Protocol

This Protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Zoe K. McQuilten, Balasubramanian Venkatesh, Vivekanand Jha, et al. Anticoagulation Strategies in Non–Critically Ill Patients with Covid-19. NEJM Evid.
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Trial Name:	Australasian COVID-19 Trial (ASCOT) ADAptive Platform Trial
Registration	ACTRN12620000445976 NCT04483960

NEJM Submission Documents for the Anticoagulation Domain Manuscript of the ASCOT ADAPT trial

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RE: NEJM Submission Documents for the Anticoagulation Domain Manuscript of the ASCOT ADAPT trial

At the onset of the pandemic, the Australasian COVID-19 Trial (ASCOT) (Denholm et al. 2020) was designed with a factorial design, incorporating 4 arms; 1) Standard Care; 2) Hydroxychloroquine (HCQ); 3) Lopinavir/Ritonavir; 4) Combination of Lopinavir/Ritonavir and Hydroxychloroquine.

After decisions by the SOLIDARITY and the RECOVERY trials to suspend their HCQ and anti-viral arms based on the absence of benefit, the ASCOT team also reviewed the evidence and decided to suspend these interventions and transitioned to an adaptive trial platform in August 2020 incorporating new treatment domains and interventions. The name of the trial was changed to ASCOT ADAPT (Denholm et al. 2022). It is still registered under the old CTN Registration Number (CT-2020-CTN-01218-1).

ASCOT ADAPT has multiple modules comprising a Core Protocol (overview and design features of the study), a Statistical Analysis Appendix (details and principles of the overall statistical analysis plan, models and stopping criteria), multiple Domain-Specific Appendices (detailing treatment interventions being studied in each domain), and separate Statistical Analysis Plans that further detail exact statistical analyses as specific domains close.

In the attached document, we have submitted both the original ASCOT protocol and amendments and the current ASCOT ADAPT protocol and amendments. We have also attached the Anticoagulation Domain Statistical Analysis Plan, finalised, date stamped on the 16th of May 2022 and posted on the ASCOT website, which is in the public domain. The database was locked on the 3rd of June 2022.

Please do not hesitate to contact us, if you need any further information.

Kind regards,
On behalf of the ASCOT trial investigators

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References

Denholm, J.T., Davis, J., Paterson, D., Roberts, J., Morpeth, S., Snelling, T., Zentner, D., Rees, M., O'Sullivan, M., Price, D. and Bowen, A., 2020. The Australasian COVID-19 Trial (ASCOT) to assess clinical outcomes in hospitalised patients with SARS-CoV-2 infection (COVID-19) treated with lopinavir/ritonavir and/or hydroxychloroquine compared to standard of care: A structured summary of a study protocol for a randomised controlled trial. Trials, 21(1), pp.1-3.

Denholm, J.T., Venkatesh, B., Davis, J., Bowen, A.C., Hammond, N.E., Jha, V., McPhee, G., McQuilten, Z., O'Sullivan, M.V., Paterson, D. and Price, D., 2022. ASCOT ADAPT study of COVID-19 therapeutics in hospitalised patients: an international multicentre adaptive platform trial [online]. [Preprint]. Available from: https://doi.org/10.21203/rs.3.rs-1045085/v1

Study Title	Australasian COVID-19 Trial (ASCOT)
Abbreviated Title	ASCOT
Clinical trials registration	tbc
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Protocol number	62646
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Study Sponsor	Melbourne Health
Co-ordination	
Co-ordinating centre	Doherty Institute for Infection and Immunity (University of Melbourne)
Collaborating bodies	The Australasian Society for Infectious Diseases Clinical Research Network (ASID CRN)
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ASCOT Study Synopsis

TITLE	Australasian COVID-19 Trial (ASCOT). A multi-centre RCT to assess clinical, virological and immunological outcomes in patients with SARS-CoV-2 infection (COVID-19) treated with lopinavir/ritonavir and/or hydroxychloroquine compared to standard of care.
BACKGROUND	There are no therapies known to be efficacious for SARS-CoV-2 infections. Several agents have shown laboratory activity and are entering clinical trials. Lopinavir/ritonavir (LPV/r) has demonstrated some laboratory activity and is available as an approved oral formulation for HIV. Hydroxychloroquine has demonstrated laboratory activity and is available as an approved oral formulation for malaria. Clinicians have reported using LPV/r in individual cases of SARS-CoV-2 infection, but demonstration of benefit or appropriate indications are unknown. LPV/r improved clinical outcomes in non-randomised studies for SARS-CoV infections and is included as a therapy in a current clinical trial for MERS-CoV infections.
PRIMARY OUTCOME MEASURE	Proportion of participants alive and not having required invasive or non-invasive ventilation at 15 days after enrolment
SECONDARY OUTCOME MEASURES	Clinical 1. WHO 7-point outcome scale (clinician assessed) 2. Mortality at 7, 15, 28, 90 days 3. Time to death (up to 90 days) 4. Length of hospital stay 5. Receipt of invasive or non-invasive ventilation in first 28 days 6. Length of receipt of invasive or non-invasive ventilation 7. Length of ICU stay 8. Presence of chest infiltrates on CXR or CT at day 3 and day 7 9. Requirement for advanced respiratory support (short of invasive or non-invasive ventilation) 9.1. Days requiring >2L/min O2 to maintain SaO2 >92% 9.2. Need for humidified high flow oxygen 10. Time to defervescence from randomisation 11. Biomarker levels – CRP and LDH and D-dimer 12. Antibiotic use – number of days of use in first 10 days post randomisation 13. Safety. Any of the following adverse events in first 10 days. See section on adverse events for definitions. 13.1. Diarrhoea – grade 2 or greater 13.2. Nausea – grade 2 or greater 13.3. Vomiting – grade 2 or greater 13.4. Pancreatitis – grade 2 or greater

	13.5. QTc prolongation (>500ms) on day 2 and day 7 14. Safety. Serious ventricular arrhythmia (including ventricular fibrillation) or sudden unexpected death in hospital Virologic 15. Time to virological clearance (time from enrolment to first of 2 negative assays at least 12 hours apart) of SARS-CoV-2 by RT-PCR from upper or lower respiratory tract samples
STUDY DESIGN ***Control group*** ***Intervention groups***	Open label, multi-centre, randomized controlled trial (RCT) Standard or care without specific antiviral therapy Lopinavir (400mg) / ritonavir (100mg) (LPV/r) twice daily for 10 days OR Hydroxychloroquine 400mg three times per day for 3 days, followed by 200mg twice a day for 7 days OR LPV/r PLUS hydroxychloroquine in the above regimens
STUDY DURATION	March 2020 onwards
NUMBER OF PARTICIPANTS	Flexible (see sample size section for justification)
INCLUSION CRITERIA	1. Age ≥ 18 years 2. Confirmed SARS-CoV-2 by nucleic acid testing in the past 12 days 3. Able to be randomised within 12 days of symptom onset 4. Expected to be remain an inpatient over the next two calendar days from time of enrolment
EXCLUSION CRITERIA	1. Currently admitted to an Intensive Care Unit (ICU) 2. Currently receiving invasive or non-invasive ventilation 3. Currently taking LPV/r OR hydroxychloroquine 4. Known allergy or hypersensitivity to LPV/r OR hydroxychloroquine 5. Use of medications that are contraindicated with lopinavir/ritonavir OR hydroxychloroquine that cannot be replaced or stopped during the study period (see Table 1) 6. Currently on other investigational agents with targeted antiviral effects 7. Known cirrhosis or ALT or AST > 5x upper limit of normal 8. Previous participation in the trial 9. Known pregnancy 10. Known HIV infection not on antiretroviral therapy 11. QTc >500ms at enrolment

