Primary Care Clinical Trials Unit

PRINCIPLE
Platform Randomised Trial of Treatments in the Community for Epidemic and Pandemic Illnesses

MASTER STATISTICAL ANALYSIS PLAN

Platform **R**andomised tr**I**al of treatme**N**ts in the **C**ommunity for ep**I**demic and **P**andemic i**L**ln**E**sses Internal Reference Number / Short title: PRINCIPLE

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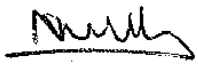
Written by	Nicola Williams		14th December 2021
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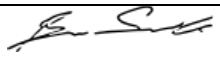
Reviewed by	Ben Saville		19th December 2021
Approved by:	Professor Chris Butler		5th January 2022

Version History

Version:	Version Date:	Changes:
0.1	25th March 2020	MS initial draft
0.2	31st March 2020	Updated post JM initial comments
0.3	12 May 2020	JM/UG writing SAP
0.4	10 Aug 4th August 2020	Updated to protocol version 4.0 NW updating SAP
0.5	11th August 2020	Merging of 2 0.4 versions
0.6	1st October 2020	Updates following comments from JG, ST and CB Update primary outcomes and sample size Remove references to RCGP data as this is stored in the notes review
0,7	15th October 2020	Updates following meetings with JG, ST, LMY Remove much of text from introduction/DMC sections and refer to protocol/DMC charter Update analysis of binary outcomes to logistic regression
0.8	29th October 2020	Updates following review from LMY Health service use split into participant reported and GP reported health service use Addition of sustained recovery outcome Addition of appendix III – analysis of HYDROXYCHLOROQUINE arm
0.9	30th October 2020	Further update to definition of sustained recovery. Also changed the definition of duration of severe symptoms.

0.10	3rd November 2020	Update following comments from CB
0.11	4th November 2020	Incorporated Jienchi Dorward & Ben Saville's comments
0.12	6th November 2020	Incorporated Richard Hobbs' comments and made changes following meeting with LMY, RH, CB, BS, JD: Updated definition of sustained recovery Change 'consumption' to 'prescription' for antibiotics Addition of WHO ordinal scale
0.13	18th November 2020	Amending typos Addition of appendices detailing analysis of azithromycin and doxycycline Addition of subgroup analyses
0.14	24th November 2020	Update to protocol v6.0 New outcome: new infections in the household Addition of appendix detailing analysis of inhaled corticosteroid arm Update subgroup analysis section Accept changes from BS and CB from previous version
0.15	26th November 2020	Updates following comments from Philip Hannaford – update to ICS dose and subgroup analyses to include deaths and deaths/hospitalisation combined
1.0	1st December 2020	Change to version 1.0 for signing off
1.1	20th January 2021	Remove viral shedding outcome Update timing of swab results

		Clarification of censoring for time to event outcomes Addition of moderation analyses
1.2	9th February 2021	Updated objectives to protocol version 6.3 30.12.2020. Inclusion of Addendum 1.1 and clarification of analysis populations. Updated derivation of: hospitalisation primary outcome (hierarchy of data sources); duration of hospital admission; Definition of last contact date for time to event outcomes Schedule of procedures and flow diagram of trial participants updated Updated timing of swab results Updated handling missing data
2.0	10th February 2021	Signatures
2.1	26th February 2021	Updated to reflect protocol V7.0, addition of colchicine, target population, Appendices. Addition of new secondary outcome
2.2	16th March 2021	Updated to reflect protocol V7.1. Addition of safety as a secondary endpoint. Addition of favipiravir treatment arm. The primary analysis population defined as those with a COVID-19 positive test.
3.0	16th March 2021	Change to version 3.0 for signing
3.1	30th March 2021	Addition of sensitivity analysis specific to Budesonide. Clarification of analysis population for sensitivity analysis. Definition of Vaccination status and addition

		as covariate, update to definition of sustanined recovery (secondary outcome). Moved derivation of COVID-19 test status to section 2.2.4
3.2	2nd July 2021	Updated to protocol version 8.1. Addition of Ivermectin arm Updated definition of vaccination status in section 2.2.5 Daily diary added as a source for derivation of COVID-19 status Sources of data for derivation of mortality updated, section 3.2.2.1 All cause death or non-elective/urgent hospitalisation within 28 days of randomisation added as secondary outcome Section 3.3.2 Duration of symptoms: derivation of time to event outcomes updated Section 9. Moderation analyses added and intervention specific subgroups specified Section 4.6.4 clarification of population for safety analysis. Updates to intervention specific appendices for colchicine, favipirivir and ivermectin Appendix II Participant flow diagram updated Section 6.2 Removal of secondary analysis of the secondary outcomes using all participants analysis population Section 3.3.2.5 addition of secondary outcome, worsening of symptoms following randomisation.
4.0	2nd July 2021	Signatures
4.1	2nd September 2021	Updated to protocol version 9.0 - Inclusion criteria updated – participants must have a positive

		test for SARS-CoV-2 and removal of requirement for comorbidity and shortness of breath - Hospitalisation primary outcome wording updated for clarity - Removal of secondary outcome "to determine if effects are specifi to those with a positive test for SARS-CoV-2" Section 2.2.2 Addition of date of death to last contact date Section 2.3.2.2 Duration of severe symptoms – clarification of symptoms included and addition of worsening of symptoms after randomisation Section 2.3.2.5 Hospital assessment without admission added Section 3.3.2.1 Time to alleviation of symptoms – clarification about censoring of deaths Section 3.3.2.3 Change to 'early' sustained recovery Section 3.3.2.5 Defining 'worsening of symptoms after randomisation' Section 6.2.2.5 Analysis added for worsening of symptoms Section 3.3.2.1 Time to alleviation of symptoms – explicitly state that those who die will be censored at 28 days
4.2	10th November 2021	Update to most recent protocol v11.0 (no changes relevant to SAP) Accept changes following comments from BS on v4.1
4.3	14th December 2021	Add table of dates to Appendix VI Budesonide

		Clean document for signatures
5.0	14th December 2021	Signatures

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1 INTRODUCTION

1.1 PREFACE

Chief Investigator: Professor Chris Butler

Co-study lead: Professor Richard Hobbs

Senior Trial Manager(s): Dr Hannah Swayze, Dr Emma Ogburn, Dr Emily Bongard, Julie Allen

Trial Manager: Jared Robinson

Data manager: Jenna Grabey

Lead Trial Statistician(s): Dr Ly-Mee Yu and Dr Ben Saville

There are two teams of unblinded statisticians involved in the PRINCIPLE trial. The unblinded statisticians in Oxford Primary Care Clinical Trials Unit (PC-CTU) are responsible for data management, derivation of outcomes, transfer of data to the Statistical Analysis Committee (SAC) of Berry Consultants and analysis of the secondary and safety outcomes. The unblinded SAC is responsible for the interim analysis and to provide a summary of results for the Data Monitoring Safety Monitoring Committee (DMSC) members in an interim analysis report. The SAC will be responsible for the co-primary analyses and any related sensitivity and subgroup analyses requiring a similar Bayesian framework.

This version of the Statistical Analysis Plan was written based on protocol version 11.0 19th October 2021, and may be updated in the light of further amendments to the study protocol.

1.2 PURPOSE AND SCOPE OF THE PLAN

This Master Statistical Analysis Plan (M-SAP) will detail the statistical design and methods of the PRINCIPLE trial. It will include an appendix titled "Adaptive Design Report" (ADR), which will provide complete specifications for the primary analyses and pre-specified adaptive algorithm. In addition, the M-SAP will be accompanied by arm-specific appendices to describe any planned deviations from the M-SAP. Plans for the analysis of qualitative outcomes is beyond the scope of this statistical analysis plan, and therefore will not be covered in this M-SAP.

Analyses-related decisions may need to be made based on the observed data, such as a review of the distribution of outcome data. These decisions will be made prior to the proposed statistical analyses.

The plan draws on statistical guidance ICH Harmonised Tripartite Guideline: Statistical Principles for Clinical Trials and PSI Guidelines for the Standard Operating Procedures (SOP) for Good Statistical Practice in Clinical Research, the CONSORT statement for operating trials and PC-CTU statistical SOPs.

Analyses will be carried out in accordance with the M-SAP and corresponding appendices. Any additional analysis that is not specified in the M-SAP/appendices or any unplanned deviation(s) from the M-SAP/appendices will be specified in the Statistical Report. Reasons for these changes will be documented and authorised by the Chief Investigator.

Due to the nature of the design of this trial, results for specific treatments will be analysed while the trial is ongoing. This will be done with prior agreement from the Trial Steering Committee (TSC) and DMSC, and the trial team will remain blind to these analyses until such time as the TSC, informed by data and advice from the DMSC, advise that findings should be declared.

1.3 Trial overview

PRINCIPLE is an open, adaptive, platform trial to evaluate emerging treatments for COVID-like-illness. A "platform trial" is a trial in which multiple treatments for the same disease are tested simultaneously. The backbone of the trial is an adaptive clinical trial design. Pre-specified decision criteria allow for dropping a treatment for futility, declaring a treatment superior, or adding a new treatment to be tested. If at any point a treatment is deemed superior to the Usual Care arm, the superior treatment may replace the Usual Care arm as the new standard of care within the trial. However, the primary analysis of subsequent interventions will correspond to the comparison versus the original Usual Care arm. Because the process of dropping and adding treatments may be on-going for an indefinite period of time, platform trials may be better conceived of as a process rather than a single clinical trial. In the context of the COVID-19 pandemic, the trial may continue as long as the pandemic persists.

The PRINCIPLE trial began as a two arm, 1:1 randomised trial but with the capability to add additional interventions over time. The evaluation of any new interventions is governed by the master protocol and M-SAP (including adaptive algorithm and decision criteria), with any planned deviations from the master protocol and M-SAP to be specified in arm-specific appendices. The inclusion of any new interventions will require additional arm-specific appendices to the master protocol and M-SAP.

1.4 Objectives

The primary and secondary objectives as well as time points to evaluate these outcome measures as stated in the protocol.

