



Statistical Analysis Plan

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Nuffield Department of
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Abbreviations

ADaM	Analysis Data Model
AE	adverse event
CDISC	The Clinical Data Interchange Standards Consortium
CI	confidence interval
CoV	Coronavirus
COVID	coronavirus-induced disease
CPAP	Continuous Positive Airway Pressure
CRP	C-reactive protein
CTU	clinical trials unit
CTSU	Clinical Trials Service Unit
DMC	Data Monitoring Committee
ECMO	Extra Corporeal Membrane Oxygenation
eCRF	Electronic case report form
FiO ₂	fraction of inspired oxygen
ICD	International Classification of Diseases
IFN	interferon
ICNARC	Intensive Care National Audit and Research Centre
IQR	interquartile range
ITT	intention to treat
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East Respiratory Syndrome
NPEU	National Perinatal Epidemiology Unit
OPCS-4	NHS Classification of Interventions and Procedures
PaO ₂	partial pressure of oxygen
RR	risk ratio
SAE	serious adverse event
SARS	severe acute respiratory syndrome
SARS-CoV-2	virus causing COVID-19
SSAR	Suspected serious adverse reaction
SUSAR	Suspected unexpected serious adverse reaction
SD	standard deviation
SC	Steering Committee

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Roles and responsibilities

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Role: To develop the statistical analysis plan and conduct the final comparative analysis. Blinded to trial allocation.

Data Monitoring Committee (DMC) Statisticians

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Role: To conduct regular interim analyses for the DMC. Contribution restricted up until unblinded to trial allocation.

Trial IT systems & Programmers

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Role: To generate and prepare reports monitoring the randomisation schedule. To supply data snapshots for interim and final analysis. Responsibility for randomisation system, clinical databases and related activities.

Bob Goodenough

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Role: Validation of IT systems

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NDPH, University of Oxford

Role: To produce analysis-ready datasets according to CDISC standards.

1 INTRODUCTION

This document details the proposed presentation and analysis for the main paper(s) reporting results from the multicentre randomised controlled trial RECOVERY (ISRCTN50189673) to investigate multiple treatments on major outcomes in inpatients for COVID-19 (clinically suspected or laboratory confirmed).

The results reported in these papers will follow the strategy set out here, which adheres to the guidelines for the content of a statistical analysis plan.¹ Any subsequent analyses of a more exploratory nature will not be bound by this strategy, and will be detailed in a separate analysis plan.

Suggestions for subsequent analyses by oversight committees, journal editors or referees, will be considered carefully in line with the principles of this analysis plan.

Any deviations from the statistical analysis plan will be described and justified in the final report to the funder. The analysis will be carried out by an identified, appropriately qualified and experienced statisticians, who will ensure the integrity of the data during their processing e.g. by parallel programming.

This statistical analysis plan is based on the latest version of the protocol. A record of amendments to the protocol can be found in the RECOVERY trial directory: <https://www.recoverytrial.net/for-site-staff/site-set-up-1>.

2 BACKGROUND INFORMATION

2.1 Rationale

In early 2020, as the protocol was being developed, there were no approved treatments for COVID-19. The aim of the trial is to provide reliable evidence on the efficacy of candidate therapies (including re-purposed and novel drugs) for suspected or confirmed COVID-19 infection on major outcomes in hospitalised adult patients receiving standard care.

2.2 Objectives of the trial

2.2.1 *Primary objective*

To provide reliable estimates of the effect of study treatments on all-cause mortality within 28 days of randomisation.

2.2.2 *Secondary objectives*

To investigate the effect of study treatments on the duration of hospital stay, the need for (and duration of) ventilation, and the need for renal replacement therapy.

2.3 Trial design

This is a multi-centre, multi-arm, adaptive, open-label, randomised controlled trial with three possible stages of randomisation. In the main randomisation patients are allocated to no additional treatment or one of 4 anti-viral or host-directed treatments. In addition, in a

factorial design, eligible patients can also be allocated simultaneously to no additional treatment or convalescent plasma. Patients who deteriorate according to predefined criteria can be further randomised to no additional treatment or an immunomodulatory treatment. The trial is designed with streamlined processes in order to facilitate rapid large-scale recruitment with minimal data collection.