	12. Treating team deems enrolment in the study is not in the best interest of the patient 13. Unable to provide consent 14. Death is deemed to be imminent and inevitable within the next 24 hours
RANDOMISATION	Eligible participants will be randomized 1:1:1:1 in a factorial design. Randomization will be stratified by site and be in permuted blocks of variable size.
BLINDING	This will be an open-label study.
SAMPLE SIZE CALCULATION	At this stage in the epidemic it is not clear the likely numbers of patients that will present to study sites. To detect a reduction in the primary endpoint from 5% to 2.5% would require a sample size of 2,440. To detect a reduction in duration of viral shedding from the respiratory tract from 5 days to 3 days (or from 10 days to 6 days) would require a sample size of 132.
ANALYSIS	Analysis of the primary outcome will be by modified intention to treat (all participants with data available for the primary endpoint will be analysed according to the treatment allocation, regardless of what treatment they received). A per protocol analysis will also be performed. The per protocol population is defined as 1) for the control group: did not receive any LPV/r or hydroxychloroquine; 2) for the intervention group: received at least 80% of possible doses of LPV/r AND/OR hydroxychloroquine; 3) has available data. We also plan pre-specified subgroup analyses for the following groups: a) Aged >65 or ≤65 years b) Participants receiving ACE inhibitor/ATII blocker therapy at the time of presentation c) Receipt of study drug within 96 hours of fever onset d) Receipt of study drug within 96 hours of first symptom onset e) Mild disease vs moderate disease

1. Introduction

1.1 Abbreviations

ADR	Adverse drug reaction
AE	Adverse event
ASID CRN	The Australian Society for Infectious Diseases Clinical Research Network
CI	Chief Investigator – A researcher who contributes to the funding, planning, and running of the entire study
Co-I	Co-investigator (a clinician or research assistant who aids the PI at a site)
CRP	C-reactive protein
CTN	Clinical trial notification (to the Therapeutic Goods Administration)
DOB	Date of Birth
DSMB	Data safety monitoring board
EDC	Electronic data capture
EUC	Electrolytes, urea & creatinine
eCRF	Electronic case report forms
FBC	Full blood count
GCP	Good clinical practice
GP	General practitioner
HRN	Hospital record number
HREC	Human research ethics committee
ICH	International Conference on Harmonisation
ICU	Intensive care unit
ID	identification
ID physician	Infectious disease physician
LFT	Liver function test
NHMRC	National Health and Medical Research Council
PI	Principal Investigator (a clinician responsible for one site)
RC	research co-ordinator (responsible for multiple sites)
RCT	Randomised control trial
SAE	Serious adverse events
SOP	Standard Operating Procedure
SUSAR	Suspected unexpected serious adverse reaction
TGA	Therapeutic Goods Administration

1.2 Background and Rationale

1.2.1 Overview

In December 2019 a novel coronavirus emerged from Wuhan China as the cause of a pneumonia syndrome. This SARS-CoV-2 is a betacoronavirus and related to SARS. At the time of writing (15/3/20) there were over 150,000 reported cases globally with 250 cases in Australia. The case fatality rate is still unknown but likely to be ~1%.

There are no known effective therapeutic options at this stage. Clinical trials have begun in China with lopinavir/ritonavir (LPV/r) and a novel nucleotide analogue remdesivir. While clinical trials in China initially provide the best opportunity for appropriate sample sizes to assess the impact on clinical outcomes, there will continue to be a role for studies outside of China to: 1) contribute to understanding of clinical efficacy in local healthcare settings; 2) allow detailed assessments of virological and immunological outcomes in a blinded manner; 3) ongoing recruitment in China may be difficult with the reduction in cases in China.

1.2.2 Clinical spectrum of disease

SARS-CoV-2 causes a clinically significant and transmissible respiratory tract infection. In the large case series patients commonly had fever, cough and evidence of pneumonia on chest xray[1].

1.2.3 Therapeutic options

Several broad approaches to improving outcomes for severe viral infections can be considered, beyond optimal supportive care as appropriate. These approaches may include host immune modulation (for example, with the use of treatments such as steroids to reduce inflammation, or immune globulin to enhance specific responses), or interventions which aim to interfere with viral activity. Several antiviral medications have been previously investigated in clinical and laboratory studies for Sudden Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), diseases caused by related coronaviruses (SARS-CoV and MERS CoV respectively). These have not established definite efficacy for these coronaviruses, but have suggested potential benefit from the use of LPV/r with or without interferon B[2-4]. Other antivirals, including ribavirin, appear to have been associated with increased mortality and are not considered suitable candidates for SARS-CoV-2.

As SARS-CoV-2 is a novel viral pathogen, no clinical trial data on antiviral therapy and impact on outcomes exists. Laboratory studies have demonstrated that several agents, including chloroquine and LPV/r, have activity in vitro against SARS-CoV-2[5]. Remdesivir, a novel nucleoside analogue, has been shown to have in vitro activity against a range of coronaviruses, but is not in clinical use[5,6]. The use of LPV/r has been reported in clinical practice, including both China and Australia, but no systematic evidence of efficacy yet exists. WHO have recommended that specific treatments for COVID-19 should not be occurring outside of clinical trials given the current lack of evidence and potential for harm of therapeutic agents.

1.2.4 Rationale for selection of therapeutic agents

As outlined above, LPV/r and chloroquine have both had *in vitro* demonstration of effectiveness against SARS-CoV-2 replication[5]. Both medications are currently available for use in Australia and New Zealand for other indications and have well-established safety profiles.

1.2.5 Rationale for conducting a RCT in Australasia

It is expected that a substantial number of Australian and NZ residents may be infected with SARS-CoV-2, and based on international experience, a significant proportion will require hospitalisation (up to 20%) and be at risk for intensive care admission (up to 5%) and death (~1%). No established treatment to prevent these poor outcomes exists, and ASCOT will provide a controlled trial environment for two candidate medications to be used and evaluated.

The ASCOT study will allow for the efficacy and safety of these medications, alone and in combination, to be considered under closely monitored conditions.

Even if the study does not recruit sufficient numbers in itself for definitive conclusions for the primary endpoint of alive and not having required invasive or non-invasive ventilation at 15 days, it will contribute to broader global understanding and contribute to meta-analyses with other trials. It will also be important to determine the efficacy and safety of trial interventions within an Australasian context as the healthcare standards may differ from that of trials conducted elsewhere. Furthermore, detailed collection of samples will provide virological and immunological mechanistic insights into the efficacy or lack of efficacy of trial interventions.

An underlying principle is that we should provide randomised care rather than random care. At this stage, it is unknown whether the agents to be tested will provide benefit, harm or neither. There may be limited supply of these agents and until there is clear evidence of benefit or harm, the most judicious use is within the context of a clinical trial.

1.3 Objectives and hypotheses

We hypothesise that treatment with LPV/r +/- hydroxychloroquine will lead to improved clinical outcomes for hospitalised patients with SARS-CoV-2 infection.

Primary Objective: To determine if 10 days of LPV/r +/- hydroxychloroquine will reduce the proportion of participants who survive without requiring invasive or non-invasive ventilation, 15 days after enrolment, in adult participants with non critically ill SARS-CoV-2 infection.