	Objectives	Outcome Measures	Timepoint (s)
Primary	To assess the effectiveness of trial treatments in reducing 1) Time to recovery, for patients	1) Time to self-reported recovery, defined as the first instance that a participant reports feeling recovered from possible COVID-19, and	Within 28 days of randomisation Patient report, Study Partner report, daily online symptom scores
	2) Hospitalisation and/or death.	2) Hospitalisation and/or death due to confirmed SARS-CoV-2 infection	Within 28 days of randomisation

	Objectives	Outcome Measures	Timepoint (s)
			Patient report, Study Partner report, medical records
Secondary	To explore whether trial treatment will affect 1) participant-reported illness severity reported by daily rating of how well participant feels 2) Duration of severe symptoms and symptom recurrence	Participant reports of daily and monthly (after 28 days) symptoms.	Daily online symptom scores. Telephone call or text on days 2, 7, 14 and 28 and once a month for 12 months if data is not obtained through the online diary
	3) Contacts with the health services	Contacts with health services reported by patients and/or captured by reports in patients' medical records if the practice is a member of the RCGP RSC network	GP notes review if available through Oxford RCGP RSC network; otherwise, other sources of routinely collected data after 28 days. Medical notes review for up to 10 years.
	4) Prescription of antibiotics	Bi-weekly reports from participants' primary care medical records	
	5) Hospital assessment without admission 6) Oxygen administration 7) Intensive Care Unit admission 8) Mechanical ventilation 9) Duration of hospital admission	Patient report/carer report/medical record in primary and secondary care	HES/ONS/EMIS/Medical record data linkage after 28 days if patients have been assessed in hospital
	10) Negative effects on well being	WHO-5 Well Being Index	WHO 5 Well Being Index at baseline, day 14, and

	Objectives	Outcome Measures	Timepoint (s)
			day 28 and monthly for up to 12 months, either via online diary or telephone
	11) New infections in household	Reports of new infections in the household (from daily questionnaire)	Within 28 days of randomisation
	12) To investigate the safety of treatments that are not licensed in the UK	Evaluation of overall safety of drugs by the monitoring of adverse events (AEs as defined in the Intervention specific Appendices (ISAs))	For the duration of the treatment course and a defined period after the treatment finishes.
Qualitative sub-study (not covered in this M-SAP)	1. To explore patients' experiences of consulting, being tested and taking (trial) medication for suspected COVID-19. 2. To explore healthcare professionals' views of taking part in research during pandemics.	1. Telephone interviews with patients. 2. Telephone interviews with healthcare professionals.	1. After 28 days. 2. Once practice has completed recruitment.
Intervention(s)	All trial interventions are detailed in the Appendices of the protocol. Further interventions may be added or replaced during the course of the trial, subject to suitable interventions becoming available and all necessary approvals being obtained.		
Comparator	PRINCIPLE began as a two-arm trial, with the intervention arm being Usual Care without the addition of a trial drug. There will be no placebo control in this study. Additional arms may be added as the trial progresses. These will be detailed in the Appendices of the protocol. If an intervention arm is shown to be superior, then this will become the new standard of care. However, the primary analysis of subsequent interventions will correspond to the comparison versus the original Usual Care arm.		

2 TRIAL DESIGN

PRINCIPLE is an open, adaptive, platform trial to evaluate emerging treatments of COVID-like-illness. A "platform trial" is a trial in which multiple treatments for the same disease are tested simultaneously. The backbone of the trial is an adaptive clinical trial design. Pre-specified decision criteria allow for dropping a treatment for futility, declaring a treatment superior, or adding a new treatment to be tested. If at any point a treatment is deemed superior to the control arm, the superior treatment will replace the control arm as the new standard of care, and all subsequent treatments may be compared to the new standard of care within the trial. Because the process of dropping and adding treatments may be on-going for an indefinite period of time, platform trials may be better conceived of as a process rather than a single clinical trial. In the context of the COVID-19 pandemic, the trial may continue as long as the pandemic persists, and while there is a need to evaluate treatments for acute respiratory tract infections in the community.

The PRINCIPLE trial began as a 1:1 randomised trial of standard care versus standard care plus hydroxychloroquine but with the capability to add additional interventions over time. The evaluation of any new interventions is governed by the master protocol, including adaptive and decision criteria. In addition, the inclusion of any new interventions will require amendments and/or supplements to the protocol and M-SAP.

2.1 ADAPTIVE DESIGN

The pre-specified design will allow adaptations to the trial based on the observed data. These adaptations include the declaration of success or futility of an intervention at an interim analysis, the addition or removal of treatment arms, and changes in the randomisation probabilities. Adaptations will occur at a given interim analysis if pre-specified conditions are satisfied. The adaptive algorithm will be documented in the Adaptive Design Report, including pre-specified criteria for decisions regarding futility or effectiveness of interventions and/or replacing interventions in the trial.

2.2 DEFINITIONS

2.2.1 FOLLOW-UP PERIOD

Patients will be followed from date of randomisation to 28 days by daily symptom diary and/or telephone, and review of their medical records. Participant records will be accessed up to 3 months following randomisation to ascertain outcome data up to 28 days from randomisation. Participants will be followed up on a monthly basis for up to 12 months after enrolment (via email, text message or phone call) to collect information about any ongoing symptoms, hospitalisations and well-being.

2.2.2 LAST CONTACT DATE

In the derivation of time to event outcomes, the last contact date will be defined as the maximum of;

- Last diary entry
- Last call CRF completed
- Date of hospital admission
- Date of hospital discharge

- Date of death

2.2.3 Duration of illness prior to randomisation

Duration of illness prior to randomisation will be derived using the date the participant reported starting to feel unwell (Screening CRF) and date of randomisation. If date patient started to feel unwell (screening CRF) is missing, the date the screening form was completed will be used instead.

2.2.4 Derivation of COVID-19 test status

Participants will be categorised as being infected or not, based on any swab result obtained 14 days or less prior to randomisation and up to and including 7 days following randomisation. Swab result data is collected in the screening CRF, baseline CRF, daily diary, Lab results CRF and notes review CRF.

Any swab result obtained 14 days or less prior to randomisation and up to and including 7 days following randomisation will be used to classify participants into two groups. A positive test result at any time will put them into group 1, regardless of other negative results within the window specified;

1. COVID-19 positive test result
2. COVID-19 negative test result or no swab result available

2.2.5 Vaccination status

Vaccination status will be categorized as “Yes" vs. “other", where “yes" indicates at least one COVID-19 vaccination dose was given two weeks (or more) prior to randomisation and “other" indicates either no vaccination at least 2 weeks prior to randomisation or no vaccine information is available.

2.3 Outcomes

2.3.1 Primary outcome

There are two co-primary outcomes as listed below:

- Time to recovery from suspected COVID-19 infection within 28 days from randomisation, where recovery is defined as the first instance that a participant reports feeling recovered.
- Hospital admission or death due to confirmed COVID-19 infection within 28 days from randomisation

2.3.2 Secondary outcomes

2.3.2.1 Patient reported illness severity

Participants are asked to rate how well they are feeling overall each day on a scale of 1-10 (1 being the worst and 10 being the best). This is captured on the patients’ daily diaries and the Call CRF.

2.3.2.2 Duration of severe symptoms and symptom recurrence

Participants are asked to rate their symptoms of fever, cough, shortness of breath, muscle ache, nausea/vomiting, diarrhoea, generally feeling unwell, loss of smell/taste (added 26th February 2021), and headache (added 26th February 2021) on a four point scale from 0=no problem, 1=mild problem,

2=moderate problem and 3=major problem. From the start of the trial until 22nd March 2021 participants were asked to rate their symptoms whilst they did NOT feel recovered. From 23rd March 2021 participants were asked to rate symptoms irrespective of recovery. The additional symptoms of abdominal pain, symptoms of UTI, visual disturbance, confusion and seizures have been collected for adverse event monitoring only.The outcomes to be analysed will be time to alleviation of symptoms, time to initial reduction in severe symptoms, time to early sustained recovery, time to sustained alleviation of symptoms and worsening of symptoms after randomisation.

2.3.2.3 Contacts with health services between randomisation and day 28 of follow-up (FU).

This is captured on patients' daily diaries, telephone call CRFs, and medical notes review

2.3.2.4 prescription of antibiotics between randomisation and day 28 of FU

Notes review at 28 days will record information regarding prescription of antibiotics. Hospital assessment without admission overnight

This is captured on patients' daily diaries, telephone call CRFs, notes review and hospitalisation and death CRF.

2.3.2.5 Hospital assessment without admission

This is captured on patients' daily diaries, Call CRF, notes review and the death and hospitalisation CRF. All sources will be considered and if any indicates a hospital assessment without admission it will be coded as such. If there are discrepancies between the sources of data the diary data will be assumed to be correct.

2.3.2.6 Oxygen Administration

This is captured in patients' daily diaries, telephone call CRF, Notes review and hospitalisation and death CRF.

2.3.2.7 Intensive care unit admission

This is captured in patients' daily diaries, telephone call CRF, Notes review, and hospitalisation and death CRF.

2.3.2.8 Mechanical ventilation

This is captured in patients' daily diaries, telephone call CRF, Notes review and hospitalisation and death CRF.

2.3.2.9 Duration of hospital admission

Patient report/carer report/medical record in primary care and hospital care in relation to duration of hospital admission between date of randomisation and day 28 of follow-up.

This is captured in patients' daily diaries, Call CRF, Notes review and hospitalisation and death CRF.

2.3.2.10 Negative effects on well-being (WHO-5)

The WHO-5 well-being index is collected from daily diaries or telephone call at baseline, day 14 and day 28, and monthly for up to 12 months.

2.3.2.11 New infections in the Household

This is collected in the daily diary and telephone call CRF through the question "has anybody else in your house become unwell today with a respiratory illness?"

2.3.2.12 Safety of treatments not licensed in the UK

Medication side-effects and SAEs will be collected from participant daily diaries, calls to participants/study partners, medical records, notes reviews and RCGP data downloads.

2.3.2.13 All cause death or non-elective/urgent hospitalisation within 28 days of randomisation

The derivation will follow that for the co-primary outcome of hospital admission or death, but with no requirement for cause of death or reason for admission to be related to suspected COVID-19. Hospitalisations will be limited to non-elective/urgent admissions.

2.4 Target population

The trial aims to include symptomatic participants with confirmed, COVID-19 (a positive test for SARS-CoV-2 infection with in the past 14 days). , and who are well enough to remain in the community.

Participants must be aged 18 and over.

The study is for people who have ongoing symptoms.

See protocol for detailed inclusion and exclusion criteria.

2.5 Treatments

Based on version 11.0 of the protocol the main randomisation will be between the following treatment arms (although not all treatments may be available at any one time and not all participants are eligible for all treatments). However, the trial design accommodates treatments being added and dropped as appropriate.

- Usual care
- Usual care plus hydroxychloroquine, 200mg twice daily for 3 days (discontinued)
- Usual care plus azithromycin, 500mg once daily for 3 days (discontinued)
- Usual care plus doxycycline, 200mg on day 1 followed by 100mg daily for 6 days (discontinued)
- Usual care plus the inhaled corticosteroid, budesonide, 400mcg daily (as two puffs bd) for 14 days (discontinued)

- Usual care plus colchicine, 500 microgram (µg) once daily for 14 days (discontinued)
- Usual care plus favipiravir 1800mg twice a day on day one, and then 800mg twice a day for four days
- Usual care plus ivermectin, one dose each day for 3 days at 300µg/kg body weight

Subsequent reference to a treatment group refers to treatment plus usual care, and subsequent reference to usual care group refers to the usual care without a study drug.

