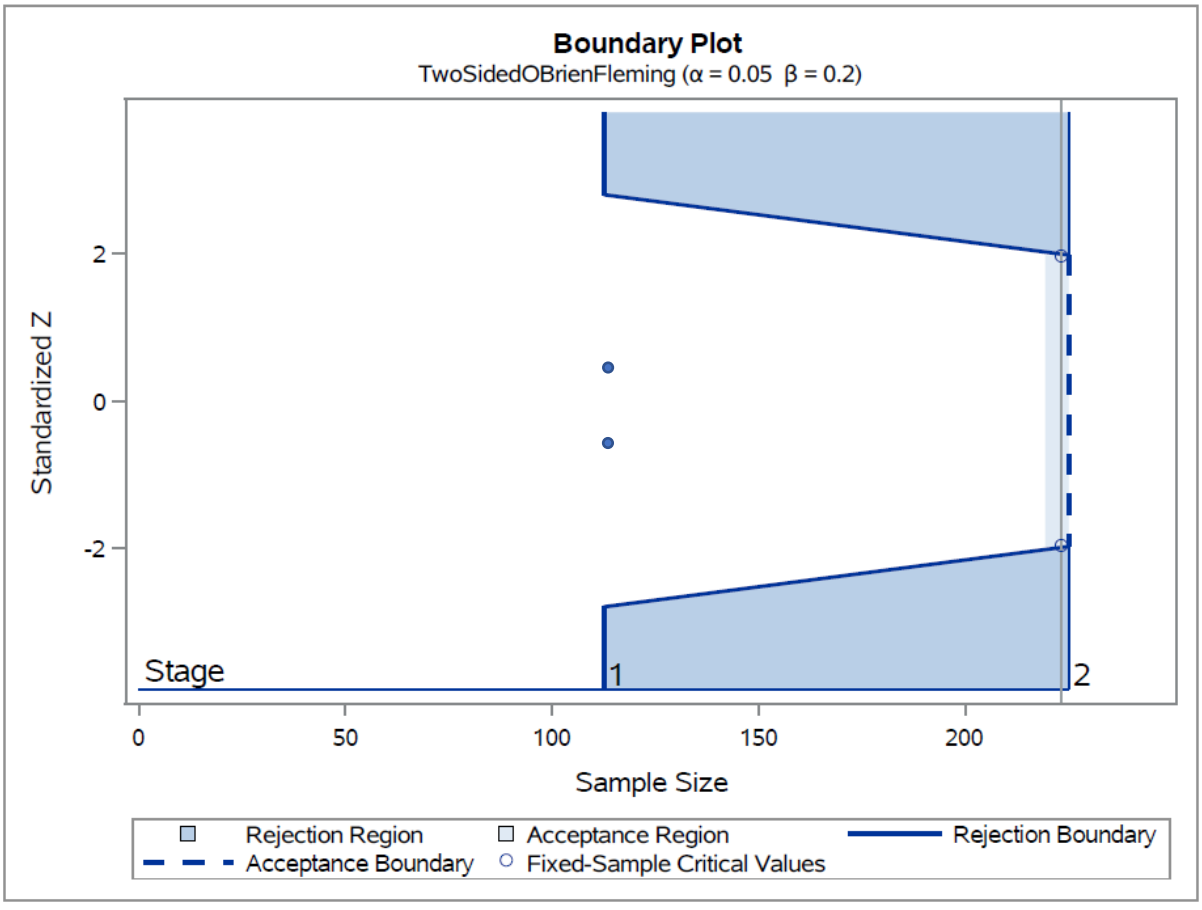

Figure 1. Primary outcome (DAOH within 14 days from recruitment): Boundaries of an O'Brien-Fleming sequential design involving the ProPAC-COVID trial. Two Z-values have been plotted since arms are blinded. The actual Z-values are + 0.49 and - 0.49.

2.2 All-cause mortality rate 30 days after recruitment

	Treatment group A (n=25)	Treatment group B (n=19)
Dead (all-cause), n (%)	1 (4,0)	1 (5,3)
Alive, n (%)	24 (96,0)	18 (94,7)

P-value (Fischer Exact Test): 1.00

2.3 Readmission (any cause) or all-cause mortality within 30 days after recruitment

	Treatment group A (n=25)	Treatment group B (n=19)
Readmitted or dead, n (%)	3 (12,0)	4 (21,1)
Not readmitted and alive, n (%)	22 (88,0)	15 (78,9)