1.4 Trial design

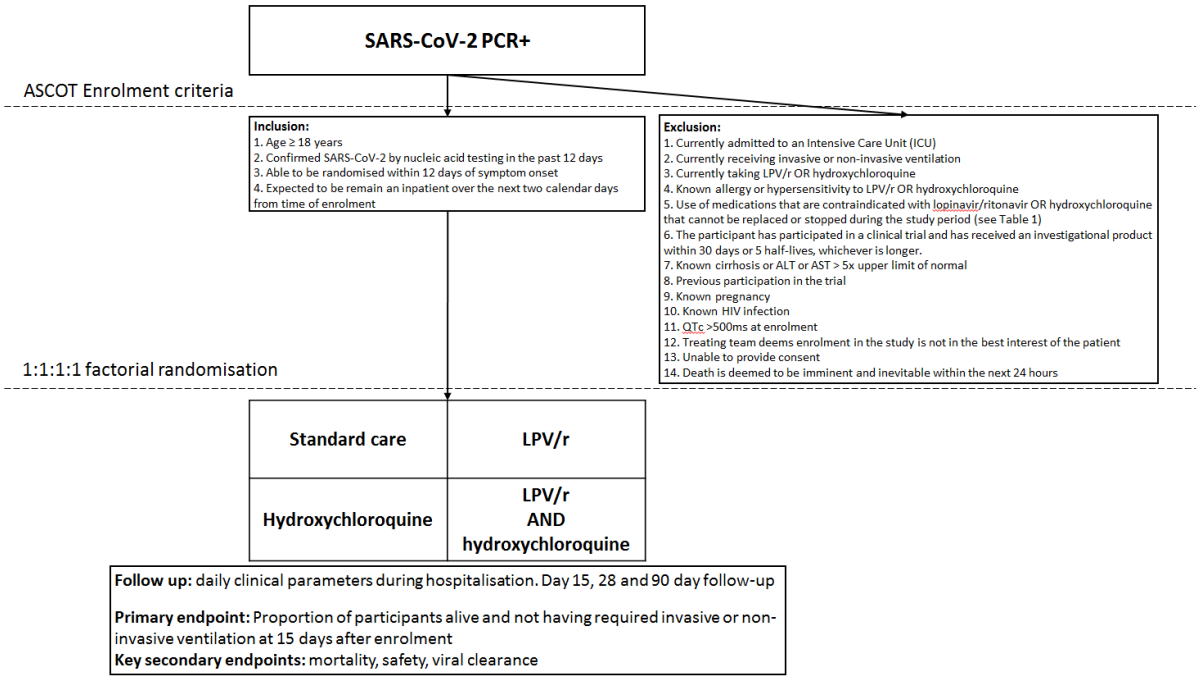
ASCOT is an investigator-initiated, multi-centre, open-label, randomised controlled trial. The study design will allow harmonisation with existing frameworks such as the Sentinel Travellers Research Preparedness Platform for Emerging Infectious Diseases (SETREP-ID, PI Thevarajan), SPRINT-SARI (Australian PI Cheng), and the Randomized, embedded, multifactorial adaptive platform trial for community-acquired pneumonia (REMAP-CAP) study (CI Steve Webb). Patients enrolled in ASCOT and who progress to requiring invasive or non-invasive ventilation can be enrolled in REMAP-CAP.

As it is too early to accurately predict the size and distribution of the SARS-CoV-2 epidemic the feasibility and sample size requirements of the study will be progressively considered.

In the initial design, consented participants will be randomised 1:1:1:1 on day 1 to receive either i) LPV/r, ii) hydroxychloroquine, iii) LPV/r + hydroxychloroquine for 10 days, or iv) standard of care without LPV/r or hydroxychloroquine. For patients that are clinically worsening at day 5 or beyond, the protocol allows for (but does not encourage) the treating

clinician to commence LPV/r +/- hydroxychloroquine from day 5 onwards. Daily data will be collected for the first 10 days or until discharge, whichever is earlier. There will be a core dataset collected for all patients at all sites and enhanced and research data and biological samples for sites with capacity. Data will be harmonised with the ISARIC SARS-CoV-2 and REMAP-CAP protocols and CRFs (https://isaric.tghn.org/novel-coronavirus/). As long as the participant remains an inpatient, their medical records will be reviewed weekly until discharge or the 90 day time point, whichever occurs first.

Figure 1 – Overview of trial design



2. Methods

2.1 Study setting

We are aiming to recruit from sites across Australia with the potential for NZ sites to be involved. Sites will be selected on the basis of i) Estimated (or known) numbers of cases with a focus on larger sites; ii) the availability of a committed principal site investigator and site research team; and iii) capacity to collect samples as per the protocol.

2.2 Eligibility criteria

2.2.1 Participant Inclusion criteria

1. Age ≥ 18 years
2. Confirmed SARS-CoV-2 by nucleic acid testing in the past 12 days
3. Able to be randomised within 12 days of symptom onset
4. Expected to be remain an inpatient over the next two calendar days from time of enrolment

2.2.2 Participant Exclusion criteria

1. Currently admitted to an Intensive Care Unit (ICU)
2. Currently receiving invasive or non-invasive ventilation
3. Currently taking LPV/r OR hydroxychloroquine
4. Known allergy or hypersensitivity to LPV/r OR hydroxychloroquine
5. Use of medications that are contraindicated with LPV/r (see Table 1) OR hydroxychloroquine that cannot be replaced or stopped during the study period
6. Currently on other investigational agents with targeted antiviral effects
7. Known cirrhosis or ALT or AST > 5x upper limit of normal
8. Previous participation in the trial
9. Known pregnancy
10. Known HIV infection not on antiretroviral therapy (see note below*)
11. QTc >500ms at enrolment
12. Treating team deems enrolment in the study is not in the best interests of the patient
13. Unable to provide consent
14. Death is deemed to be imminent and inevitable within the next 24 hours

Table 1: Drugs which should not be co-administered with study drugs

Drug Class	Drug Within Class Not to Be Co-administered
3A4 inhibitors	clarithromycin, erythromycin, diltiazem, itraconazole, ketoconazole, verapamil, fluconazole
3A4 inducers	phenobarbital, phenytoin, rifampicin
2D6 inhibitors	bupropion, fluoxetine, paroxetine, quinidine, metoclopramide
2D6 inducers	adalimumab, certolizumab, etanercept, golimumab, infliximab
QT prolongation	quetiapine, amiodarone
HCV antivirals	glecaprevir/pibrentasvir

* For people with HIV on antiretroviral therapy significant drug-drug interactions may occur and potential changes in the antiretroviral regimen to facilitate enrolment in the trial should be done in conjunction with an experienced HIV prescriber. As guidance it is not recommended that individuals already receiving protease inhibitor, ritonavir, cobicistat, efavirenz, nevirapine or biktarvy should then be administered lopinavir/ritonavir. Antiretrovirals that are considered safe with lopinavir/ritonavir include tenofovir disoproxil fumarate (TDF) or tenofovir alefenamide (TAF), dolutegravir (DTG) and rilpivirine (RPV). It is recommended that individuals randomised to receive lopinavir/ritonavir should receive the lower dose formulation of tenofovir alefenamide if that forms part of their antiretroviral regimen.

2.3 Treatment of Study Participants

Participants will be randomised to either the standard of care arm (2.3.1) or active treatment factorial (2.3.2). The standard of care arm will receive usual clinical care without LPV/r or hydroxychloroquine. The day of randomisation is considered day 1 of treatment. Randomisation and allocation must occur within 14 days of index sample collection that detected SARS-CoV-2 and within 14 days of symptom onset. The LPV/r or

hydroxychloroquine will be prescribed by a doctor from the treating team. Storage conditions of LPV/r and hydroxychloroquine will be as per hospital pharmacy policy and will not be monitored for the study purposes. The participant's drug charts (electronic and/or paper) will be reviewed for compliance with study treatment. Any missed dose/s in the active treatment arms, and any use of LPV/r or hydroxychloroquine in the standard of care arm will be recorded on the CRFs.