2.6 SAMPLE SIZE

Given the open perpetual trial structure, the trial does not have a prespecified end based on sample size. Rather, the trial will continue until either superiority or futility is claimed for each intervention, or until the pandemic expires in the population. We estimate that approximately 400 participants per arm (800 participants total if only a single intervention vs. Usual Care) will be required to provide 90% power for detecting a hazard ratio of 1.3 in the primary population (approximate difference of 2 days in median recovery time). This calculation is based on the assumption of an exponential distribution for time to recovery with a median of 9 days in the Usual Care arm, with some adjustments for missing data and multiple interim analyses. On average, we expect fewer participants to be required when there is a large treatment benefit or complete lack of benefit. For example, if the true hazard ratio is 1.5 (3 day benefit in median time to recovery), on average only 150 subjects per arm are required to provide sufficient power. The primary advantage of the adaptive design is the ability to adapt the sample size to the observed data, thus addressing the primary hypothesis as quickly and as efficiently as possible.

We estimate that approximately 1500 participants per arm (3000 participants total if only a single intervention vs. usual care) will be required to provide 90% power for detecting a 50% reduction in the relative risk of hospitalisation and/or death in the primary analysis population. This calculation is based on the assumption of an underlying 5% combined hospitalisation and/or death rate in the Usual Care arm, with an intervention lowering the hospitalisation and/or death rate to 2.5%, with some adjustments for the multiple interim analyses. We expect fewer participants to be required to detect a 50% reduction if the event rate in the Usual Care arm is greater than 5%.

Virtual trial simulations

Because of the adaptive platform trial structure, there exists no simple formula(s) to calculate power and Type I error (false positive rate). Hence, virtual trial simulations will be used to fully characterize and quantify the power and Type I error of the design. These simulations will be conducted prior to the first interim analysis (with results described in the Adaptive Design Report), and will be used to optimize the adaptive decision criterion and RAR parameters. The simulations will include a comprehensive evaluation of trial performance across a wide range of assumptions (e.g. underlying distribution of outcome in Usual Care arm, treatment effect, accrual rates, etc.). This will include summaries regarding the number of subjects required to make a success or futility conclusions for each intervention. Complete details of the simulations will be provided in the Adaptive Design Report.

2.7 Randomisation and blinding in the analysis stage

Participants will be randomised using a fully validated and compliant web-based randomisation system called Sortition. Once deemed eligible, the clinician or a member of the trial team will randomise the participant. The randomisation process will take only a few moments via the online system and will not delay trial participation. Participants will be randomised to the arm/arms they are eligible for (at least two arms, usual care and at least one intervention), automatically by Sortition.

Initially, randomisation will be fixed 1:1 for a comparison between two trial arms, with stratification by age (less than 65, greater than or equal to 65), and comorbidity (yes/no). If a second intervention arm is added to the study, randomisation allocation will be modified and the additional intervention will be included in the interim analyses (with evaluation for success and futility) as detailed in the Adaptive Design Report. If there are at least 3 arms (2) treatment and Usual Care) in the study, each interim analysis may incorporate modified randomisation probabilities via response adaptive randomisation (RAR). Full details for implementing RAR will be provided in the Adaptive Design Report; the general idea is to allocate more participants to the intervention arms that have the best observed outcomes. Except for the CTU programmer, the rest of the trial team are blinded to RAR ratios.

PRINCIPLE is an open-label trial. The participant, a person guiding the participant through the randomisation process, and the participants' primary care clinician will know the participant's allocation. Therefore, no unblinding or code breaking is required in the event of a relevant emergency. However, those managing the data will be blind to participant allocation.

The trial team and recruiting clinicians will be blinded to emerging results. During the course of the trial, only the unblinding statisticians, SAC and independent members of the Data Monitoring and Safety Committee will have access to the unblinded interim results.

3 Data management and Derivation of outcomes

3.1 Sources of Data

Data is collected from multiple sources. For the derivation of outcomes, should data be collected from more than one source, we will specify which source should be utilised. For example, if data for an outcome are obtained from both daily diary and telephone calls, the daily diary data will be utilised first.

(i) Death and hospitalisation CRF
(ii) Online daily diaries for 28 days, and then monthly up to 12 months
(iii) Telephone call CRF at day 7, 14 and 28, and then monthly up to 12 months
(iv) Lab results CRF
(v) Notes review CRF
(vi) When available, the Secondary Uses Services data, which is a collection of healthcare data in England provided by NHS Digital, and other sources of hospital data.

Data management for derivation of primary and secondary outcomes will be carried out by PC-CTU statisticians, and primary outcomes (and any data that are relevant to the analysis of the primary outcomes) data transferred to SAC. The PC-CTU unblinded statistician will ensure that data transfer to the SAC for each treatment comparison includes only participants that meet the definition of the analysis population as defined in Section 4.6.

3.2 PRIMARY OUTCOMES

3.2.1 TIME TO RECOVERY

The first primary outcome is time to recovery from suspected COVID-19 infection within 28 days from randomisation, where recovery is defined as the first instance that a participant reports feeling recovered.

Time (in days) taken to self-reported recovery will be computed as time to reported "Yes" to the question "Do you feel recovered today (I.e. symptoms associated with illness are no longer a problem)?". The variable is recorded as (**WELLYN**=1). This will be calculated as date from randomisation to date (VISDAT_P) of participant self-report of recovery if using the patient diary. If the call CRF is being used then the date to feeling fully recovered is '**WELLDAT**'. Where patient recall of date of feeling recovered (as recorded on the call CRF) is prior to date of randomisation, the date of feeling recovered will be assumed to be day 0.

If a participant has more than one date for when they reported feeling recovered (i.e. relapse or more than one data source completed), the date of first reported recovery will be taken.

If the participant is in hospital on the date of feeling recovered then this will still be counted as a recovery (hospitalisation recorded in any 1 or more of the following sources: notes review; death and hospitalisation CRF; daily diaries; call CRF).

Participants who withdraw or are lost to follow-up will be censored at their last contact date (definition 2.2.2).

Participants who die will be censored at 28 days.

3.2.2 HOSPITAL ADMISSION OR DEATH

The second primary outcome is hospital admission or mortality related to suspected or confirmed COVID-19 measured within 28 days from randomisation.

3.2.2.1 DERIVATION OF MORTALITY

Mortality related to suspected COVID-19 within 28 days of randomisation

Data collected via the death and hospitalisation CRF, call CRF, medical notes review, electronic health record data such as HES, mortaility data, SUS, and GP prescription data provided by NHS Digital, and data extracted from RSC, will be used to derive the primary outcome. If the following is true from any source then the patient will be recorded as having death related to suspected COVID-19 within 28 days of randomisation.

DDYN =1 AND date of death (**DDDAT**) ≤28 days from randomisation AND COVID-19 contributed to death [**DD_CV19=1**].

If death is recorded as "Yes" but the COVID-19 related variable is missing, then the outcome will be cross checked with the SAE data. Any death not related to suspected COVID-19 should be recorded as an SAE.

3.2.2.2 Derivation of hospital admission

Hospital admission within 28 days will be defined as an overnight stay in hospital and likely to be related to COVID-19. This can be recorded from the daily diaries, calls at days 7, 14 and 28, notes review CRF, death and hospitalisation CRF and data from NHS digital. The data sources will be considered in the following hierarchy; (1) Patient reported (daily diaries, calls, hospitalisation CRF), (2) Notes review, (3) data from NHS digital. The NHS digital data will only be used if no data can be obtained from sources 1 and 2. Data from NHS digital will be adjudicated by two clinicians blind to randomised group as to whether the hospital admission is likely to be related to COVID-19. Hospital admissions on the day of randomisation will be assumed to have occurred post randomisation and will be included in the analysis.

3.2.2.2.1 Death and hospitalisation CRF

Participant attended hospital [**HOSP_HOOCCUR = 1**] AND attendance likely related to COVID-19 [**CVYN** = 1] AND [number of days in hospital > 1 or not yet discharged [**HOSP_HOENYN=0**] AND date they were admitted to hospital (**HOSP_HOSTDAT**) is ≤28 days from date of randomisation.

3.2.2.2.2 Daily diary data

Have you attended hospital in the last 24 hours [**HOSP_HOOCCUR** = 1] AND attendance likely related to COVID-19 [**CVYN** = 1] AND admitted overnight [**HOSP_NIGHTYN** = 1] AND first date of overnight hospital stay (**HOSP_HOSTDAT**) is ≤28 days from date of randomisation.

3.2.2.2.3 Calls at 7, 14, 28 days

Admitted to hospital [**HOSP_HOOCCUR** = 1] AND was the admission related to suspected COVID-19 infection [**CVYN** = 1] AND admitted overnight [**HOSP_NIGHTYN** = 1] AND first date of overnight hospital stay (**HOSP_HOSTDAT**) is ≤28 days from date of randomisation.

3.2.2.2.4 Notes review

Participant attended hospital [**HOSP_HOOCCUR** = 1] AND attendance likely related to COVID-19 [**CVYN** = 1] AND admitted overnight [**HOSP_NIGHTYN**=1] AND date they went to hospital is ≤28 days from date of randomisation.

If either hospital admission (as derived above) OR mortality (as derived above) occurs then this primary outcome has occurred (Primary outcome = 1).

Early versions of online daily diaries and call CRF did not include a qualification for suspected COVID-19 infection so these will be cross checked with the SAE data. Any hospitalisation or death not thought to be related to suspected COVID-19 should be recorded as an SAE.

3.3 SECONDARY OUTCOMES

3.3.1 PATIENT REPORTED ILLNESS SEVERITY

Participants are asked to rate how well they are feeling each day on a scale of 1-10 (1 being the worst and 10 being the best). This is captured on the participants' daily diaries and the Call CRF.

Day 7, 14 and 28 data will be obtained from the call CRF if not available in the daily diary.

Four variables will be derived; illness severity on day 7, illness severity on day 14, illness severity on day 21 and illness severity on day 28. If day 7, 14 or 28 is not available from the daily diaries, then data from the call CRF will be used. If no data available from diaries or calls on days 7, 14, 21 and 28 illness severity will be regarded as missing for that time point.

3.3.2 DURATION OF SEVERE SYMPTOMS

Participants are asked to rate their symptoms of fever, cough, shortness of breath, muscle ache, nausea/vomiting, diarrhoea, generally feeling unwell, loss of smell/taste (added 26th February 2021) and headache (added 26th February 2021) on a four point scale from 0=no problem, 1=mild problem, 2=moderate problem and 3=major problem. From the start of the trial until 22nd March 2021 participants were asked to rate their symptoms whilst they did NOT feel recovered. From 23rd March 2021 participants were asked to rate symptoms irrespective of recovery.