P-value (Fischer Exact Test): 0.44

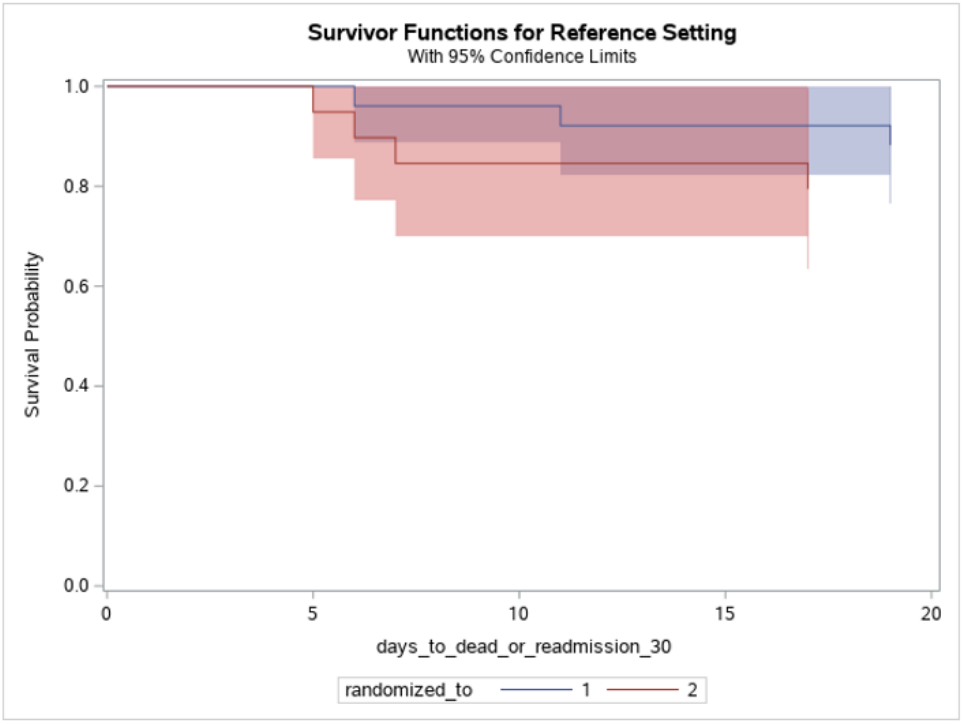

Figure 2. Kaplan-Meier plot: Time to readmission (any cause) or all-cauase mortality within 30 days from recruitment. Log-rank test: p = 0.40 (randomized_to=1: treatment group A; randomized_to=2: treatment group B).

2.4 Any ECG at baseline and day 2-5 withy QTc (F) > 500 ms

	Treatment group A (n=37)	**Treatment group B (n=28)**
QTc (F) > 500 ms at baseline, n (%)	0 (0,0)	1 (3,6)
QTc (F) > 500 ms at day 2-5, n (%)	0 (0,0)	0 (0,0)

1st planned interim analysis:

Proactive Protection with Azithromycin and hydroxyChloroquine in hospitalized patients with COVID-19 (ProPAC-COVID):

A Randomised, Good-Practice-monitored, Placebo-controlled, double-blind trial to clarify hospital length and risk of intensive care may reduce in hospitalized patients who have COVID-19 treated with azithromycin and hydroxychloroquine for 15 days after inclusion.

Report date: January 28 ,2021

Conducted and reported by:

Tobias Wirenfelt Klausen, M.Sc., Statistician, Department of Hematology, Herlev and Gentofte Hospital, University of Copenhagen, Herlev, Denmark.

Alexander Svorre Jordan, Bach.Med, Respiratory Research Unit, Section of Pumonary Medicine, Herlev and Gentofte Hospital, University of Copenhagen, Herlev, Denmark.

Josefin Eklöf, MD, PhD, Respiratory Research Unit, Section of Pumonary Medicine, Herlev and Gentofte Hospital, University of Copenhagen, Herlev, Denmark.

Principal investigator / Study director and scientific sponsor:

Jens-Ulrik Stæhr Jensen, MD, Professor: Respiratory Research Unit, Section of Pulmonary Medicine, Herlev and Gentofte Hospital, University of Copenhagen, Hellerup, Denmark.

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8. Department of Internal Medicine, Slagelse Hospital, Denmark.

Aim of the study:

The aim of this randomised GCP-controlled trial is to clarify whether combination therapy with macrolide azithromycin and hydroxychloroquine via anti-inflammation/immune modulation, antiviral efficacy and pre-emptive treatment of supra-infections can shorten hospitalisation duration (measured as "days alive and out of hospital"; primary outcome), reduce the risk of non-invasive ventilation, intensive care and death.