2.3.1 Standard of care arm

Participants will receive usual medical care. The protocol does not allow the use of LPV/r or hydroxychloroquine in the first 5 days. If at day 5 the treating team decides to prescribe LPV/r or hydroxychloroquine, this will be permitted within the protocol and recorded. However, such action is not encouraged as:

1. There is no evidence to support either benefit or harm of antiviral agents in this setting.
2. The WHO has a clear statement that use of unproven therapeutic agents should occur in the context of a clinical trial.
3. In the setting of limited drug supplies, use should be prioritised to address clinical questions.

If LPV/r and / or hydroxychloroquine are used, the reasons for this decision will be recorded on the CRF and specifically will be:

1. Development of severe disease as per American Thoracic Guidelines for community acquired pneumonia as detailed in Table 2
2. Impending need for invasive or non-invasive ventilation

Use of LPV/r or hydroxychloroquine outside of these reasons and if prior to day 5 will be considered protocol violations and a specific reason will be recorded.
Use of corticosteroids is discouraged[7] but recorded if used. Use of other potential therapies will also be discouraged but recorded if used. Antibiotic use will be recorded.

Table 2: American Thoracic Society criteria for severe community acquired pneumonia

Either one major criterion or three or more minor criteria
Minor criteria
Respiratory rate ≥ 30 breaths/min
PaO2/FiO2 ratio ≤ 250
New onset confusion/disorientation
Uremia (blood urea nitrogen level ≥ 7.14 mmol/L)
Leukopenia* (white blood cell count < 4,000 cells/µl)
Thrombocytopenia (platelet count < 100,000/µl)
Hypothermia (core temperature < 36°C)
Hypotension requiring aggressive fluid resuscitation
Major criteria

Septic shock with need for vasopressors
Respiratory failure requiring mechanical ventilation

Note: Multilobar infiltrates has been removed as this is typical for COVID-19

2.3.2 Active treatment factorial arm

Participants will be randomised 1:1:1:1 to 1) standard of care; 2) lopinavir (400mg) / ritonavir (100mg) twice daily for 10 days in tablet form; 3) hydroxychloroquine (400mg) three times per day for 3 days, followed by 200mg twice a day for 7 days; 4) lopinavir / ritonavir plus hydroxychloroquine. For patients who are unable to take medications by mouth, the LPV/r (400 lopinavir mg / 100 mg ritonavir) will be administered as a 5-ml suspension every 12 h via a pre-existing or newly placed nasogastric tube. Hydroxychloroquine can be suspended and administered with the same dose and schedule as the tablet formulation.

The dose of LPV/r is the standard dosing used for treatment of HIV. If the oral solution is used, it should be administered with food to increase absorption (there is no recommendation for use with food for the tablets). Because LPV/r oral solution contains ethanol and propylene glycol, it is not recommended for use with polyurethane feeding tubes due to potential incompatibility. Feeding tubes that are compatible with ethanol and propylene glycol, such as silicone and polyvinyl chloride (PVC) feeding tubes, can be used.

The initial dose of hydroxychloroquine is higher than the standard Australian recommendations (800mg/day max), which are for long term use. Current Chinese guideline recommendations include the higher initial dose of 1200mg per day in three divided doses. Although a recent study suggested that a lower initial dose would be sufficient to achieve levels above the EC_{50} of hydroxychloroquine for SARS-CoV-2, the pharmacokinetic modelling used data from healthy volunteers[8]. Given the trial population will be unwell with variations in weight and actual bioavailability, the investigator group has opted for a higher loading dose to have greater confidence in achieving adequate drug levels. PK/PD sub-studies are planned to better define the appropriate dosage.

The schedule for dosing of hydroxychloroquine will be 400 mg, administered 8 hourly, until 9 doses have been administered. Subsequently, the dose will be 200 mg administered 12 hourly.

There is a risk of Torsades de Pointes with hydroxychloroquine and LPV/r and hence the study will exclude those with known QTC prolongation >500ms and monitor QTc during treatment. Additionally, for participants with a known history of ischaemic heart disease or cardiac dysrhythmias, the loading dose of hydroxychloroquine of 1200mg per day will only be given for the first day. Subsequent doses for these participants will be 200mg twice daily.

The duration of treatment is based on the natural history of worsening of clinical status at approximately one week of illness for patients who develop more severe disease. Treatment for 10 days will therefore extend past this critical time point.

Use of corticosteroids is discouraged but recorded if used. Use of other potential therapies will also be discouraged but recorded if used. Antibiotic use will be recorded.

2.3.3 Criteria for discontinuing or modifying allocated interventions

2.3.3.1 Adjusting for renal function

Adjustment for renal function is not required for LPV/r or HCl.

2.3.4 Strategies to improve adherence to protocol

2.3.4.1 Training of site PIs

All site PIs will be trained in the study protocol, SOPs and their reporting requirements by the project manager, or a study chief investigator, prior to the site being opened for recruitment. All site PIs will need to have completed an accredited Good Clinical Practice training course.

The project manager will have regular phone contact with all enrolling site investigators, including after the enrolment of participants number 1, 2 and 5 at each site, and every 10 participants thereafter.

2.3.4.2 Documentation in patient's medical record and bedside chart

A sticker will be placed in the patient's medical record (one on the progress notes on the day of randomisation, and one in the front inside cover of the medical record ["old note"] if one exists). This sticker will alert clinicians that the patient has been randomised to the ASCOT study, with a brief explanation of the study.

A copy of the study synopsis will be placed in the bedside chart (observations and drug chart) of the patient. A checklist of study procedures will also be placed in the bedside chart.

For sites with electronic medical records and/or prescribing, an electronic "sticker" will be used, and appropriate annotations will be made to the electronic drug chart.

2.3.4.3 Checking of drug charts

The medication chart (be it paper or electronic) will be checked each day (apart from weekends) by the site PI or their delegate (registrar or research nurse) for the first 10 days whilst an inpatient to ensure adherence to the study protocol.

2.4 Outcomes

2.4.1 Primary outcome

Proportion of participants alive and not having required invasive or non-invasive ventilation at 15 days after enrolment.

2.4.2 Secondary outcomes

2.4.2.1 Clinical

1. WHO 7-point outcome scale (clinician assessed)
2. Mortality at 7, 15, 28, 90 days
3. Time to death
4. Length of hospital stay
5. Receipt of invasive or non-invasive ventilation in first 28 days
6. Length of receipt of invasive or non-invasive ventilation
7. Length of ICU stay
8. Presence of chest infiltrates on CXR or CT at day 3 and day 7

9. Requirement for advanced respiratory support (short of invasive or non-invasive ventilation)
    9.1 Days requiring >2L/min O2 to maintain SaO2 >92%
    9.2 Need for humidified high flow oxygen
10. Time to defervescence from randomisation
11. Biomarker levels – CRP and LDH and D-dimer
12. Antibiotic use – number of days of use in first 10 days
13. Safety. Any of the following adverse events in first 10 days. See section on adverse events for definitions.
    13.1 Diarrhoea – grade 2 or greater
    13.2 Nausea – grade 2 or greater
    13.3 Vomiting – grade 2 or greater
    13.4 Pancreatitis – grade 2 or greater
    13.5 QTc prolongation (>500ms) on day 2 and day 7
14. Safety. Serious ventricular arrhythmia (including ventricular fibrillation) or sudden unexpected death in hospital

2.4.2.2 Virologic

15. Time to virological clearance (time from enrolment to first of 2 negative assays at least 12 hours apart) of SARS-CoV-2 by RT-PCR from upper or lower respiratory tract samples

2.4.3 Rationale for these outcome measures

It is not clear at this stage how many patients will be suitable for enrolment. Therefore, there may not be sufficient patient numbers to power the study on clinical outcomes. If the case fatality rate is ~1%, the study will almost certainly not be powered for showing a difference in mortality. If the requirement for ventilation or mortality at 15 days is 5%, the study will require 2440 patients to demonstrate a difference of 2.5% in the primary endpoint. Nonetheless, the investigator group felt that the primary endpoint should be one of clinical significance. There is also value in conducting the study to assess virologic and immunologic outcomes. If viral clearance can be achieved more rapidly, in addition to potentially improving the clinical course, it would have implications for infection control and duration of hospitalisation.