2.4 Eligibility

2.4.1 *Inclusion criteria*

Patients are eligible for the trial if all of the following are true:

- Hospitalised
- SARS-Cov-2 infection (clinically suspected or laboratory confirmed)
- No medical history that might, in the opinion of the attending clinician, put the patient at significant risk if they were to participate in the trial.

2.4.2 *Exclusion criteria*

If one or more of the active drug treatments is not available at the hospital or is believed, by the attending clinician, to be contraindicated (or definitely indicated) for the specific patient, then this fact will be recorded via the web-based form prior to randomisation; random allocation will then be between the remaining (or indicated) arms.

2.5 Treatments

All patients will receive standard management for the participating hospital. The main randomisation will be between the following treatment arms (although not all arms may be available at any one time). The doses listed are for adults; paediatric dosing is described in the protocol.

2.5.1 *Main randomisation part A:*

- **No additional treatment**
- **Lopinavir 400mg-Ritonavir 100mg** by mouth (or nasogastric tube) every 12 hours for 10 days.
- **Corticosteroid** in the form of dexamethasone, administered as an oral liquid or intravenous preparation 6 mg once daily for 10 days. In pregnancy, prednisolone 40 mg administered by mouth (or intravenous hydrocortisone 80 mg twice daily) should be used instead.
- **Hydroxychloroquine** by mouth for 10 days (4 doses in first 24 hours and 1 dose every 12 hours for 9 days).
- **Azithromycin 500mg** by mouth (or nasogastric tube) or intravenously once daily for a total of 10 days.

2.5.2 *Main randomisation part B:*

In a factorial design, eligible patients may be randomised to the arms below. The doses listed are for adults; paediatric dosing is described in the protocol.

- **No additional treatment**
- **Convalescent plasma** Single unit of ABO compatible convalescent plasma (275mls +/- 75 mls) intravenous per day on study days 1 (as soon as possible after randomisation) and 2 (with a minimum of 12 hour interval between 1st and 2nd units). ABO identical plasma is preferred if available. The second transfusion should not be given if patient has a suspected serious adverse reaction during or after the first transfusion.

2.5.3 *Second randomisation for patients with progressive COVID-19*

Patients enrolled in the main RECOVERY trial and with clinical evidence of a hyper-inflammatory state may be considered for a second randomisation if they meet the following criteria:

- Randomised into the main RECOVERY trial no more than 21 days ago
- Clinical evidence of progressive COVID-19:
 - oxygen saturation <92% on room air or requiring oxygen (or in children, significant systemic disease with persistent pyrexia, with or without evidence of respiratory involvement); and
 - C-reactive protein (CRP) ≥75 mg/L
- No medical history that might, in the opinion of the attending clinician, put the patient at significant risk if they were to participate in this aspect of the RECOVERY trial

Eligible participants may be randomised between the following treatment arms:

- **No additional treatment**
- **Tocilizumab** by intravenous infusion with the dose determined by body weight.

2.6 *Definitions of primary and secondary outcomes*

Outcomes will be assessed at 28 days and then 6 months after randomisation. Analysis of longer-term outcomes collected beyond this will be described in a separate Statistical Analysis Plan.

2.6.1 *Primary outcome*

Mortality (all-cause)

2.6.2 *Secondary clinical outcomes*

- Time to discharge from hospital
- Use of mechanical ventilation/Extra Corporal Membrane Oxygenation (ECMO) or death (among patients not on ventilation or ECMO at baseline)

2.6.3 *Subsidiary clinical outcomes*

- Cause-specific mortality (COVID-19; cardiovascular; non-vascular; other)
- Use of renal dialysis or haemofiltration
- Serious cardiac arrhythmia (recorded in a subset)

- Use of ventilation (overall and by type)
- Duration of ventilation (overall and by type)

2.6.4 *Detailed derivation of outcomes*

The detailed derivation of outcomes included in statistical analysis will be described separately in a data derivation document and included in the Study Data Reviewer's Guide.