'Severe' symptoms will be defined as a score of 3 (major) on the four point rating scale.

For time to event outcomes for overall symptoms, the following symptoms will be considered; fever, cough, shortness of breath, muscle ache, nausea/vomiting, diarrhoea, generally unwell, loss of smell/taste and headache.

Participants can have a missing symptom severity rating for the following reasons

- Participant feels recovered so was not required to complete symptom data (before 23rd March 2021)
- Symptom was added to daily diary CRF at a later date than when patient completed the diary

If a participant has reported they have recovered AND not rated individual symptoms, they will be assumed to have a rating of 0 for symptom severity for each symptom not rated.

For each participant, only symptoms that were collected at baseline will be used when assessing the overall and individual time to event symptom outcomes.

3.3.2.1 TIME TO ALLEVIATION OF SYMPTOMS

Time to alleviation of symptoms will be defined as the time from randomisation to all symptoms or each symptom being rated as mild or none among participants who reported that symptom at baseline. For those who have call data only, the time to alleviation will be defined as the day the call was made. Participants who die will be censored at 28 days. Patients who report none/mild symptoms at baseline will be censored at time 0. Participants who withdraw or are lost to follow-up will be censored at their last contact date (definition 2.2.2).

Time to alleviation of overall symptoms will be the time for all symptoms specified in section 3.3.2 to be rated as none or mild.

3.3.2.2 Time to initial reduction of severity of symptoms

Time to initial reduction of severity of symptoms will be defined as time from randomisation to reduction in severity of each individual symptom to at least one grade lower among participants who reported that symptom at baseline. For those who have call data only, the time that the symptoms reduced to at least one grade lower will be defined as the day the call was made. This will be calculated for each symptom and also for overall symptoms. Participants who withdraw or are lost to follow-up will be censored at their last contact date (definition 2.2.2). Participants who die will be censored at 28 days. Participants with symptoms rated as none at baseline will be censored at time 0.

3.3.2.3 Time to early Sustained Recovery

Time to early sustained recovery will be defined as the time from randomisation to first reported recovery on the question 'Do you feel recovered today?' with subsequent responses of 'yes' to this question until day 28. For those who have call data only, the time to sustained recovery will be defined as the date at which they felt recovered or if this information is missing, the date the call was made. Subsequent calls must report feeling recovered. Participants who withdraw or are lost to follow-up will be censored at their last contact date (definition 2.2.2). Participants who die will be censored at 28 days. Where information from call data is not consistent with diary data, the diary data will take precedence. Where call data at days 7, 14 and 28 days report inconsistent dates of recovery, the date furthest from randomisation will be used as the date for early sustained recovery (assuming recovery sustained).

In addition a binary variable shall be derived as early sustained recovery or otherwise.

Early sustained recovery will be derived as being recovered within the first 14 days and reports feeling recovered for the next 14 days. Where the participant has only call data, they require to have reported feeling recovered at both 14 days and 28 days. Where participants have got incomplete diary data for days 14-28 and no call data at 28 days, they are classified as otherwise.

Only participants who have reached day 28 follow-up will be included in the analysis of time to early sustained recovery.

3.3.2.4 Time to Sustained symptoms alleviation

This will follow the same principle as time to initial reduction in severity of symptoms but there must be no subsequent symptom severity recorded as moderate or major among participants who reported that symptom at baseline. This will be calculated for individual symptoms separately and also for overall symptoms. Time to sustained alleviation for overall symptoms will be the time for all symptoms specified in section 3.3.2 to be rated as mild or none with no subsequent symptom severity coded as moderate or major.

3.3.2.5 WORSENING OF SYMPTOMS AFTER RANDOMISATION

Participants who report symptoms worsening over the period of 28 days follow up. Worsening of symptoms is defined as worsening symptom by at least one grade from none or mild to moderate/major or from moderate to major Those who report major symptoms at baseline will be excluded as they cannot get worse. Those who go from none to mild will not be considered as worsening. Worsening of symptoms will be calculated separately for each symptom and overall.

3.3.3 CONTACTS WITH HEALTH SERVICES BETWEEN RANDOMISATION AND DAY 28 OF FOLLOW-UP.

This will be split into participant reported health service use and health service use from GP records.

3.3.3.1 PARTICIPANT REPORTED HEALTH SERVICE USE

Sources of data for this outcome are participant daily diaries and telephone call CRF (day 7, day 14 and day 28).

This will be presented as 2 outcomes:

1. A binary outcome indicating whether the participant has had any contact with health services during 28 days of follow-up. This will be 'yes' if any of the following are recorded as yes in the daily diary or call CRF:

    - GP (**GP_HOOCCUR**)
    - Other primary care services (**PCS_HOOCCUR**)
    - NHS 111 and other central advice resources (**NHS_HOOCCUR**)
    - A&E (**AE_HOOCCUR**)
    - Hospital (**HOSP_HOOCCUR**)
    - Other (**OTH_HOOCCUR, OTH_HOOCCUR_DEF**– free text)

2. A continuous variable of the number of health service contacts whilst alive during 28 days of FU.

    The number of health service contacts from the diary data will be the total number of times the participant has responded 'yes' to any of the following:

    GP_HOOCCUR, PCS_HOOCCUR, NHS_OOCCUR, AE_OOCUR, OTH_OOCCUR

    If the diary data is missing then the call CRF data will be utilised. The number of health service contacts from the call CRF will be the total of the following for each of the 7, 14 and 28 day calls:

    GP_HOOCCURNUM, PCS_HOOCCURNUM, NHS_HOOCCURNUM, AE_HOOCCURNUM, OTH_HOOCCURNUM

3.3.3.2 HEALTH SERVICE USE FROM GP RECORDS

Data for this outcome will come from the GP notes review after 28 days.

This will be presented as 2 outcomes:

1. A binary outcome indicating whether the participant has had any contact with health services during 28 days of FU. This will be 'yes' if any of the following are recorded as yes in the notes review:
    - GP (**GP_HOOCCUR**)
    - Other primary care services (**PCS_HOOCCUR**)
    - NHS 111 and other national resources (**NHS_HOOCCUR**)
    - A&E (**AE_HOOCCUR**)
    - Hospital (**HOSP_HOOCCUR**)
    - Other (**OTH_HOOCCUR, OTH_HOOCCUR_DEF**– free text)

2. A continuous variable of the number of health service contacts whilst alive during 28 days of FU. This will be derived by totalling the following for those with a notes review:

    GP_NUM, PCS_NUM, NHS_NUM, AE_NUM, OTH_NUM

3.3.4 Prescribing of antibiotics between randomisation and day 28 of FU

Notes review at 28 days will record information regarding prescription of antibiotics.

- Antibiotic prescribed (Yes = 1, No=1) (**ATBYN**)

This outcome will consider prescription of antibiotics whilst alive to account for truncation by death.

3.3.4.1 Derivation of outcome

Antibiotic prescribed = Yes, IF prescribed antibiotic [**ATBYN**=1] AND start date of antibiotic ≤28 days from data of randomisation. If case note review is available for a participant but no information is provided regarding antibiotics, it will be assumed that NO antibiotic was prescribed. If no notes review is available for a participant this will be recorded as missing with respect to antibiotic prescribing.

3.3.5 Hospital assessment without admission

This is captured on patients' daily diaries, Call CRF, notes review and the death and hospitalisation CRF. All sources will be considered and if any indicates a hospital assessment without admission it will be coded as such. If there are discrepancies between the sources of data the diary data will be assumed to be correct.

3.3.5.1 Derivation

Notes review, patient diary and call CRF:

Hospital assessment without admission = YES if on any day the participant reports going to hospital [**HOSP_HOOCUR** = Yes] AND on that date they were not admitted overnight [**HOSP_NIGHTYN** = No]

Death and hospitalisation CRF:

Hospital assessment without admission = YES if the patient has been admitted to hospital since they joined the trial (**HOSP_HOOCCUR**=1) and Date of admission (**HOSP_HOSTDAT**) = date of discharge (**HOSP_HOENDAT_DD**)

3.3.6 Oxygen administration

This is captured in patients' daily diaries, Call CRF, Notes review and death and hospitalisation CRF.

This outcome will reflect oxygen administration whilst alive to account for truncation due to death

3.3.6.1 Derivation

Oxygen administration = yes if patient reports receiving oxygen whilst in hospital [**OXY_HOOCCUR**=Yes] AND date of admission to hospital is ≤28 days from date of randomisation.

If oxygen use is reported via any data source then it will be counted as yes.

3.3.7 Intensive care unit admission

This is captured in patients' daily diaries, Call CRF, Notes review and the death and hospitalisation CRF. It will be calculated in 2 ways:

1. To reflect ICU admission whilst alive to account for truncation due to death prior to ICU admission. This definition of the outcome would give an estimate of the requirement for ICU between the randomised groups from a healthcare resource use perspective. This is derived as:

   Intensive care unit admission = yes if report of participant staying in ICU [ICUYN=Yes or ICU_HOOCCUR=Yes] AND date of admission to ICU is ≤28 days from date of randomisation. If intensive care unit admission is reported via any data source then it will be counted as an ICU admission.

2. To consider this outcome from a patient benefit perspective the outcome will be defined as a composite by assigning a "poor" outcome (i.e. ICU admission) to participants who die before requiring ICU admission. This is derived as:

   Intensive care unit admission = yes if report of participant staying in ICU [**ICUYN**=Yes or **ICU_HOOCCUR**=Yes] AND date of admission to ICU is ≤28 days from date of randomisation) OR participant has died.

If an ICU admission is recorded on any data source then it will be coded as an ICU admission.

3.3.8 MECHANICAL VENTILATION.

a. This outcome will reflect mechanical ventilation whilst alive to account for truncation due to death. This definition of the outcome would give an estimate of the requirement for ventilation between the randomised groups from a healthcare resource use perspective.
b. To consider this outcome from a patient benefit perspective the outcome will be defined as a composite by assigning a "poor" outcome to participants who die before requiring ventilation.

This is captured in patients' daily diaries, Call CRF, Notes review and death and hospitalisation CRF and captured from the question related to receiving mechanical ventilation.

3.3.8.1 DERIVATION

(a) Mechanical ventilation = yes if report of participant on mechanical ventilation [**MV_HOOCCUR**=Yes] AND date of admission to hospital is ≤28 days from date of randomisation.
(b) Mechanical ventilation = yes if participant dies OR (participant on mechanical ventilation AND date of admission to hospital is ≤28 days from date of randomisation [**MV_HOOCCUR**=Yes])

If mechanical ventilation is recorded on any data source then it will be coded as mechanical ventilation=YES.

3.3.9 DURATION OF HOSPITAL ADMISSION

This is captured in patient diaries, Call CRF, notes review and death and hospitalisation CRF.