The WHO Master Protocol is using a primary endpoint of an ordinal score at day 15:

1. Not hospitalized, no limitations on activities
2. Not hospitalized, limitation on activities;
3. Hospitalized, not requiring supplemental oxygen;
4. Hospitalized, requiring supplemental oxygen;
5. Hospitalized, on non-invasive ventilation or high flow oxygen devices;
6. Hospitalized, on invasive mechanical ventilation or ECMO;
7. Death.

To allow harmonisation with these WHO Master Protocol outcomes, the components for the ordinal scale will be part of the data collection. The ASCOT investigator group decided that analysis of these ordinal outcomes is complicated and a large sample size would be

needed to evaluate any distinguishable/meaningful differences amongst these categories. We have preferred a binary primary endpoint.

2.5 Trial Procedures

2.5.1 Participant timeline

See Figure 1 and Table 3.

Table 3. Schedule of visits, data collection and follow-up.

Visit Day	Pre-Screen	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11-14	Day 15	Day 21	Day 28
CORE															
Check eligibility	X														
ECG	X		X					X							
Informed consent		X													
Demographic data		X													
Clinical details		X													
Randomise		X													
Check treatment as per allocated		X	X	X	X	X	X	X	X	X	X				
Clinical observations[1]		X	X	X	X	X	X	X	X	X	X	X			
Vital and ICU status		X	X	X	X	X	X	X	X	X	X	X	X		X
If discharged, activity													X		X
Respiratory tract sample results[1]	X	X		X				X							
FBC, EUC, LFTs, CRP[1]		X		X				X							
ENHANCED BIOLOGICAL and IMAGING															
Daily bloods[1]		X	X	X	X	X	X	X	X	X	X		X		
Rectal swab sample[1]		X			X			X							
Respiratory tract sample results[1]	X	X	X	X	X	X	X	X	X	X	X	X			
Serum stored		X		X				X					X	X	X

Visit Day	Pre-Screen	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11-14	Day 15	Day 21	Day 28
Chest imaging[1, 2]		X		X				X							
RESEARCH BIOLOGICAL															
Plasma, serum, PBMCs stored		X		X				X					X	X	X
Respiratory tract sample stored	X	X		X		X		X							
Plasma stored for PK/PD		X	X	X	X			X			X				

1. While still in hospital
2. Either CXR or CT chest

2.5.2 Screening

All patients with a positive nucleic acid detection for SARS-CoV-2 will be referred by the pathology laboratory to the site investigator or their delegate (sub-investigator or properly qualified research nurse), as soon as identified. The following information will be transcribed onto a screening log by a member of the study team at the time of referral: date and time the sample was collected, the hospital record number (HRN), name & date of birth (DOB) of the patient and date and time the referral was received. The site investigator or their delegate will approach the doctors of the treating team and ask permission to approach the patient) for potential recruitment onto the study and record their response in the screening log. The screening CRF (CRF1) will be filled in for all potentially eligible patients to determine eligibility. The site investigator will do this using information gathered from the medical record and the patient's treating clinician. If the patient is clearly not eligible (e.g., age < 18 years), they will not be approached for consent. The data pertaining to their eligibility will be de-identified and entered onto eCRF1 (screening form). If the patient appears to be possibly eligible, they will be approached for an informed consent discussion. For ineligible patients or who decline to participate, data may be able to be collected for observational studies such as SPRINT-SARI.

2.5.3 Informed Consent

Due to the stringent measures in infection control in hospitals, verbal consent will be obtained instead of written consent. All patients will be in strict contact and droplet precautions and there will be an imperative to minimise use of personal protective equipment (PPE) by staff due to resource limitations. This has implications for recording of consent:

- Bringing a consent form and pen to the bedside and then taking these out of the room will violate the infection control rules.
- To minimise PPE use, only one person should enter a room to discuss the study with the patient. Therefore a witness will not be present. Neither will a next of kin be present.
- It will be acceptable to bring the Patient Information Sheet and Consent form (PICF) into the room for viewing by the patient, and for these documents to be left in the room.
- We considered taking a photo of the signed consent form, but digital devices should not be used (outside of clinical requirements) with PPE.

An informed consent discussion will be held with each participant by a site investigator or their delegate. The information for the discussion will be provided in written and oral formats that have been approved by the HREC and in a language comprehensible to the potential participant, using interpreters if necessary. The information presented in the PICF and by the investigator will detail the exact nature of the trial and what is expected of the participant including any risks or benefits in taking part. It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason without prejudice to

future care, and with no obligation to give the reason for withdrawal. The participant will be allowed time to ask questions and consider whether or not to participate in the research. A copy of the PICF will stay in the patient's room and will not be taken out of the room.

After allowing the potential participant time to read the PICF, the investigator will answer any additional questions they may have and will obtain verbal agreement to participate in the research. The person must clearly and orally indicate that they consent to participation in the study. The verbal consent will be recorded in the participant's medical record and the study consent form after the site investigator or delegate has left the room. This will state that the terms and conditions were all read and agreed to and all questions asked were answered. The following day, the investigator or clinical team will verbally confirm with the participant that they have consented to participate.

If a form is not available in a person's own language, the form must be translated verbally by an interpreter who should indicate on the consent form that such a verbal and literal translation has been given. Where an interpreter is required, the interpreter will need to use appropriate PPE and follow local policy procedures.

2.5.4 Randomisation and blinding

Prior to proceeding with randomisation, the site investigator or their delegate will ensure that documented informed consent has been obtained and that the participant is eligible to be enrolled. To randomise the participant the site investigator or their delegate will log onto the web-based interactive randomisation system (IXRS) and enter the details required to obtain the treatment allocation assigned for that participant. The participant will be assigned a randomisation number and group allocation. Compulsory fields required prior to randomisation are screening number, confirmation of eligibility, age, confirmation of consent, and recruitment site.
Participants will be randomised in a 1:1:1:1 ratio to the standard of care or treatment arms, the randomisation schedule will be generated by an independent statistician.
Randomisation will be stratified by site and will be in permuted blocks of variable block size. The randomised sequence allocation will be stored on the secure server of the web-based IXRS provider, and will not be available to any investigators or member of study staff. This will be an open-label study. As this study is open label, in the event of medical emergency the treating clinicians of all study participants will already know whether or not the participant is receiving the study drug and hence there is no unblinding procedure necessary.

2.5.5 Day 2–14

The site PI or their delegate will make contact (either by phone or preferably in person on the ward) with the treating team every day for the first 10 days, with the exception of weekends and public holidays. The purpose of this contact is to check compliance with the protocol in terms of study drug prescribing and ordering of routine clinical blood tests.

CRFs will be filled out within 48 hours of the relevant day. So the day 1 CRF will be filled out on day 2–3, day 3 on day 4–5 and day 7 on days 8–9. Standard Operating Procedures (SOPs) will contain step by step details on how to recruit patients and collect data.

2.5.6 Day 15, 28 and 90

The site PI or their delegate will review the medical records or make contact (either by phone or in person) with the participant or treating team to assess vital status, ICU status and activities status (no limitations to normal activities or some limitations to normal activities).