Analyses:

Data is analyzed using intention-to-treat (ITT) principles, as stated in the trial protocol.
All randomized patients were analyzed in the groups, to which they were originally allocated, regardless of whether they actually received the intended treatment or whether a protocol violation or protocol deviation occurred.

Following outcomes are included in the interim analyses:

1. Days alive and out of hospital (DAOH) within 14 days after recruitment (primary outcome)
2. All-cause mortality rate 30 days after recruitment
3. Readmission (any cause) or all-cause mortality within 30 days after recruitment

Total number of patients that are planned to be recruited to the trial: 226
Total number of patients recruited: 117 (52%)
First patient in: April 2020

Total number of patients allocated to Treatment group A: 61
Total number of patients allocated to Treatment group B: 56

Number of patients who have completed 14 days follow-up: n=117 (100%)
Number of patients who completed 30 days follow-up: n=117 (100%)

Conditional power analysis (see page 4):

This analysis was performed on the primary outcome (DAOH within 14 days after recruitment) of the trial (using t-test, non-equality design and two-sided significance level of 0.05).
A post-conditional power <0.20 for efficacy should be considered with the integrated impression of the entire report, as well as other available publications in the field, as a stopping guide for futility.

Descriptive analyses of the study population:

Baseline characteristics of the study population (n=117) are described in Table 1.

In case of patients with missing values, the total of number of patients assessed are noted in the row of the corresponding missing variable.

Table 1. Baseline characteristics of study population (n=116)

Variables:	**Treatment group A (n=61)**	**Treatment group B (n=56)**
Age, years, median (IQR)	67 (52-80)	62 (52-74.5)
Male, n (%)	36 (59.0)	29 (51.8)
Pack-years tobacco, median (IQR)	1 (0-20)	0 (0-20)
Oxygen consumption, L/min, median (IQR) (Treatment group 1: n=57, Treatment group 2: n=52)	0 (0-2)	1 (0-2)
CRP, mg/L, median (IQR) (Treatment group 1: n=55, Treatment group 2: n=54)	58 (36-101)	81.5 (34-136)
Diabetes mellitus, n (%)	17 (27.9)	11 (19.6)
Heart failure, n (%)	5 (8.2)	3 (5.4)
Atrial fibrillation, n (%)	13 (21.7)	6 (10.7)

Results - outcome analyses:

1. Days alive and out of hospital (DAOH) within 14 days after recruitment

	Treatment group A (n=61)	Treatment group B (n=56)	P-value
DAOH, mean (95% CI)	7,5 (6,4-8,6)	8,0 (7,0-9,0)	0,4922 (T-test)
DAOH, median (IQR)	9,0 (3,0-11,0)	9,0 (7,0-10,0)	0,9093 (Wilcoxon)