2.7 Hypothesis framework

For each of the primary, secondary and subsidiary outcomes, the null hypothesis will be that there is no true difference in effect between any of the treatment arms.

2.8 Sample size

The larger the number randomised, the more accurate the results will be, but the numbers that can be randomised will depend critically on how large the epidemic becomes. If substantial numbers are hospitalised in the participating centres then it may be possible to randomise several thousand with moderate disease and a few thousand with severe disease. Some indicative sample sizes and projected recruitment will be estimated using emerging data for several different scenarios. Sample size and recruitment will be monitored by the Steering Committee (SC) throughout the trial.

2.9 Randomisation

Eligible patients will be randomised using a 24/7 secure central web-based randomisation system, developed and hosted within NDPH, University of Oxford. Users of the system will have no insight into the next allocation, given that simple randomisation is being used. In the event that a patient is randomised inadvertently more than once during the same hospital admission, the first allocation will be used.

The implementation of the randomisation procedure will be monitored by the Senior Trials Programmer, and the SC notified if an error in the randomisation process is identified.

2.9.1 *Main randomisation part A*

Simple randomisation will be used with a 2:1:1:1:1 allocation ratio to one of the following treatment arms (in addition to usual care), which is subject to change:

- No additional treatment
- Lopinavir-Ritonavir
- Corticosteroid
- Hydroxychloroquine
- Azithromycin

The randomisation programme will allocate patients in a ratio of 2:1 between the no additional treatment arm and each of the other arms that are not contra-indicated and available. Hence if all 4 active treatment arms are available, then the randomisation will be in the ratio 2:1:1:1:1. If one or more of the active drug treatments is not available at the hospital or is believed, by the attending clinician, to be contraindicated (or definitely indicated) for the

specific patient, then this fact will be recorded via the web-based form prior to randomisation; random allocation will then be between the remaining arms (in a 2:1:1:1, 2:1:1 or 2:1 ratio).

2.9.2 *Main randomisation part B*

In a factorial design, eligible patients will be randomised simultaneously using simple randomisation with allocation ratio 1:1 to one of the following arms:

- No additional treatment
- Convalescent plasma

2.9.3 *Second randomisation for patients with progressive COVID-19*

Eligible participants may be randomised using simple randomisation with an allocation ratio 1:1 between the following arms:

- No additional treatment
- Tocilizumab

2.10 Blinding

This is an open-label study. However, while the study is in progress, access to tabular results of study outcomes by treatment allocation will not be available to the research team, CIs, trial statisticians, clinical teams, or members of the SC (unless the DMC advises otherwise). The DMC and DMC statisticians will be unblinded.

2.11 Data collection schedule

Baseline and outcome information will be collected on trial-specific electronic case report forms (eCRFs) and entered into a web-based IT system by a member of the hospital or research staff. Follow-up information will be collected on all study participants, irrespective of whether or not they complete the scheduled course of allocated study treatment. Study staff will seek follow-up information through various means, including routine healthcare systems and registries.

All randomised participants will be followed up until death or 6 months post-randomisation to the main trial (whichever is sooner). NHS Digital and equivalent organisations in the devolved nations will supply data fields relevant to trial baseline and outcome measures to NDPH, University of Oxford on a regular basis, for participants enrolled into the trial. This will be combined with the trial-specific data collected via the web-based IT system and adjudicated internally.

Longer term (up to 10 years) follow-up will be sought through linkage to electronic healthcare records and medical databases including those held by NHS Digital, Public Health England and equivalent bodies, and to relevant research databases (e.g. UK Biobank, Genomics England).

2.12 Data monitoring

During the study all study data will be supplied in strict confidence to the independent DMC for independent assessment and evaluation. The DMC will request such analyses at a frequency relevant to the emerging data from this and other studies.