2.5.7 Data and sample collection

There will be three tiers for collection of samples and associated data. All sites will need to collect core clinical data. Sites may opt-in to different parts of the enhanced biological and research biological tiers.

2.5.7.1 Core

These are the core clinical data that contribute to the primary endpoint, key secondary outcomes, and key potential confounders. It includes baseline clinical information, receipt of study interventions, clinical observations during hospitalisation and at day 15, standard blood test (FBE, CRP) results while hospitalised for days 1, 3, 7 and respiratory tract specimen SARS-CoV-2 rRT-PCR results while hospitalised for days 1, 3, 5, 7, chest imaging results at day 1, 3, 7.

2.5.7.2 Enhanced biological and imaging

Additional specimens and results may include: Respiratory tract specimen SARS-CoV-2 rRT-PCR results daily while hospitalised until 2 negative test results. Rectal specimen SARS-CoV-2 rRT-PCR results while hospitalised for days 1, 4, 7. Storage of serum at days 1, 3, 7, 15, 21, 28. Chest imaging on days 1, 3 and 7.

2.5.7.3 Research biological

Additional specimens may include: Storage of primary respiratory tract specimens; storage of serum, plasma, PBMCs at days 1, 3, 7, 15, 21, 28; storage of plasma at days 1-4, 7 and 10 for PK/PD studies.

2.5.8 Discontinuation/Withdrawal of participants from trial treatment

The participants have the right to choose to withdraw from the study at any time and the investigator may discontinue a participant from the study or from treatment if deemed appropriate at any time. Reasons why a participant may be withdrawn from the study include, but are not limited to, participant request, primary treating clinicians request, participant was enrolled and is ineligible (either arising during the study or was overlooked at time of screening and enrolment). Participants will not be withdrawn due to adverse events. The decision to withdraw a participant from the study must be discussed with the coordinating investigators.

If the participant withdraws consent from participating in the study and also withdraws consent for disclosure of future information, no further evaluations will be performed, and

no additional data will be collected. The co-ordinating investigators may retain and continue to use any data or samples collected before such withdrawal of consent. Participants that abscond will continue to be followed until the end of the trial to avoid missing data, if they did not complete treatment their data will be used in the intention-to-treat analysis, if they completed treatment their data will be used in the as per protocol analysis. Participants that are lost to follow up will continue to be followed until the end of the trial to avoid missing data, if the participant completed treatment their data will be used in the as per protocol analysis. Participants withdrawn from the treatment by the treating clinicians will continue to be followed up to the end of the trial to avoid missing data and will be used in the intention-to-treat analysis.

If a participant is withdrawn the reason will be recorded in the database.

The study drug the participant is randomised to will be discontinued if a participant chooses to withdraw from the study.

If a participant is admitted to ICU due to progressive disease, the treating clinician can continue treatment using the allocated study drug for a total of 10 days.

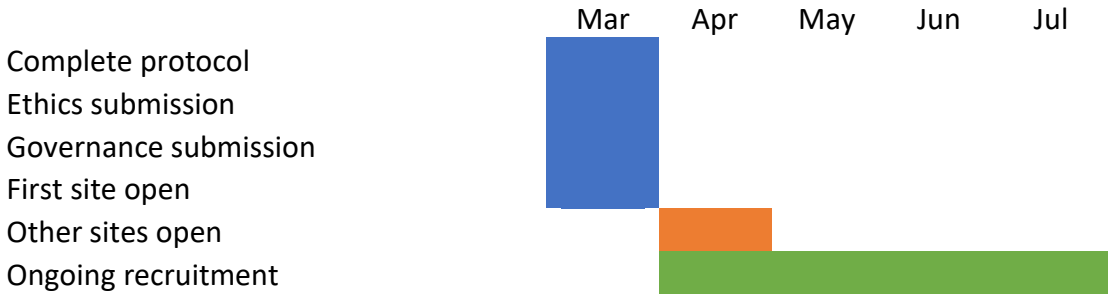
2.5.9 End of trial

At this stage this is an open-ended study given the uncertainties of the epidemiological course of SARS-CoV-2. The trial steering committee will continually assess the epidemiological situation, trial progress and interim results, and emerging external evidence of efficacy of the study and other interventional agents. The trial protocol may be adapted as the situation changes.

2.6 Study timeline

This project will aim to commence as soon as possible in 2020.

Figure 2 – Study timelines



2.7 Sample size

There is great uncertainty at this early stage of the epidemic. Until further information becomes available there is not sufficient data to predict likely numbers of patients presenting with COVID-19.

2.7.1 Primary endpoint

Estimated rates of need for ventilation among hospitalised patients have varied. In an early report from China of 1099 hospitalised cases, 5% required ICU admission with 2.3% undergoing invasive ventilation [1]. In Italy, ICU admissions (n=556) represented 16% of all patients (n=3420) who tested positive for COVID-19 [9].

The following table provides an example of a 2x2 factorial design assuming relative risk 0.5 by LPV/r and by hydroxychloroquine (HCQ) and no interaction between LPV/r and HCQ. Percentages in each cell are the event rate.

	HCQ - Yes	HCQ – No	Total – main comparison for HCQ
LPV/r – Yes	1.25%	2.5%	1.875%
LPV/r – No	2.5%	5% (standard)	3.75%
Total – main comparison for LPV/r	1.875%	3.75%	

Given the 2x2 factorial design, each main comparison (either LPV/r or HCQ) is comparing 3.75% vs 1.875% (across rows, or across columns), then the sample size would be 610 per arm (per cell) with a two-sided significance level (alpha) of 5% and 80% power. The total sample size would be 2440 allowing for two comparisons.

We will use the Haybittle-Peto approach for interim analyses. Other rules (e.g., O'Brien-Fleming), while preferable in standard settings, require specification of the number and timing of interim analyses which does not allow for sufficient flexibility at this stage. We note that the Haybittle-Peto approach will be an overly conservative approach throughout, necessary in this situation.

The calculations in the below table are for power of 70%, 80% and 90%, and for alpha of 0.05 and 0.045. The 0.45 value is investigated as a conservative estimate to adjust for the interim analyses according to the Haybittle-Peto rule, without knowing a priori the number, timing and type of the interim analyses (i.e., efficacy/ harm/ futility). Numbers refer to total and in each study arm.

	70%	80%	90%
0.045	1988 (497)	2520 (630)	3356 (839)
0.05	1920 (480)	2440 (610)	3264 (816)

The below table provides estimated sample sizes for different proportions of hospitalised patients needing ventilation.

For a reduction in the primary endpoint from 10% to 5%:

	70%	80%	90%
0.045	968 (242)	1224 (306)	1628 (407)

For a reduction in the primary endpoint from 15% to 10%:

	70%	80%	90%
0.045	1376 (344)	1740 (435)	2320 (580)

2.7.2 Viral clearance endpoint

There is also some uncertainty as to the usual duration of viral shedding. Among 14 patients from Guangdong[10] with sufficient data for calculations, the median duration of remaining positive by PCR was 5 days from the time of admission (mean 4.6, st dev 2.9). Among 18 patients from Singapore[11], the median duration of remaining positive by PCR was 12 days from the time of admission (mean 11.5, st dev 5.3).