The duration of hospital admission is calculated in the following ways from the different data sources:

Notes review: **HOSP_DUR**

Death and hospitalisation CRF: Difference between date of admission and date of discharge

Participant diaries: **HOSP_DUR**

Call CRF: **HOSP_NONIGHTS**

If a participant has been admitted with suspected COVID-19 more than once in the FU period of 28 days, the duration of hospital stay will be the sum of all admissions during FU, truncated at day 28.

All sources of data will be considered and if any indicates a hospital stay it will be coded as such. If there are discrepancies between the sources of data the diary data will be assumed to be correct. Only participants with a hospitalisation likely to be related to COVID-19 will be included in the analysis.

Participants admitted with likely COVID-19 and who die whilst in hospital will not be included in the estimate of mean duration and the number in each arm who die whilst in hospital will be reported in a footnote.

3.3.10 Negative effect on well-being (WHO-5)

Well-being is measured using the WHO well-being index which includes 5 items relating to well-being measured on a five point scale (scale of 5 =all of the time, 4=most of the time, 3=more than half the time, 2=less than half the time, 1=some of the time, 0=at no time). A total score is computed by summing the scores to the five individual questions to give a raw score ranging from 0 to 25 which is then multiplied by 4 to give the final score from 0 representing the worst imaginable well-being to 100 representing the best imaginable well-being. Negative effect on well-being is collected at baseline, 14 days and 28 days via the daily diary and call CRF.

From a patient benefit perspective participants who die before the measured time point will be given a score of 0 for that time point and included in the analysis.

3.3.11 WHO Ordinal Scale of Clinical Progression

There are various versions of this scale. We will use a score based on a number of factors including hospitalisation, use of oxygen, ventilation and death. It ranges from 1 (not hospitalised) to 6 (dead) and is defined as follows:

1 = Not hospitalised

2 = Hospitalised without need for supplemental oxygen

3 = Hospitalised with need for supplemental oxygen

4 = Hospitalised with need for non-invasive positive pressure ventilation or high-flow nasal cannula

5 = Hospitalised with need for mechanical ventilation or extracorporeal membrane oxygenation

6 = Death

This outcome will be derived at days 7, 14 and 28.

3.3.12 New infections in the household

This will be coded as 'yes' if the answer to the question "has anybody else in your house become unwell today with a respiratory illness?" is yes in the daily diary and/or the telephone call CRF at any time during the 28 days after randomisation.

3.3.13 Safety of treatments not licensed in the UK

For each treatment not licensed in the UK, the following AEs from the start of medication until the specified follow-up period, will be assessed by a clinician for causality and severity (See protocol for definitions): i) pre-defined AEs detailed in the intervention specific appendices (ISA) that are rated by the participant as 'moderate' and ii) other reported 'major' AEs. Severity will be rated by the clinician

as Grade 1 (mild), grade 2 (moderate) and grade 3 (severe).Derivation of COVID-19 positive test result population

3.3.14 ALL CAUSE DEATH OR NON-ELECTIVE/URGENT HOSPITALISATION WITHIN 28 DAYS OF RANDOMISATION

The derivation will follow that detailed in sections 3.2.2.1 and 3.2.2.2 with no requirement for cause of death or reason for admission to be related to suspected COVID-19. Hospitalisations will be limited to non-elective/urgent admissions.

4 ANALYSIS – GENERAL CONSIDERATIONS

The following sections detail the final analysis for any treatment comparison within 28 days of randomisation. Methods for the primary analyses, including interim analyses, are specified in the Adaptive Design Report.

4.1 PARTICIPANT THROUGHPUT

The flow of participants through the trial will be reported following CONSORT and will include number of participants randomly assigned, receiving allocated treatment, followed up, withdrawn and analysed for primary outcome. Protocol deviations and information regarding screening information and number of ineligible participants randomised will be reported.

4.2 DESCRIPTIVE STATISTICS

Baseline characteristics of participants will be summarised both overall and by randomised group, including stratification factors and important prognostic, demographic and clinical characteristics. Binary and unordered categorical variables will be summarised using number, number missing and proportions. Continuous variables that are approximately normally distributed will be summarised using number, number missing, mean and standard deviation. Continuous variables that are not normally distributed or ordered categorical variables will be summarised using number, number missing, median and interquartile range.

There will be no tests of statistical significance nor confidence intervals for differences between randomised groups with respect to any baseline variable.

4.3 CHARACTERISTICS OF PARTICIPANTS

Characteristics of participants to be described include age, sex (male/female/other), presence of comorbidities (Asthma COPD or other lung disease, Diabetes, Heart problems, High blood pressure, Liver disease, Stroke or other neurological problem), duration of symptoms prior to randomisation, symptoms (fever, cough shortness of breath, muscle ache and nausea/vomiting, other) rated as no problem, mild, moderate or major, medications, use of antibiotics , contact with health care services (GP, other primary care services, NHS 111, A&E, Hospital and other), test results for SARS-CoV-2 infection (not tested, missing, positive, negative), care home residency and ethnicity (collected at 28 days in addition to baseline in case these data were missed at baseline). Stratification factors will be described.

Tables of baseline characteristics will include only participants in the analysis population (as per section 4.6 i.e. excluded participants post randomisation will not be included). The number of randomised participants excluded from the analysis will be reported.

4.4 DESCRIPTION OF AVAILABLE DATA

The number of participants with available data for primary and secondary outcomes for the final analysis will be reported by treatment group.

Details describing methods for dealing with missing data with respect to the primary outcome will be described within the Adaptive Design Report (ADR).

4.5 COMPLIANCE WITH MEDICATION

Participants are asked in the online daily diaries to record whether they have taken their medication and if not, the reason why. The call CRF records the number of days they took the trial medication. For participants in randomised groups receiving medication, compliance with medication will be reported. The number of days that the allocated medication was taken will be reported along with withdrawals from treatment.

4.6 DEFINITION OF POPULATION FOR ANALYSIS

The analysis population will include all participants as defined by the protocol eligibility criteria.
As per ICH E9 guidance the following participants will be excluded from the analysis population;
(a) Participants randomised but subsequently found to be not eligible for randomization
(b) Participants previously randomised to an arm in the PRINCIPLE trial (subsequent randomisations will be excluded)
In addition, the following participants will be excluded;
(c) Participants who withdraw consent for data linkage and notes review and for whom no outcome data has been collected.

4.6.1 PRIMARY ANALYSIS POPULATION

The primary analysis population is defined as all randomised participants with a COVID-19 positive test for whom data were available with participants analysed according to the groups they were randomly allocated to, regardless of deviation from protocol. In the setting of an adaptive platform trial with sequential overlap of treatment arms, the primary analysis for each intervention may be based on a distinct population. For each intervention that stops randomisation (due to futility) or becomes standard of care (due to superiority) based on interim analysis criteria, the date of the implementation of change in randomisation per interim decision will determine the intervention primary analysis population. For example, if randomisation is stopped for an intervention due to interim futility criteria, the final primary analysis includes all trial participants enrolled up to the date when randomisation was stopped to that intervention. If the randomisation is stopped for an intervention for other reasons (e.g. external reasons not related to the trial design), the primary analysis population will be specified in the intervention specific Appendix. Generally speaking, the primary analysis for a given intervention

will be based on complete 28-day follow-up of these participants, but the duration of follow-up may be impacted by public disclosure of interim results as determined by the Trial Management Group.

4.6.2 Concurrent Randomised and Eligible Analysis population

Analysis of the secondary outcomes for a given intervention will be based on participants who were randomised to the usual care arm during the same time frame when the intervention was actively randomised and who were eligible for randomisation to the intervention (i.e. Concurrent Randomised and Eligible Analysis Population).

4.6.3 Concurrent Randomisation Analysis Population

Sensitivity analyses of the primary analysis for a given intervention will be based on participants with a positive COVID-19 test result randomised during the same time frame when the intervention was actively being randomised, i.e. a concurrent randomisation analysis population.

4.6.4 Safety Analysis Population

Safety analysis will be conducted on the as treated population (i.e. the treatment that participants have received). Participants randomised to receive an intervention, but whom do not receive , or do take at least one dose of the intervention or for whom there is no information will belong to the usual care (non-treatment arm) arm for the safety analysis. Safety analysis will be conducted using the concurrent randomisation population, irrespective of COVID-19 swab status.

4.7 Comparative analysis

For all outcomes the primary analysis will be performed on the primary analysis population at 28 days after randomisation.

Each treatment arm will be compared with the usual care arm. If a treatment is deemed superior to usual care on both co-primary endpoints and replaces the usual care arm as the new standard of care, subsequent treatments will be compared with the original usual care arm.

There will be no formal adjustment for multiple comparisons.

4.8 Pooling of investigational sites

Data from all sites will be combined and analysed collectively. A sensitivity analysis of the primary outcomes may be carried out adjusting for geographical clinical research network (CRN) if deemed necessary.

4.9 Data Monitoring Committee And Interim Analyses

Details of the data monitoring committee and interim analyses can be found in the interim analysis report and the DMC charter.

5 PRIMARY ANALYSIS

5.1 PRIMARY OUTCOMES

Refer to ADR for details.

5.1.1 SUMMARY OF BAYESIAN ANALYSES TO BE CONDUCTED BY STATISTICAL ANALYSIS COMMITTEE

Below is a summary of the pre-specified Bayesian analyses that may be requested from the Statistical Analysis Committee (SAC) for interventions that stop randomisation (due to futility) or become standard of care (due to superiority) based on interim analysis criteria:

B1. Bayesian interim analysis that satisfies the interim decision criteria

a. Details in ADR
b. Subgroup estimates from Bayesian model corresponding to categories in ADR

B2. Bayesian primary analysis on "final data"

a. Details in ADR
b. Include subgroup estimates

B3. Sensitivity analysis: Repeat Bayesian primary analysis on concurrent randomisation analysis population

a. Details in ADR
b. Include subgroup estimates

B4. Secondary analysis: Repeat Bayesian primary analysis on overall population (i.e. regardless of COVID-19 test status). These models will be identical to the primary analysis models, but will include an additional baseline covariate and corresponding parameters for COVID-19 status (negative, positive, unknown).

a. Details in ADR
b. Includes subgroup estimates

The specific pre-specified Bayesian analyses required for each intervention will be specified in the intervention specific appendices (III to IX).

6 SECONDARY ANALYSIS

6.1 PRIMARY OUTCOME ON OVERALL POPULATION

The primary outcomes will be analysed using the same method as detailed in the adaptive design report, but using the overall population with additional baseline covariate for COVID-19 test status, where applicable (see B4 above).