The DMC has been requested to determine if, in their view, the randomised comparisons in the study have provided evidence on mortality that is strong enough (with a range of uncertainty around the results that is narrow enough) to affect national and global treatment strategies. Hence, multiple reviews by the Data Monitoring Committee have no material impact on the final analysis. In such a circumstance, the DMC will inform the SC who will make the results available to the public and amend the trial arms accordingly.

2.13 Trial reporting

The trial will be reported according to the principles of the CONSORT statements.^{2, 3, 4} The exact composition of the trial publication(s) depends on the size of the epidemic, the availability of drugs, and the findings from the various pairwise comparative analyses (with the no additional treatment arm) in the main trial.

3 ANALYSIS POPULATIONS

3.1 Population definitions

The intention to treat (ITT) population will be all participants randomised, irrespective of treatment received. This ITT population will be used for analysis of efficacy and safety data.

For interim analyses, baseline data will be reported for all participants with data available and outcome data will be reported for all participants who have died, been discharged from hospital, or reached day 28 after the first randomisation.

4 DESCRIPTIVE ANALYSES

4.1 Participant throughput

The flow of participants through the trial will be summarised for each separate pairwise comparison using a CONSORT diagram, for the main and second randomisation separately. The flow diagram for the nested factorial design (main randomisation part B to convalescent plasma) will be stratified by the 5 arms included in the main randomisation part A. The flow diagrams will describe the numbers of participants randomly allocated, who received allocation, withdrew consent, and included in the ITT analysis population. The flow diagrams for arms in the main randomisation will also report the number of participants who underwent the second randomisation.

4.2 Baseline comparability of randomised groups

The following characteristics will be described separately for patients randomised to each main comparison (for each separate pairwise comparison of active treatment with the no additional treatment arm), and separately for the first and second randomisation.

4.2.1 Main randomisation (part A and B)

- Age at randomisation
- Sex
- Ethnicity
- Time since COVID-19 symptoms onset
- Time since hospitalisation
- Current respiratory support requirement
- Currently requiring renal dialysis or haemofiltration
- Comorbidities (diabetes, heart disease, chronic lung disease, tuberculosis, human immunodeficiency virus, severe liver disease, severe kidney impairment)
- If female, known to be pregnant

4.2.2 Second randomisation

In addition to the above:

- Type of ventilation support currently required (none, CPAP alone, non-invasive ventilation, high-flow nasal oxygen, mechanical ventilation, ECMO)
- Latest oxygen saturation measurement (%)
- Latest CRP measurement (mg/L)
- Latest ferritin measurement (ng/mL)
- Latest creatinine measurement ($\mu\text{mol/L}$)
- Allocation in first randomisation
- Interval between first and second randomisation

The number and percentage will be presented for binary and categorical variables. The mean and standard deviation or the median and the interquartile range will be presented for continuous variables, or the range if appropriate.

4.3 Completeness of follow-up

All reasonable efforts will be taken to minimise loss to follow-up, which is expected to be minimal as data collection for primary and secondary outcomes using trial-specific eCRFs is combined with linkage to routine clinical data on study outcomes from NHS Digital, ICNARC, and similar organisations in the devolved nations.

The number and percentage of participants with follow-up information at day 28 and at 6 months after the main randomisation will be reported. Data will be shown for each of the following: all-cause mortality, hospital discharge status, ventilation status, and will be shown for each randomised group for the main and second randomisation separately.

4.4 Adherence to treatment

The number and proportion of patients who did not receive the treatment they were allocated to will be reported. If any other trial treatment options were known to be received, instead of or in addition to, the allocated treatment during the 28 day follow-up period after the first randomisation, these will be collected and reported. Details on the number of days

(or doses) of treatment received will be reported for all trial treatments received where available.

5 COMPARATIVE ANALYSES

For all outcomes, the primary analysis will be performed on the intention to treat (ITT) population at 28 days after the main randomisation. An ITT analysis of all outcomes at 6 months post-randomisation will also be conducted.