Using a 2x2 factorial design assuming hazard ratio of 1.67 by LPV/r and by hydroxychloroquine (HCQ), if we are assessing a reduction in time to negative PCR from 5 days to 3 days:

	HCQ – Yes	HCQ – No	Total – main comparison for HCQ
LPV/r – Yes	Hazard = 0.3851 Survival prop= 0.31% MST = 1.8	Hazard = 0.2310 Survival prop = 3.13% MST = 3	Hazard = 0.2888 Survival prop = 1.31% MST= 2.4 (N=306)
LPV/r – No	Hazard= 0.2310 Survival prop = 3.13% MST = 3	Hazard = 0.1386 Survival prop = 12.51% MST = 5 (standard)	Hazard = 0.1733 Survival prop = 7.43% MST = 4 (N=306)
Total – main comparison for LPV/r	Hazard = 0.2888 Survival prop = 1.31% MST = 2.4 (N=306)	Hazard = 0.1733 Survival prop = 7.43% MST = 4 (N=306)	

Assumes hazard = natural log (2)/median survival time (MST), and Survival proportion at end point: S(15 days) = exp(-hazard*15). The 15 day end point is in line with the primary endpoint.

For the 2x2 factorial design, each main comparison (either LPV/r or HCQ) is comparing MST of 4 vs 2.4 days, then the sample size is 33 per arm with a two-sided alpha level of 5% and power of 80%. The total sample size would be 132 allowing for two comparisons.

	70%	80%	90%
0.045	108 (27)	136 (34)	184 (46)
0.05	104 (26)	132 (33)	176 (44)

2.8 Assignment of interventions

2.8.1 Allocation

Participants will be randomised in a 1:1:1:1 ratio to active treatment or standard of care treatment arms, using a web-based interactive randomisation system, available 24 hours per day, 7 days per week.
Randomisation will be stratified by site and will be in permuted blocks of variable block size.

2.8.2 Allocation concealment

The randomised sequence allocation will be stored on the secure server of the web-based IXRS provider, and will not be available to any investigators or member of study staff.

2.8.3 Implementation

The allocation sequence will be generated by a statistician not involved in the day to day trial procedures and implemented through the web-based IXRS. Participants will be enrolled by site principal investigators or their delegates (research nurse or co-investigator). The person enrolling the patient will, following obtaining verbal informed consent, obtain the treatment allocation by logging onto the web-based IXRS and will then assign the allocated treatment to the patient.

2.8.4 Blinding

This will be an open-label study, but the investigators assessing the laboratory outcomes will be blinded to treatment allocation. Although blinding was considered, the added complications and expense were deemed prohibitive. Furthermore, no placebo of LPV/r was available from AbbVie at the time of trial design.

2.9 Data Management and Quality Assurance

2.9.1 Source data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include but are not limited to, hospital records both electronic & paper (which will include medical history, previous and current medications, any relevant radiography test, blood test results, haemodynamic parameters and medical correspondence) and electronic clinic records (which will include vital status, recent medical history and relevant blood culture results). A further data source will be through telephone conversations with the study participant or GP.
Storage and archiving of study documents (CRF's and consent forms) will be the responsibility of the site principal investigator and will remain at the site of recruitment and retained for 15 years. All study participants will be allocated a unique number at time of screening (screening number), this screening number will be added to all the CRF's for that participant. The participants will also have their HRN recorded on the CRF's as this information will be required

to ensure the correct medical record is accessed during medical record reviews. The date and time will be captured on the CRF for all telephone conversations with study participants or GP.

2.9.2 Data Recording and Record Keeping

Data for this study will be recorded via a secure, Electronic Data Capture (EDC) web-based system using the eCRFs. It will be transcribed by the site PI or their delegate from the paper CRFs onto the eCRF (in no case is the eCRF to be considered as source data for this trial). Data will be stored in a re-identifiable manner in the database, using a unique screening number for each patient.

The database will contain validation ranges for each variable to minimise the chance of data entry errors. An audit trail will maintain a record of initial entries and changes made; reasons for change; time and date of entry; and user name of person who made the change. Data queries will be raised by the project manager and study monitor, and missing data or suspected errors will be raised as data queries and resolved prior to database lock and analysis. The database will contain in-line capability so that these queries and answers are logged as part of the audit trail.

For each potential participant screened (even those who are not eligible), the screening eCRF will be completed by the site PI or their delegate. For each participant enrolled, eCRFs must be completed. This also applies to records for those patients who fail to complete the study. The site PI should ensure the accuracy, completeness and timeliness of the data reported to the sponsor in the eCRFs and in all required reports. A comprehensive validation check program will verify the data and automatically generate discrepancies for resolution by the investigator. Manual discrepancies can also be raised if necessary.

In addition, accurate and reliable data collection will be assured by verification of the eCRFs against the investigator's records by the study monitor (source document verification), and the maintenance of medication compliance will be captured in the CRF's from the participant's medication chart (source document) by the investigator.

Storage and archiving of hard-copy study documents (CRFs and consent forms) will be the responsibility of the principal investigator at each site and will remain at the site of recruitment following local security guidelines. Hard-copy study documents will be kept for a minimum of 15 years and confidentially destroyed at the end of this period only with the express consent of the study sponsor.

2.10 Statistical methods

2.10.1 Statistical analysis plan

Data will be reported in accordance with the CONSORT guidelines for reporting of randomised trials. Proportions will be compared between treatment groups with Fisher's exact or χ^2 tests, and the absolute difference in proportions reported with corresponding 95% confidence intervals. All-cause mortality will be presented in a Kaplan-Meier graph.

The ***primary analysis*** of both primary and secondary endpoints will be according to modified intention to treat principles (all participants with data available for the endpoint will be analysed according to the treatment allocation, regardless of what treatment they received). No assumptions will be made about those with missing data.

A ***secondary per-protocol analysis*** of all endpoints will be conducted. The per protocol population is defined as 1) for the control group: did not receive any LPV/r or hydroxychloroquine; 2) for the intervention group: received at least 80% of possible doses of LPV/r; 3) has available data.

We will perform the following **subgroup analyses**:

1. ***Age ≥65 or <65 years***. Early experience with SARS-CoV-2 infection is that older age is associated with poorer outcomes.
2. ***Receipt of study drug within or after 96 hours of symptom onset***. There is biological plausibility that early treatment to reduce viral replication will be more effective than later treatment when pulmonary pathology may already be evident.
3. ***Mild vs moderate severity at presentation***. Initial severity at presentation may predict the later clinical course and there may be a differential effect of antiviral treatment. The absolute improvement in clinical outcomes may be more evident in the moderate severity group due to a higher event rate.
    a. Mild severity at presentation is defined as: SaO2≥95% on room air AND not requiring supplemental oxygen AND not tachypnoeic (respiratory rate <24 breaths/min)
    b. Moderate severity at presentation is defined as SaO2≤94% on room air OR requiring supplemental oxygen OR tachypnoeic (respiratory rate ≥24 breaths/min)
4. ***Baseline use of ACE inhibitors or ATIII blockers***. These medications affect the renin angiotensin aldosterone system pathway, which may also be affected by SARS-CoV-2, which uses ACE2 as its cellular receptor. Use of these medications may result in differential susceptibility to SARS-CoV-2 infection, with the direction of effect uncertain.
5. **Those with baseline immunosuppression vs those without.** These are different patient groups with regards to underlying comorbidities and risk for severe sepsis. Patients will be considered immunosuppressed if in receipt of immunosuppressing medication considered by the site investigator to be equivalent to ≥20 mg of prednisolone for ≥2 weeks, or with a known haematological malignancy.

2.10.2 Interim analyses and stopping guidelines

The Data and Safety Monitoring Board (DSMB) will conduct an interim analysis after 80 patients have been randomised. There will be continued review of the need for further interim analyses.