6.2 SECONDARY OUTCOMES

For all secondary outcomes, the analysis will compare each treatment arm with the usual care arm, in a pairwise comparison. For each analysis the Concurrent Randomisation and Eligible Analysis Population will be used. The analysis will be conducted on the Concurrent Randomisation and Eligible Analysis population with a COVID-19 positive test result. Regression models (appropriate for each endpoint) will include randomised group (treatment/usual care) and stratification factors (age (continuous), comorbidity (Yes/no)). They will also include duration of illness at randomisation and vaccination status (as far as possible). Should it be necessary to compare more than one intervention with control at the same time, a covariate indicating which arms of the trial the participant was eligible to be randomised to will also be included. For binary outcomes with a low event rate, results will be reported descriptively by treatment group and a Chi-square test or Fisher's exact test may be used instead of the analysis detailed below. For continuous outcomes where the data are skewed, alternative non-parametric methods will be considered.

6.2.1 PATIENT REPORTED ILLNESS SEVERITY

A linear mixed model will be used to analyse this outcome. The illness severity at each time point (7, 14, 21 and 28 days) will be included as the response variable, along with randomised group, age, presence of comorbidity, eligibility for treatment arm, duration of illness prior to randomisation vaccination status and time as fixed effects. Participant will be included as a random effect. Mean scores at each time point by randomised group will be described graphically.

6.2.2 DURATION OF SEVERE SYMPTOMS

6.2.2.1 TIME TO ALLEVIATION OF SYMPTOMS

Time to alleviation of symptoms will be compared between each treatment arm with the usual care arm using Cox proportional hazards model, adjusting for randomised group, age and presence of comorbidity at baseline. The model will also be adjusted for duration of illness (days) prior to randomisation and vaccination status. This will be calculated as the date of randomisation minus the start date of symptoms as reported on the screening CRF. If this date is unavailable then the date the patient registered with Principle will be used. The adjusted hazard ratio and 95% CI will be estimated from the model. A Kaplan Meier plot will also be presented. If the assumption of proportionality is not met, then an alternative survival model such as restricted mean survival method will be used.

Separate analyses will be carried out for overall and for each symptom separately.

6.2.2.2 TIME TO INITIAL REDUCTION OF SEVERITY OF SYMPTOMS

This will be analysed using the method described for time to alleviation of symptoms.

6.2.2.3 TIME TO SUSTAINED RECOVERY

This will be analysed using the method described for time to alleviation of symptoms.

6.2.2.4 TIME TO SUSTAINED SYMPTOMS ALLEVIATION

This will be analysed using the method described for time to alleviation of symptoms.

6.2.2.5 WORSENING OF SYMPTOMS AFTER RANDOMISATION

The number and percentage of participants with worsening of symptoms after randomisation will be presented for treatment and usual care groups. This outcome will be analysed using a logistic regression model. Randomised group, age, presence of comorbidity, duration of illness and vaccination status will be included as covariates. The adjusted odds ratios will be reported for each pairwise comparison along with their associated 95% confidence interval and P-value. In addition, the adjusted absolute risk differences will be reported.

6.2.3 CONTACTS WITH HEALTH CARE SERVICES

The number and percentage of participants with at least one contact with health services will be presented for treatment and usual care groups. This outcome will be analysed using a logistic regression model. Randomised group, age, presence of comorbidity, duration of illness and vaccination status will be included as covariates. The adjusted odds ratios will be reported for each pairwise comparison along with their associated 95% confidence interval and P-value. In addition, the adjusted absolute risk differences will be reported.

The number of contacts with health care services over 28 days will be analysed using a Poisson model. Randomised group, age, presence of comorbidity, duration of illness and vaccination status will be included as covariates. Adjusted incidence ratios will be presented with their 95% confidence intervals and related P value.

6.2.4 PRESCRIBING OF ANTIBIOTICS

The count and percentage of participants with an antibiotic prescription will be presented for each treatment group. This outcome will be analysed using a logistic regression model. Randomised group, age, presence of comorbidity, duration of illness and vaccination status will be included as covariates. The adjusted odds ratios will be reported for each pairwise comparison along with their associated 95% confidence interval and P-value. In addition, the adjusted absolute risk differences will be reported.

6.2.5 HOSPITAL ASSESSMENT WITHOUT ADMISSION

The count and percentage of participants with hospital assessment without admission will be presented for each treatment group. This outcome will be analysed using a logistic regression model. Randomised group, age, presence of comorbidity, duration of illness and vaccination status will be included as covariates. The adjusted odds ratios will be reported for each pairwise comparison along with their associated 95% confidence interval and P-value. In addition, the adjusted absolute risk differences will be reported.

6.2.6 OXYGEN ADMINISTRATION

The count and percentage of participants with oxygen administration will be presented for each treatment group. This outcome will be analysed using a logistic regression model. Randomised group, age, presence of comorbidity, duration of illness and vaccination status will be included as covariates. The adjusted odds ratios will be reported for each pairwise comparison along with their associated 95% confidence interval and P-value. In addition, the adjusted absolute risk differences will be reported.

6.2.7 Intensive care unit admission

The count and percentage of participants with intensive care unit administration will be presented for each treatment group. This outcome will be analysed using a logistic regression model. Randomised group, age, presence of comorbidity, duration of illness and vaccination status will be included as covariates. The adjusted odds ratios will be reported for each pairwise comparison along with their associated 95% confidence interval and P-value. In addition, the adjusted absolute risk differences will be reported.

6.2.8 Mechanical ventilation

The count and percentage of participants with mechanical ventilation will be presented for each treatment group. This outcome will be analysed using a logistic regression model. Randomised group, age, presence of comorbidity, duration of illness and vaccination status will be included as covariates. The adjusted odds ratios will be reported for each pairwise comparison along with their associated 95% confidence interval and P-value. In addition, the adjusted absolute risk differences will be reported.

6.2.9 Duration of hospital admission

The mean duration of hospital admission will only be considered for those with a hospital admission and will be compared between each treatment arm with the usual care arm using a multiple linear regression model. The model will include outcome as the response variable, randomised group, age, presence of comorbidity, duration of illness and vaccination status as covariates. The mean (SD) duration will be presented in each group and the adjusted difference in means and 95% CI for each pairwise treatment arm comparison with the usual care group.

6.2.10 Well-being

The distribution of the WHO well-being index will be considered. Assuming there are not a large number of deaths or hospitalisations, a linear mixed effect model will be fitted to the data. Baseline well-being score will be fitted as a covariate in the model. Fixed effects will include randomised group, age, presence of comorbidity, duration of illness, vaccination status, time and a time x randomised group interaction. The mean (SD) well-being score at 14 and 28 days will be reported for each group and the adjusted difference in means (95% CI) for each pairwise treatment comparison with the usual care group will be presented.

6.2.11 WHO Ordinal Scale of Clinical Progression

If the data are available to calculate this scale then the following analysis will be carried out. The number and percentage of participants on each level of the scale will be presented by treatment group at days 7, 14 and 28. The outcome will be analysed using an ordinal logistic regression model, including the following covariates: randomised group; age; presence of comorbidity, duration of illness and vaccination status.

6.2.12 New infections in the Household

The count and percentage of participants with a new infection in the household will be presented for each treatment group. This outcome will be analysed using a logistic regression model. Randomised

group, age, presence of comorbidity, duration of illness and vaccination status will be included as covariates. The adjusted odds ratios will be reported for each pairwise comparison along with their associated 95% confidence interval and P-value. In addition, the adjusted absolute risk differences will be reported.

6.2.13 Safety of treatments not licensed in the UK

For treatment arms that are not licensed in the UK, the number and percentage of participants reporting AEs will be reported by grade of severity.

6.2.14 All cause mortality and hospitalisation within 28 days of randomisation

The count and percentage of participants with all cause mortality or hospital admission will be presented for each treatment group. This outcome will be analysed using a logistic regression model. Randomised group, age, presence of comorbidity, duration of illness and vaccination status will be included as covariates. The adjusted odds ratios will be reported for each pairwise comparison along with their associated 95% confidence interval and P-value. In addition, the adjusted absolute risk differences will be reported.

6.3 Handling missing data

Participants who withdraw or are lost to FU will be included in the primary analysis and censored at last contact date. Participants with complete missing data (e.g. no diaries or calls) for a given endpoint will not contribute data to the respective primary analysis. The proportion of participants contributing no data to the respective primary analysis is expected to be low. Various imputation strategies will be considered when the proportion of participants contributing no data exceeds 15%.

6.4 Multiple comparisons and multiplicity

There will be no adjustment for multiplicity in the analysis of secondary outcomes.

6.5 Model assumptions

For the analysis of the secondary outcomes, model diagnostics will be checked.

7 Sensitivity analysis of co-primary outcomes using concurrent randomised analysis population

Upon conclusion of the study or intervention (and at interims as needed), a stand-alone sensitivity analysis of each co-primary analysis will be conducted for each completed intervention, in which each intervention is compared to Usual Care using the concurrent randomisation analysis population. These analyses will take the same form as the primary analysis models but may require modified priors/parameters for the temporal adjustment (carried out by the SAC and detailed in ADR and section 5.1 M-SAP). For some interventions (e.g. hydroxychloroquine), temporal adjustment may not be necessary for this sensitivity analysis.

8 SUBGROUP ESTIMATES

Model-based estimated treatment group differences in median time to recovery will be provided for each of the covariate subgroups with 95% Bayesian credible intervals from the first co-primary analysis model. Similarly, model-based estimated differences in hospitalization rates will be provided for each of the covariate subgroups with 95% Bayesian credible intervals from the second co-primary analysis model (carried out by the SAC refer to section 5.1 M-SAP).

9 MODERATION ANALYSIS

Moderation analyses of the time to recovery and death or hospitalisation outcomes will be carried out. Time to recovery will be analysed using the model specified for the analysis of time to alleviation of symptoms (section 6.2.2.1) and death or hospitalisation will be carried out using the same model used for other secondary binary outcomes (logistic regression model with randomised group, age and presence of comorbidity, duration of illness and vaccination status included as covariates). In addition the models will include an interaction between treatment group and the subgroup of interest. The P-values for the interaction effects will be presented and forest plots presented to show the effects in each subgroup and overall. Unless specified in the intervention specific appendices, the following analyses will be undertaken.

- Age group (<65/≥65 years)
- Presence of comorbidity at baseline (yes/no)
- Duration of symptoms prior to randomisation (this will be assessed as both a continuous outcome and using a cut off of ≤7 days vs. >7 days)
- Severity of symptoms at baseline (at least one symptom rated major vs no symptoms rated major)
- Using an inhaled corticosteroid steroid (ICS) at randomisation or during 28 days of FU (Yes v No). Participant report will be taken as the primary source and only if missing will prescription of ICS in the two months prior to randomisation or during follow up from notes review or NHS Digital be considered.