Pairwise comparisons will be made between each treatment arm and the no additional treatment arm (reference group) in that particular randomisation (main randomisation part A, main randomisation part B, and second randomisation). Since not all treatments may be available or suitable for all patients, those in the no additional treatment arm will only be included in a given comparison if, at the point of their randomisation, they *could* alternatively have been randomised to the active treatment of interest (i.e. the active treatment was available at the time and it was not contra-indicated). The same applies to treatment arms added at a later stage; they will only be compared to those patients recruited concurrently.

5.1 Main randomisation part A

5.1.1 *Primary outcome*

Mortality (all-cause) will be summarised with counts and percentages by randomised comparison group. A time-to-event analysis will be conducted using the log-rank test, with the p-value reported. Kaplan-Meier estimates for the time to event will also be plotted (with associated log-rank p-values). The log-rank 'observed minus expected' statistic (and its variance) will be used to estimate the average event rate ratio and confidence interval for each treatment group versus the no additional treatment group.⁵ For the primary outcome, discharge alive before the relevant time period (28 days) will be assumed as absence of the event (unless there is additional data confirming otherwise).

5.1.2 *Secondary outcomes*

5.1.2.1 *Time to discharge from hospital*

A time-to-event analysis will be used to compare each treatment group with the no additional treatment group using Kaplan-Meier and the log-rank test, as described above. Patients who die in hospital will be censored after 28 days. This gives an unbiased estimate of the recovery rate and comparable estimates to the competing risks approach in the absence of other censoring (which is expected to be very minimal).⁶

5.1.2.2 *Use of mechanical ventilation/ECMO or death (among those not on ventilation or ECMO at randomisation)*

Counts and percentages will be presented by randomised group and the risk ratio will be calculated for each pairwise comparison with the no additional treatment arm, with confidence intervals and p-values reported. The absolute risk difference will also be presented with confidence intervals. Each component of this composite outcome will also be

summarised. Patients who were already on ventilation or ECMO at randomisation will be excluded from the denominator.

5.1.3 *Subsidiary clinical outcomes*

5.1.3.1 *Cause-specific mortality*

Cause-specific mortality will be analysed in a similar manner to the primary outcome. Deaths from other causes will be censored at the date of death and a separate survival curve will be presented for each cause of death (COVID-19, other infection, cardiovascular, and other).

5.1.3.2 *Use of renal dialysis or haemofiltration*

Counts and percentages will be presented by randomised group and the risk ratio will be calculated for each pairwise comparison with the no additional treatment arm, with confidence intervals and p-values reported. The absolute risk difference will also be presented with confidence intervals. Patients who were already on renal dialysis or haemofiltration at randomisation will be excluded from the denominator.

5.1.3.3 *Major cardiac arrhythmia*

Counts and percentages will be presented by randomised group and the risk ratio for any major cardiac arrhythmia will be calculated for each pairwise comparison with the no additional treatment arm, with confidence intervals and p-values reported. The absolute risk difference will also be presented with confidence intervals. Type of arrhythmia will also be described: (i) atrial flutter or fibrillation; (ii) supraventricular tachycardia; (iii) ventricular tachycardia; (iv) ventricular fibrillation; (v) atrioventricular block requiring intervention, with subtotals for (i)-(ii) and (iii)-(iv).

5.1.3.4 *Use of ventilation (overall and by type)*

Counts and percentages will be presented by randomised group for patients who received any assisted ventilation. Patients who were already on assisted ventilation or required oxygen (as this includes people on CPAP, other non-invasive ventilation and high-flow nasal oxygen) at randomisation will be excluded from the denominator. The number of patients receiving the different types of ventilation will also be reported: non-invasive ventilation (i.e. CPAP, other non-invasive ventilation or high-flow nasal oxygen), and invasive mechanical ventilation (i.e. invasive mechanical ventilation or ECMO).

5.1.3.5 *Duration of ventilation (overall and by type)*

The mean (SD) duration of ventilation will be calculated in days from the main randomisation for each randomised group in those who received ventilation, separately for survivors and non-survivors. This will be reported overall for any assisted ventilation and separately for mechanical ventilation or ECMO. The mean difference and confidence intervals will be presented for each pairwise comparison with the no additional treatment arm.