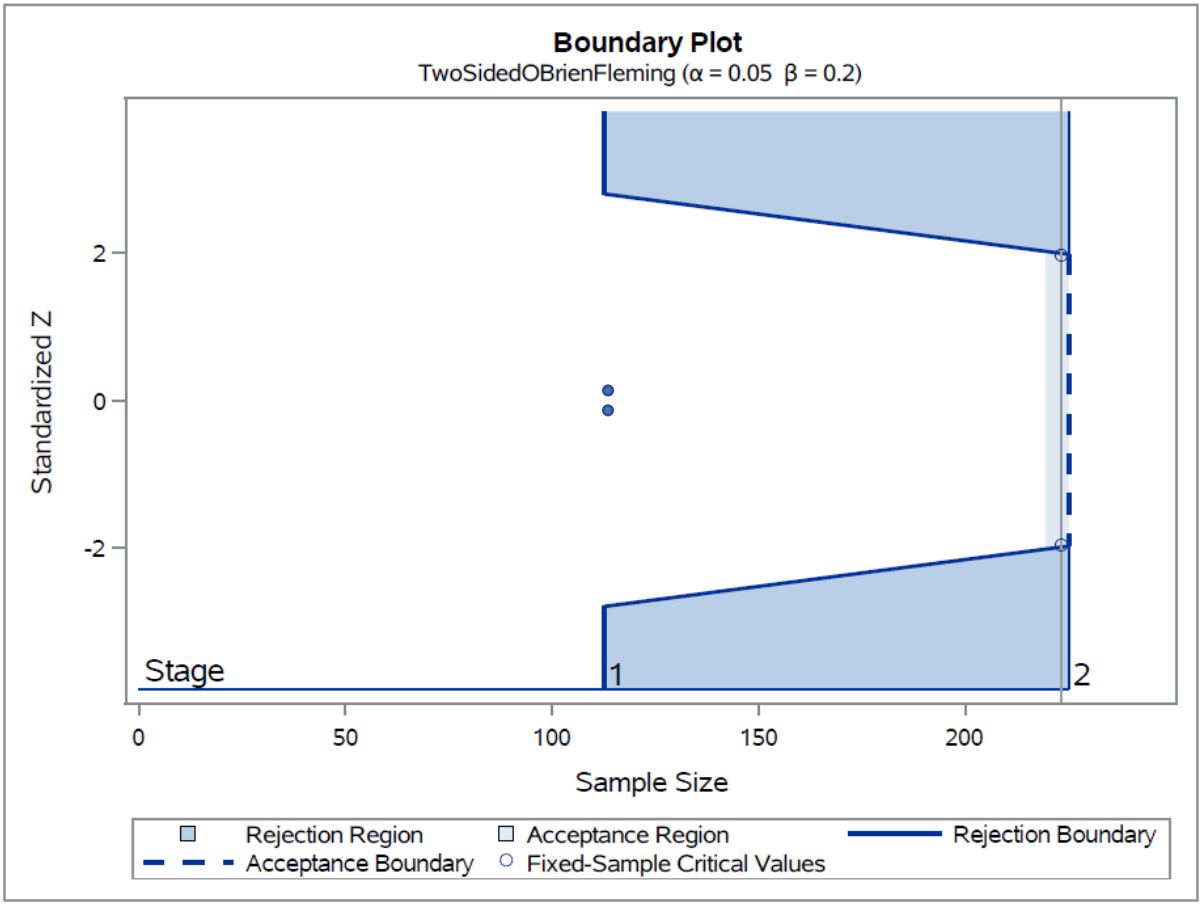

Figure 1. Primary outcome (DAOH within 14 days from recruitment): Boundaries of an O'Brien-Fleming sequential design involving the ProPAC-COVID trial. Two Z-values have been plotted since arms are blinded. The actual Z-values are + 0,1210 and - 0,1210.

Post-conditional power analysis of DAOH within 14 days from recruitment:
0.064

2. All-cause mortality rate 30 days after recruitment

	Treatment group A (n=61)	Treatment group B (n=56)
Dead (all-cause), n (%)	1 (1,6)	2 (3,6)
Alive, n (%)	60 (98,4)	54 (96,4)

P-value (Fischer Exact Test): 0.6060

3. Readmission (any cause) or all-cause mortality within 30 days after recruitment

	Treatment group A (n=61)	Treatment group B (n=56)
Readmitted or dead, n (%)	8 (13,1)	6 (10,7)
Not readmitted and alive, n (%)	53 (86,9)	50 (89,3)