10 SAFETY ANALYSIS

10.1 ADVERSE EVENTS

Number and severity of serious adverse events (SAE) will be summarised across treatment arms using numbers and proportions.

Frequencies and percentages of adverse events (AE) will be reported. Details in the intervention specific appendices.

11 VALIDATION

The analysis of the primary outcome will be validated by a second statistician from the SAC. The final analysis of the secondary and safety outcomes will be validated by a Senior Trial Statistician or suitably qualified delegate from Oxford PC-CTU.

12 CHANGES TO THE PROTOCOL OR PREVIOUS VERSIONS OF SAP

The current protocol (V11.0) has an outcome of 'consumption of antibiotics'. Information regarding antibiotics has only been collected in the notes review and therefore relates to prescriptions of antibiotics rather than patient reported consumption.

This SAP incudes an additional secondary outcome "All cause death or non-elective/urgent hospitalisation within 28 days of randomisation" which is not specified in the protocol (v11.0).

Protocol version 11.0 states that Clinical data, and information from swab and blood tests, where available, will be used to classify participants according to aetiology. Blood test results have not been used to define the infected population for the intention to treat infected analyses.

13 APPENDICES

13.1 APPENDIX I. SCHEDULE OF PROCEDURES

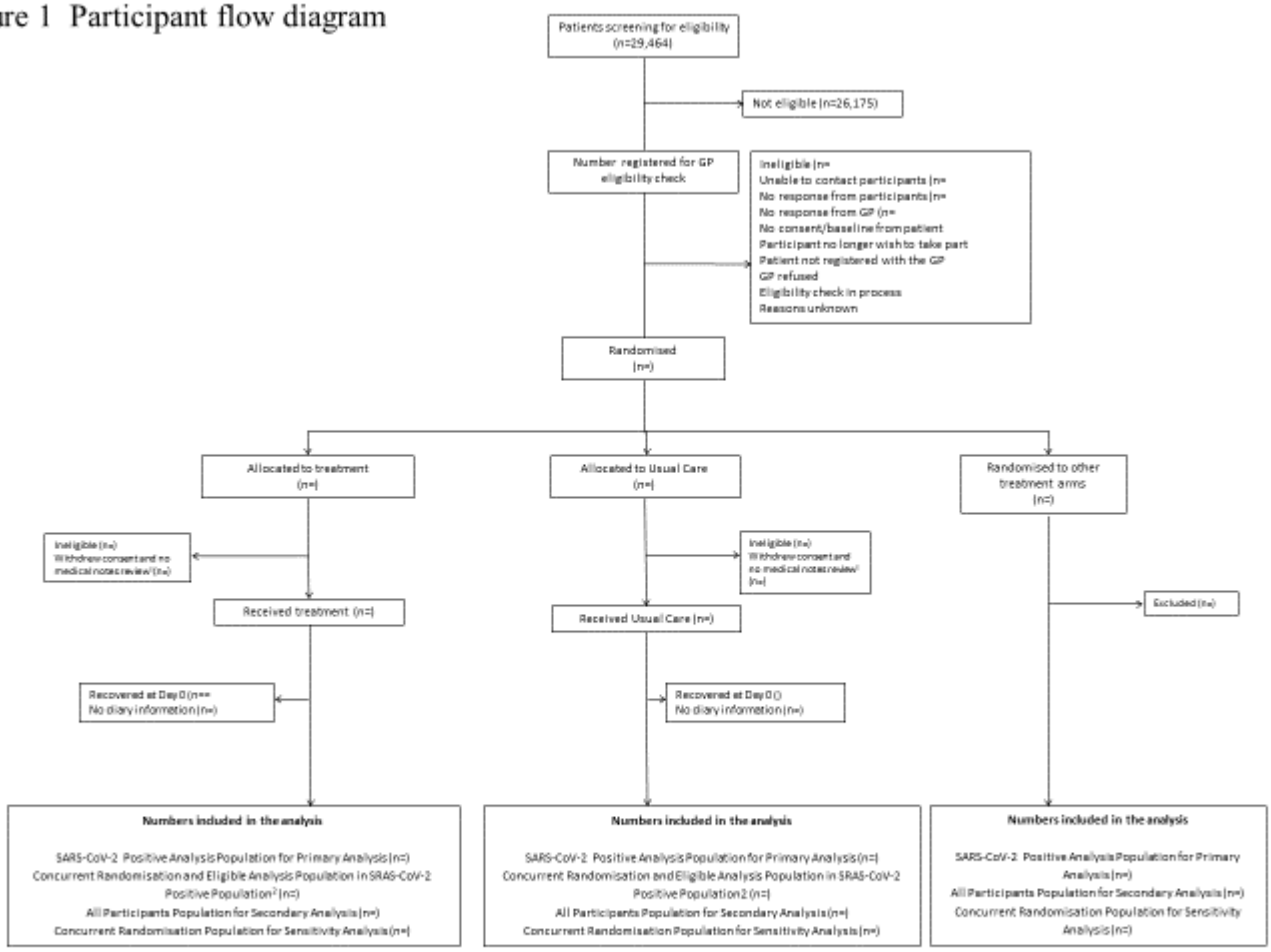
Procedures	**Participant contacts**							
	Visit timing **Day 0**	**Day 0**	**Day 0**	**Day 0**	**Daily Day 1-28 incl**	**Day 28-12 months (monthly contact)**	**Day 29-12mths**	**Up to 10 years**
	Screening completed by participant online/phone	**Eligibility completed by participant online/phone**	**Baseline completed by participant online/phone**	**Eligibility completed by Clinician online/phone**	**Symptom Diaries completed by participant online/phone**	**Contacted by study team if consent provided**	**Retrospective data collection by study team**	**By data extraction from clinical records**
Informed consent	X	X	X	X	X			
Demographics	X	X	X				X	
Medical history	X	X	X	X			X	

Swab as part of the RCGP RSC/PHE national surveillance programme	When available, preferably by self-swabbing at study entry							
Concomitant medications		X					X	
Eligibility assessment	X	X						
Randomisation				X				
Dispensing of trial drugs				X	X			
Questionnaire					X	X		
WHO 5 Well Being Index	X				Day 14 and day 28	X		
Telephone interview (for subset of					X			

patient participants)								
Compliance					X			
Adverse event assessments					X*		X	
Optional SARS-CoV-2 blood test as part of the RCGP RSC/PHE national surveillance programme							X	
Evidence of sequalae and health care utilisation						X		X

13.2 APPENDIX II. FLOW DIAGRAM OF TRIAL PARTICIPANTS

Figure 1 Participant flow diagram



[1] Participants provided no diary information.
[2] Secondary outcomes only

13.3 APPENDIX III: PLANS FOR ANALYSIS OF HYDROXYCHLOROQUINE

POPULATION OF ANALYSIS

The primary analysis population for the co-primary outcomes is defined as all randomised participants for whom data were available with participants analysed according to the groups they were randomly allocated to, at the time of the first trial interim analysis regardless of deviation from protocol and irrespective of their COVID-19 status. Although, participants randomised to other treatment arms were included in this interim analysis, only results of the hydroxychloroquine intervention will be reported.

Sensitivity and secondary analyses will be based on all participants randomised up to the point when hydroxychloroquine stopped recruitment.

DESCRIPTIVE STATISTICS

Baseline characteristics of participants will be summarised both overall and by randomised group, for all participants up to the point when randomisation to hydroxychloroquine was stopped. Data will be summarised as described in the M-SAP.

PRIMARY OUTCOME ANALYSIS

Analysis of the co-primary outcomes, i.e. time-to-recovery from randomisation and hospitalisation or death at 28 days from randomisation, are detailed in the Adaptive Design Report. Because Hydroxychloroquine was stopped for external reasons not related to the trial design, the primary analysis for Hydroxychloroquine is based on all participants enrolled up to 30th November 2020 . This date coincides with the date that randomisation was stopped to Azithromycin per interim futility criteria, and is meant to optimise precision of the Hydroxychloroquine analysis. Data from participants allocated to the hydroxychloroquine arm, and all control participants' data available at the time of the first interim analysis will be used, so there will be more control participants in the primary analysis than participants allocated to the hydroxychloroquine arm contributing to the primary analyses. However, due to the general lack of availability of swab tests during the Hydroxychloroquine testing phase, secondary analyses on the SARS-CoV-2 positive population will not be performed.

Analysis	**Date last participant randomised to be included in the analysis**	**Duration Follow-up**	**Date of data transfer/lock**
HCQ	30th Nov 2020	28 days	11th Jan 2021

SPECIFIC SENSITIVITY AND SECONDARY ANALYSIS OF PRIMARY OUTCOME

Bayesian analysis B2 and B3 (Section 5.1 M-SAP) will be requested.

CONCURRENT RANDOMISATION ANALYSIS POPULATION

	Date first participant randomised	**Date last participant randomised**	**Duration Follow-up**	**Date of data transfer/lock**
HCQ	2nd April 2020	22nd May 2020	28 days	11th Jan 2021

SECONDARY OUTCOME ANALYSIS

Secondary outcomes will be analysed as described in the M-SAP. All secondary outcomes will be analysed as detailed in the M-SAP.

ANALYSIS OF SAFETY DATA

All serious adverse events will be reported as described in the M-SAP.

13.4 APPENDIX IV: PLANS FOR ANALYSIS OF AZITHROMYCIN

POPULATION OF ANALYSIS

The primary analysis population for the co-primary outcomes is defined as all randomised participants for whom data were available with participants analysed according to the groups they were randomly allocated to, at the time of the interim analysis regardless of deviation from protocol and irrespective of their COVID-19 status. Although, participants randomised to other treatment arms were included in this interim analysis, only results of the azithromycin intervention will be reported.

Sensitivity and secondary analyses will be based on all participants randomised between the first and last dates a patient was randomised to receive azithromycin. Only concurrent controls eligible for the azithromycin arm will be included.

DESCRIPTIVE STATISTICS

Baseline characteristics of participants will be summarised both overall and by randomised group, for all participants included in the primary analysis population. Data will be summarised as described in the M-SAP.

PRIMARY OUTCOME ANALYSIS

Analysis of the co-primary outcomes, i.e. time-to-recovery from randomisation and hospitalisation or death at 28 days from randomisation, are detailed in the Adaptive Design Report. All relevant data available at the time of the interim will be used in the primary analysis.

Analysis	Date last participant randomised to be included in the analysis	Duration Follow-up	Date of data transfer/lock
Azithromycin	30th Nov 2020	28 days	11th Jan 2021

SPECIFIC SENSITIVITY AND SECONDARY ANALYSIS OF PRIMARY OUTCOME

Bayesian analysis B1, B2, B3, B4 (Section 5.1 M-SAP) will be requested.