5.2 *Main randomisation part B*

For the evaluation of treatment effect in the factorial design, the main effect of convalescent plasma across all arms in main randomisation part A combined, will be presented and tested,

as described in 5.1. Data stratified by allocation in part A will also be reported to aid interpretation, but no tests for statistical interaction will be performed.

Additional safety data will be collected in a subset of patients randomised to part B. These will be tabulated separately by allocation (convalescent plasma versus no additional treatment): (i) sudden worsening in respiratory status; (ii) severe allergic reaction; (iii) temperature $>39^{\circ}\text{C}$ or $\geq 2^{\circ}\text{C}$ rise since randomisation; (iv) sudden hypotension, clinical haemolysis and thrombotic event.

5.3 Second randomisation

Evaluation of treatment effects in the main randomisation and the second randomisation will be conducted independently, as described in 5.1. In addition to the overall comparison for Tocilizumab vs no additional treatment, results will be stratified according to allocation in the main randomisation (part A and part B), however no interaction tests will be performed between the allocations in the two stages.

5.4 Pre-specified subgroup analyses

Pre-specified subgroup analyses will be conducted for the main randomisation (part A and part B) and the second randomisation, for the following outcomes:

- Mortality (all-cause)
- Time to discharge from hospital
- Use of mechanical ventilation/ECMO or death

The analyses will be conducted using a test for heterogeneity (or test for trend for 3 or more ordered groups). Results will be presented on forest plots as event rate ratios, or risk ratios with confidence intervals. The following subgroups will be examined:

- Risk group (three risk groups with approximately equal number of deaths based on factors recorded at randomisation)
- Requirement for respiratory support at randomisation (None; Oxygen only; Ventilation or ECMO)
- Time since illness onset (≤ 7 days; > 7 days)
- Age (< 70 ; 70-79; 80+ years)
- Sex (Male; Female)
- Ethnicity (White; Black, Asian or Minority Ethnic)

Additional analyses will set the results for children (< 18 years) and pregnant women in the context of the overall results.

5.5 Adjustment for baseline characteristics

The main analyses described above will be unadjusted for baseline characteristics. However, in the event that there are any important imbalances between the randomised groups in key baseline subgroups (see section 5.4), emphasis will be placed on analyses that are adjusted for the relevant baseline characteristic(s). This will be done through the use of Cox regression for the estimation of adjusted hazard ratios and a log-binomial regression model for the estimation of adjusted risk ratios.

5.6 Significance levels and adjustment of p-values for multiplicity

Evaluation of the primary trial (main randomisation) and secondary randomisation will be conducted independently and no adjustment be made for these. Formal adjustment will not be made for multiple treatment comparisons, the testing of secondary and subsidiary outcomes, or subgroup analyses. 95% confidence intervals will be presented for the main comparisons.

5.7 Statistical software employed

The statistical software SAS version 9.4, R Studio 3.6.2 and Stata/SE version 15 (or later) for Windows will be used for the interim and final analyses.

5.8 Data standards and coding terminology

Datasets for analysis will be prepared using CDISC standards for SDTM and ADaM. Wherever possible, clinical outcomes (which may be obtained in a variety of standards, including ICD10 and OPCS-4) will be coded using MedDRA version 20.1.

6 SAFETY DATA

Suspected serious adverse reactions (SSARs) and suspected unexpected serious adverse reactions (SUSARs) will be listed by trial allocation.

7 ADDITIONAL EXPLORATORY ANALYSIS

Any post-hoc analysis requested by the oversight committees, a journal editor or referees will be labelled explicitly as such. Any further future analyses not specified in the analysis protocol will be exploratory in nature and will be documented in a separate statistical analysis plan.

8 DIFFERENCES FROM PROTOCOL V6.0

Use and duration of ventilation are described as secondary objectives in the protocol, and listed as subsidiary outcomes in the statistical analysis plan. The testing of multiple treatment arms will not formally be adjusted for, but given the number of comparisons, due allowance will be made in their interpretation. Formal methods of adjustment for multiplicity were not adopted because of treatment arms being added over time (including the factorial convalescent plasma comparison), unequal recruitment into each arm, and the ultimate number of treatments under evaluation not known in advance. While methods for these situations exist it was felt that the resulting change in level of significance was not appropriate.