P-value (Fischer Exact Test): 0.7800

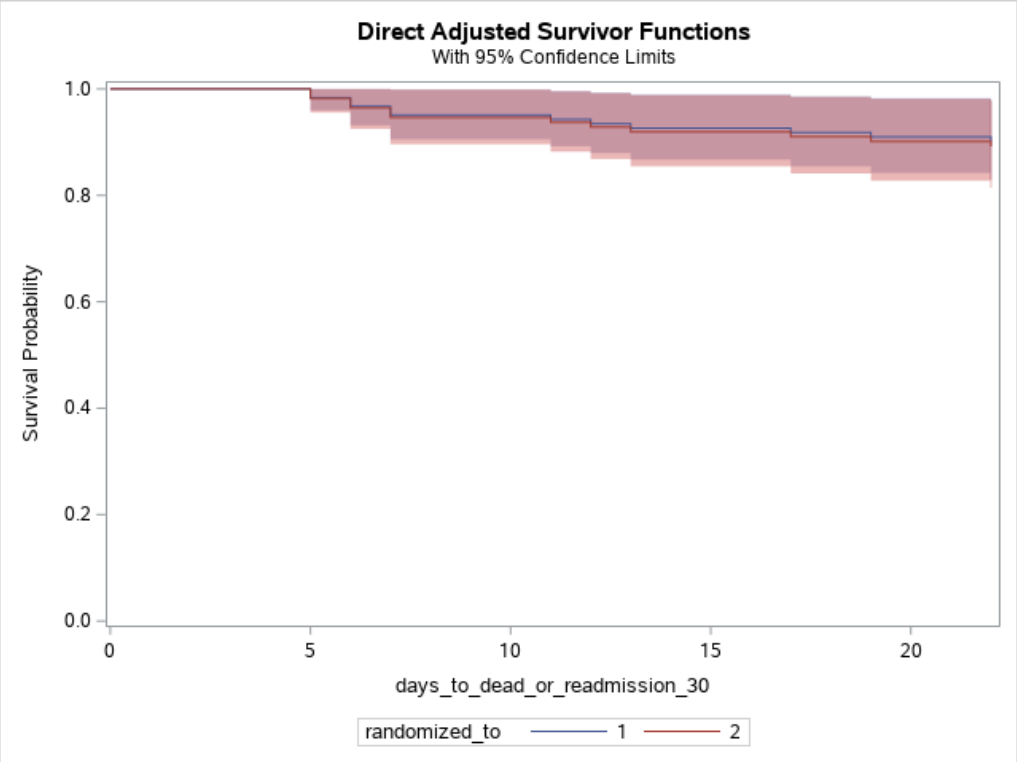

Figure 2. Kaplan-Meier plot: Time to readmission (any cause) or all-cauase mortality within 30 days from recruitment. Log-rank test: p = 0.9109 (randomized_to 1= treatment group 1; randomized_to 2= treatment group 2).

UCL RESPIRATORY

Royal Free Campus

3rd June 2020

Dear Jens-Ulrik

This letter confirms that it was the unanimous decision of the ProPAC-COVID Data Safety and Monitoring Board to recommend continuation of the ProPAC-COVID study.

Data from 65 participants were reviewed at an Extraordinary Meeting of the DSMB today, June 3rd 2020. We saw no evidence of a difference in the primary outcome 'Days Alive and Out of Hospital' between the two groups, or in all cause mortality at thirty days. The event rate is low suggesting that there is no safety concern in either arm.

Recent controversy around observational data in relation to these drugs in COVID only serves to emphasise the importance of completing randomised trials such as ProPAC-COVID.

Yours sincerely,

Professor John Hurst, Chair of the DSMB, and on behalf of:
Professor Dr. med. Philipp Schuetz, Medizinische Universitätsklinik, Aarau, Switzerland
Professor Bodil Steen Rasmussen, Aalborg University Hospital, Denmark

Professor John Hurst PhD FRCP FHEA

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Jens Ulrik Stæhr Jensen

Fra: Hurst, John <j.hurst@ucl.ac.uk>
Sendt: 1. februar 2021 11:14
Til: Jens Ulrik Stæhr Jensen
Cc: 'Schütz Philipp'; 'Bodil Steen Rasmussen'
Emne: ProPAC-COVID DSMB Recommendaiton

1st February 2021

Dear Jens-Ulrik

Re: Proactive Prophylaxis With Azithromycin and Chloroquine in Hospitalised Patients With COVID-19 (ProPAC-COVID) Study

The DSMB met on Friday 29th January 2021 to discuss results of the pre-planned interim analysis of the ProPAC-COVID study, provided to us by Josefin Eklöf and Tobias Wirenfeldt Klausen.

The interim analysis was completed when 117/226 (52%) of patients had been recruited. We remained blinded to the treatment allocation.

The data were complete with 100% availability of primary outcome data, analysed using ITT principles.

We noted some minor differences between the two groups at baseline such that Group 1 were a little older, more likely to be male and had more frequent co-morbidities. In contrast, Group 2 appeared to have a higher median serum CRP concentration. We did not conclude that any differences here materially affected the interim analysis.

With regard to safety, we did not see any concerning safety signal for the variables available to us: the primary outcome of Days alive and out of hospital (DAOH) within 14 days after recruitment, all-cause mortality and re-admission rate.

With regard to efficacy, we also did not observe any meaningful difference between the groups in these outcomes. The pre-specified stopping criteria for futility was met with a post-conditional power analysis of DAOH within 14 days from recruitment of 0.064 (so pre-specified <0.20).

In light of the rapidly expanding literature on the use of Azithromycin and Chloroquine in COVID, which your results are consistent with, and the stopping criteria for futility being met, it was the unanimous opinion of the DSMB to recommend stopping the trial at this point.

We congratulate you and all the recruiting centres for the excellent data quality and rapid set-up of this important study during the initial phase of the COVID-19 pandemic.

Yours sincerely,

Professor John Hurst, UCL Respiratory, University College London, London, UK (Chair)
Bodil Steen Rasmussen, Department of Anaesthesia and Intensive Care, Aalborg University Hospital, Aalborg, Denmark
Prof. Dr. med. Philipp Schütz, Chefarzt Allgemeine Innere & Notfallmedizin, Titularprofessur an der Universität Basel

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