CONCURRENT RANDOMISATION ANALYSIS POPULATION

	Date first participant randomised	Date last participant randomised	Duration Follow-up	Date of data transfer/lock
Azithromycin	23rd May 2020	30th Nov 2020	28 days	11th Jan 2021

SECONDARY OUTCOME ANALYSIS

Secondary outcomes will be analysed as described in the M-SAP. All secondary outcomes will be analysed as detailed in the M-SAP.

ANALYSIS OF SAFETY DATA

All serious adverse events will be reported as described in the M-SAP.

13.5 APPENDIX VI: PLANS FOR ANALYSIS OF DOXYCYCLINE

POPULATION OF ANALYSIS

The primary analysis population for the co-primary outcomes is defined as all randomised participants for whom data were available with participants analysed according to the groups they were randomly allocated to, at the time of the interim analysis regardless of deviation from protocol and irrespective of their COVID-19 status. Although, participants randomised to other treatment arms were included in this interim analysis, only results of the doxycycline intervention will be reported.

Sensitivity and secondary analyses will be based on all participants randomised between the first and last dates a patient was randomised to receive doxycycline. Only concurrent controls eligible for the doxycycline arm will be included.

DESCRIPTIVE STATISTICS

Baseline characteristics of participants will be summarised both overall and by randomised group, for all participants included in the primary analysis population. Data will be summarised as described in the M-SAP.

PRIMARY OUTCOME ANALYSIS

Analysis of the co-primary outcomes, i.e. time-to-recovery from randomisation and hospitalisation or death at 28 days from randomisation, are detailed in the Adaptive Design Report. All relevant data available at the time of the interim will be used in the primary analysis.

Analysis	Date last participant randomised to be included in the analysis	Duration Follow-up	Date of data transfer/lock
Doxycycline	14th Dec 2020	28 days	14th Jan 2021

SPECIFIC SENSITIVITY AND SECONDARY ANALYSIS OF PRIMARY OUTCOME

Bayesian analysis B1, B2, B3, B4 (Section 5.1 M-SAP) will be requested.

CONCURRENT RANDOMISATION ANALYSIS POPULATION

Analysis	Date first participant randomised	Date last participant randomised	Duration Follow-up	Date of data transfer/lock
Doxycycline	24th July 2020	14th Dec 2020	28 days	14th Jan 2021

SECONDARY OUTCOME ANALYSIS

Secondary outcomes will be analysed as described in the M-SAP. All secondary outcomes will be analysed as detailed in the M-SAP.

ANALYSIS OF SAFETY DATA

All serious adverse events will be reported as described in the M-SAP.

13.6 APPENDIX VI: PLANS FOR ANALYSIS OF INHALED CORTICOSTEROID BUDESONIDE

POPULATION OF ANALYSIS

The primary analysis population for the co-primary outcomes is defined as all randomised participants with a positive COVID-19 test result for whom data were available with participants analysed according to the groups they were randomly allocated to, at the time of the interim analysis regardless of deviation from protocol. Although, participants randomised to other treatment arms were included in this interim analysis, only results of the inhaled corticosteroid intervention will be reported.

Sensitivity and secondary analyses will be based on all participants randomised between the first and last dates a patient was randomised to receive inhaled corticosteroid. Only concurrent controls eligible for the inhaled corticosteroid arm will be included.

DESCRIPTIVE STATISTICS

Baseline characteristics of participants will be summarised both overall and by randomised group, for all participants included in the primary analysis population. Data will be summarised as described in the M-SAP.

PRIMARY OUTCOME ANALYSIS

Analysis of the co-primary outcomes, i.e. time-to-recovery from randomisation and hospitalisation or death at 28 days from randomisation, are detailed in the Adaptive Design Report. All relevant data available at the time of the interim will be used in the primary analysis.

SPECIFIC SENSITIVITY AND SECONDARY ANALYSIS OF PRIMARY OUTCOME

Bayesian analysis B1, B2, B3, B4(Section 5.1 M-SAP) will be requested.
Sensitivity analysis of co-primary outcomes using the concurrent randomised and eligible analysis population with a positive COVID-19 test result. Time to recovery will be analysed using Cox proportional hazards model, adjusting for randomised group, age, presence of comorbidity at baseline, duration of illness prior to randomisation and vaccination status. Death or hospitalisation will be carried out using a logistic regression model with randomised group, age and presence of comorbidity, duration of illness and vaccination status included as covariates. In addition, these models will be repeated on the concurrent randomised analysis population with a positive COVID-19 test result with additional adjustment for asthma/COPD at baseline as a surrogate for taking inhaled corticosteroid at baseline.

Date randomisation opened to budesonide	**Date randomisation closed to budesonide**	**Duration Follow-up**	**Date of data transfer/lock**
27th November 2020	31st March 2021	28 days	19th May 2021

SECONDARY OUTCOME ANALYSIS

Secondary outcomes will be analysed as described in the M-SAP. All secondary outcomes will be analysed as detailed in the M-SAP.

ANALYSIS OF SAFETY DATA

All serious adverse events will be reported as described in the M-SAP.

13.7 Appendix VII: plans for analysis of colchicine

Population of Analysis

The primary analysis population for the co-primary outcomes is defined as all randomised participants with a positive COVID-19 test result for whom data were available with participants analysed according to the groups they were randomly allocated to, at the time of the interim analysis regardless of deviation from protocol. Although, participants randomised to other treatment arms were included in this interim analysis, only results of the colchicine intervention will be reported.

Descriptive statistics

Baseline characteristics of participants will be summarised both overall and by randomised group, for all participants included in the primary analysis population. Data will be summarised as described in the M-SAP.

Primary Outcome Analysis

Analysis of the co-primary outcomes, i.e. time-to-recovery from randomisation and hospitalisation or death at 28 days from randomisation, are detailed in the Adaptive Design Report. All relevant data available at the time of the interim will be used in the primary analysis.

Specific sensitivity and secondary analysis of Primary Outcome

Bayesian analysis B1, B2, B3, B4 (Section 5.1 M-SAP) will be requested.

Date randomisation opened to colchicine	**Date randomisation closed to colchicine**	**Duration Follow-up**	**Date of data transfer/lock**
4th March 2021	26th May 2021	28 days	5th July 2021

Secondary Outcome Analysis

Secondary outcomes will be analysed as described in the M-SAP. All secondary outcomes will be analysed as detailed in the M-SAP.

Analysis of Safety Data

All serious adverse events will be reported as described in the M-SAP. AEs are monitored daily whilst the participant is taking the drug. Events rated as a 'major problem' (except loss of smell and/or taste) will be assessed by a clinician for potential reporting as an SAE, for the 14 days of IMP treatment. Pregnancy in the study will be reported as an AE.

Duration of IMP treatment: 14 days
Duration of AE reporting: 14 days

MODERATION ANALYSIS

The following moderation analyses or modification to subgroups will be carried out in addition to those specified in section 9.0

- Age (<50, 50-64, ≥65)
- Shortness of breath at baseline (no problem vs mild/moderate/major)

13.8 APPENDIX VIII: PLANS FOR ANALYSIS OF FAVIPIRAVIR

Population of Analysis

The primary analysis population for the co-primary outcomes is defined as all randomised patients with a positive COVID-19 test result for whom data were available with participants analysed according to the groups they were randomly allocated to, at the time of the interim analysis regardless of deviation from protocol. Although, participants randomised to other treatment arms were included in this interim analysis, only results of the favipiravir intervention will be reported.

Descriptive statistics

Baseline characteristics of participants will be summarised both overall and by randomised group, for all participants included in the primary analysis population. Data will be summarised as described in the M-SAP.

Primary Outcome Analysis

Analysis of the co-primary outcomes, i.e. time-to-recovery from randomisation and hospitalisation or death at 28 days from randomisation, are detailed in the Adaptive Design Report. All relevant data available at the time of the interim will be used in the primary analysis.

Specific sensitivity and secondary analysis of Primary Outcome

Bayesian analysis B1, B2, B3, B4 (Section 5.1 M-SAP) will be requested.

Date randomisation opened to faviprivir	**Date randomisation closed to favipirivir**	**Duration Follow-up**	**Date of data transfer/lock**
8th April 2021		28 days	

Secondary Outcome Analysis

Secondary outcomes will be analysed as described in the M-SAP. All secondary outcomes will be analysed as detailed in the M-SAP. AEs will be reported by grade of severity.

Analysis of Safety Data

All serious adverse events will be reported as described in the M-SAP. AEs are monitored daily whilst the participant is taking the drug. Pre-defined AEs rated by the participant as 'moderate' and any symptoms reported as 'major' will be reported and assessed by a clinican for severity and causality.

Duration of treatment: 5 days
Duration of AE reporting: 5 days
Pre-defined AEs : Diarrhoea, nusea, headache, urinary tract infections, vomiting

13.9 APPENDIX IX: PLANS FOR ANALYSIS OF IVERMECTIN

Population of Analysis

The primary analysis population for the co-primary outcomes is defined as all randomised patients with a positive COVID-19 test result for whom data were available with participants analysed according to the groups they were randomly allocated to, at the time of the interim analysis regardless of deviation from protocol. Although, participants randomised to other treatment arms were included in this interim analysis, only results of the Ivermectin intervention will be reported.

Descriptive statistics

Baseline characteristics of participants will be summarised both overall and by randomised group, for all participants included in the primary analysis population. Data will be summarised as described in the M-SAP.

Primary Outcome Analysis

Analysis of the co-primary outcomes, i.e. time-to-recovery from randomisation and hospitalisation or death at 28 days from randomisation, are detailed in the Adaptive Design Report. All relevant data available at the time of the interim will be used in the primary analysis.

Specific sensitivity and secondary analysis of Primary Outcome

Bayesian analysis B1, B2, B3, B4 (Section 5.1 M-SAP) will be requested.

Date randomisation opened to ivermectin	Date randomisation closed to ivermectin	Duration Follow-up	Date of data transfer/lock
23rd June 2021		28 days	

Secondary Outcome Analysis

Secondary outcomes will be analysed as described in the M-SAP. All secondary outcomes will be analysed as detailed in the M-SAP. AEs will be reported by grade of severity.

Analysis of Safety Data

All serious adverse events will be reported as described in the M-SAP. AEs are monitored daily whilst the participant is taking the drug. Pre-defined AEs (visual disturbances, confusion, seizures) rated by the participant as 'moderate' or 'major' and any symptom reported as 'major' will be reported and assessed by a clinican for severity and causality. Pregnancy will be reported as an AE.

Duration of treatment: 3 days
Duration of AE reporting: 14 days from initial drug administration
Pre defined AEs: visual disturbances, confusion, seizures.

Moderation analyses

The following moderation analyses or modification to subgroups will be carried out in addition to those specified in section 9.0

- Age (<50, 50-64, ≥65)
- Shortness of breath at baseline (no problem vs mild/moderate/major)