9 REFERENCES

9.1 Trial documents

Dummy tables and the data derivation document can be found in the RECOVERY trial directory and will be published with this SAP on the trial website.

9.2 Other references

1. Gamble C, Krishan A, Stocken D, Lewis S, Juszczak E, Doré C, Williamson PR, Altman DG, Montgomery A, Lim P, Berlin J, Senn S, Day S, Barbachano Y, Loder E. Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. *JAMA* 2017;318(23):2337-2343.
2. Schulz KF, Altman DG, Moher D for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:698-702.
3. Juszczak E, Altman DG, Hopewell S, Schulz KF. Reporting of multi-arm parallel-group randomized trials: extension of the CONSORT 2010 statement. *JAMA* 2019;321(16):1610-1620.
4. Dimairo M, Coates E, Pallmann P, Todd S, Julious SA, Jaki T, Wason J, Mander AP, Weir CJ, Koenig F, Walton MK. Development process of a consensus-driven CONSORT extension for randomised trials using an adaptive design. *BMC medicine* 2018;16(1):210.
5. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, Mantel N, McPherson K, Peto J, Smith PG. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. Part II: analysis and examples. *Br J Cancer* 1977;35:1-39.
6. Betensky RA and Schoenfeld DA. Nonparametric Estimation in a Cure Model with Random Cure Times. *Biometrics* 2001;57:282-286.

10 APPROVAL

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Steering Committee Statistician	Name: Associate Professor Ed Juszcak	
	Signature:  <small>Ed Juszcak (Jun 22, 2020 09:34 GMT+1)</small>	Date: Jun 22, 2020
Steering Committee Statistician	Name: Professor Alan Montgomery	
	Signature:  <small>Alan Montgomery (Jun 22, 2020 10:54 GMT+1)</small>	Date: Jun 22, 2020
Steering Committee Statistician	Name: Professor Thomas Jaki	
	Signature:  <small>Thomas Jaki (Jun 22, 2020 11:01 GMT+1)</small>	Date: Jun 22, 2020

11 DOCUMENT HISTORY

Version	Date	Edited by	Comments/Justification	Timing in relation to unblinded interim monitoring	Timing in relation to unblinding of Trial Statisticians
0.1	20/03/20	LL/JB	First draft.	Prior	Prior
0.2	01/04/20	LL/JB	Comments and amendments from Martin Landray, Jonathan Emberson & Natalie Staplin. Also aligned with updated protocol and CRFs.	Prior	Prior
0.3	01/04/20	EJ/LL	Further edits and comments.	Prior	Prior
0.4	07/04/20	JB/EJ/LL	Following statistics group meeting on 02/04/20.	Prior	Prior
0.5	22/04/20	JB/LL/EJ	Following statistics group meeting on 09/04/20 and further protocol update.	After	Prior
0.6	24/04/20	LL	Following statistics group meeting on 23/04/20.	After	Prior
0.7	10/05/20	LL	Protocol update.	After	Prior
0.8	15/05/20	LL	Following statistics group meeting on 15/05/20.	After	Prior
0.9	27/05/20	LL	Further comments from SC members prior to interim analysis on 28/05/20.	After	Prior
1.0	09/06/20	LL	Revised following the stopping of the hydrochloroquine arm, and prior to the trial statisticians receiving unblinded data for this arm.	After	Prior
1.1	21/06/20	LL/JB/RH	Additional clarification of ventilation denominators. Adjustment for any imbalances of subgroup characteristics between treatment arms at randomisation. Clarification of analysis of composite outcome. Removal of 'Unknown' ethnicity subgroup. Addition of section 5.5 Adjustment for baseline characteristics.	After	After unblinding of hydroxychloroquine and dexamethasone arms.












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Final Audit Report

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