The interim analysis will review outcome data and answer the following questions:

1. Are there any significant safety issues that may present an ethical issue in continuing the study? This may include adverse events, but also study conduct and protocol violations
2. Is there overwhelming data suggesting the superiority of one arm that may present an ethical issue in continuing the study? The interim analyses will be adjusted according to Haybittle-Peto, separately for the LPV/r and HCQ main effects, using an

overall two-sided 5% significance level across the interim and final analyses for each main effect. Should the result for a particular main effect (e.g., LPV/r vs no LPV/r) cross the designated boundary at an interim analysis, consideration will be given to termination of the study of that intervention (e.g., cease recruitment to the two LPV/r arms and randomize new patients to HCQ or Standard care only). Details will be provided in the DSMB charter.

3. Are there any other factors that may impact on the feasibility / usefulness of the study? E.g., rate of enrolment, unexpected low rate of outcomes, unable to fund, protocol violations etc.
4. Should the study continue in light of emerging data on treatment of SARS-CoV-2?

In addition to the planned interim analyses, the DSMB will monitor the emerging literature on the effect of antiviral and other treatments on COVID-19. If data are published which demonstrate that one of the trial interventions (LPV/r or hydroxychloroquine) are clearly superior to standard of care, then the DSMB will consider recommending dropping the standard of care arm or ceasing the trial entirely. A study with three treatment arms would address the comparative benefit of LPV/r vs hydroxychloroquine vs both drugs combined. If either LPV/r or hydroxychloroquine are clearly harmful, then the relevant treatment arms could be dropped. The trial steering committee will make the final decision on these matters.

2.10.3 Provision for a Bayesian adaptive trial approach

The trial is currently designed with a frequentist analysis framework. This approach has been necessary given the time constraints in designing and commencing recruitment as soon as possible. However, the trial steering committee will consider moving to a Bayesian adaptive trial approach after further consultation. No interim analyses will be performed until such a decision has been made. If it is decided to convert to a Bayesian adaptive trial approach, no interim analyses will be performed until a pre-specified Bayesian adaptive analysis plan has been designed and agreed upon.

2.11 Monitoring and trial co-ordination

2.11.1 Trial co-ordination

This trial will be co-ordinated from the Doherty Institute for Infection and Immunity. The study will also have input from the Australasian Society for Infectious Diseases Clinical Research Network.

2.11.2 Data safety and monitoring board (DSMB)

An independent DSMB will be established to review the progress of the study and monitor adherence to the protocol, participant recruitment, outcomes, complications, and other issues related to participant safety. They will also monitor the assumptions underlying sample size calculations for the study and alert the investigators if they see substantial departures as the data accumulate. A copy of recommendations from the DSMB will be sent to respective HRECs.

The DSMB will be composed of experts in infectious diseases, biostatistics, clinical trials, virology and immunology. The DSMB members will all be independent of the investigators (none of them will be chief investigators or site investigators).
The DSMB will make recommendations as to whether the study should continue or be terminated, consider participant safety or other circumstances as grounds for early termination, including either compelling internal or external evidence of treatment differences or feasibility of addressing the study hypotheses (e.g. poor participant enrolment, poor adherence).

2.11.3 Study monitoring

Study monitoring will be provided by the responsible monitor(s) in accordance with the Monitoring Plan and ICH GCP. The monitoring plan will be developed and will likely mainly rely on central monitoring with limited site visits depending on resources and number of sites.

2.12 Safety

All trial medications are licensed for use in Australia with established safety profiles.
Specific adverse events to be collected for all patients as pre-defined secondary outcomes are defined in Table 4. Enzyme investigations and imaging only required for pancreatitis if clinically indicated.

Table 4: Definition of adverse events

	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL	Increase of >=7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care	Life-threatening consequences; urgent intervention indicated
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	-

Vomiting	Intervention not indicated	Medical intervention indicated	Tube feeding, TPN, or hospitalization indicated	Life-threatening consequences
Pancreatitis	-	Enzyme elevation; radiologic findings only	Severe pain; vomiting; medical intervention indicated (e.g., analgesia, nutritional support)	Life-threatening consequences; urgent intervention indicated

2.12.1 Serious adverse events (SAEs)

A SAE is defined as any experience that:

- Results in death
- Is life-threatening
  The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically may have caused death, if it were more serious.
- Results in unexpected prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a medically important event or reaction

In this trial, reporting of SAEs to HREC will only be required if they are thought by the reporting clinician (the site PI or their delegate) to be related to the intervention arm study drugs (possibly, probably or definitely as defined in 2.12.3). Such SAEs will be reported on the SAE Reporting Form by the site PI or delegate to the sponsor or delegate within 24 hours of the site study team becoming aware of it. The site PI will also report the SAE to the lead HREC for their site within 72 hours. If it is also an unexpected drug reaction, the Sponsor or delegate will report to the TGA (see 2.12.2).

The occurrence of any of the following should be reported as an SAE and, where clinically appropriate, study drug should be ceased.

<u>For LPV/r</u>:

- Acute pancreatitis
- Hepatotoxicity with evidence of failure
- Anaphylaxis or other suspected serious immune-mediated reaction
- Life-threatening arrythmia requiring administration of an anti-arrhythmic medication, cardioversion, or any form of cardiac pacing.

<u>For hydroxychloroquine</u>:

- Severe hypoglycemia

- Anaphylaxis or other suspected serious immune-mediated reaction
- Life-threatening arrhythmia requiring administration of an anti-arrhythmic medication, cardioversion, or any form of cardiac pacing

2.12.2 Adverse drug reactions (ADRs)

Specific adverse drug reactions that are known to be associated with LPV/r or hydroxychloroquine will be collected routinely on CRFs for both treatment groups.

SUSARS (Suspected Unexpected Serious Adverse Drug Reactions)

ADRs which are serious (as defined for SAEs above) AND are unexpected (as defined by not being listed as an adverse effect in the approved product information) AND are related to the intervention arm study drug (i.e., the LPV/RTV or HCl) will qualify for expedited reporting to the sponsor. As for SAEs, the site PI or their delegate will also report the SUSAR to the HREC within 72 hours. In addition, the sponsor will report the SUSAR to the TGA within 7 calendar days for fatal and life-threatening unexpected serious adverse drug reactions, and within 15 calendar days for other serious adverse drug reactions.

2.12.3 Causality

The principle site investigator will make a judgement regarding whether an adverse event is clinically significant and whether or not it is related to the allocated treatment. The degree of certainty with which an adverse event is attributable to treatment or an alternative cause will be determined by how well the event can be understood in terms of:

- Temporal relationship with the administration of the treatment or cessation of treatment
- Reactions of a similar nature previously observed in the individual or others following treatment

The relationship of the adverse event to treatment will be specified as follows:

Not related	In the PI's opinion, there is not a causal relationship
Unlikely	The temporal association between treatment and the adverse event is such that treatment is not likely to have any reasonable association.
Possibly	The adverse event could have been caused by treatment.
Probably	The adverse event follows a temporal sequence from the time of treatment and cannot be reasonably explained by the known characteristics of the subject's clinical presentation/history.
Definitely	The adverse event follows a reasonable temporal sequence from the time of treatment or reappears when the treatment is repeated.

2.12.4 Summary reporting of adverse events and adverse drug reactions

In addition to the expedited reporting described above, a summary of all SAEs, SUSARs and non-serious adverse drug reactions will be provided to the HREC and DSMB on a regular basis for review, with the frequency determined by each HRECs policy and the NHMRC Guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016.

In summary: SAEs and SUSARs not thought to be related to the study drug (e.g. death from respiratory failure) do not need to be reported in this trial. SAEs thought to be possibly, probably or definitely related to LPV/r (e.g. pancreatitis) or hydroxychloroquine must be reported by the site PI or their delegate to the sponsor within 24 hours, and to the HREC within 72 hours of their becoming aware of it. If it is an expected side effect (i.e., one listed in the product information, such as allergic reaction or diarrhoea), it does not need to be reported to the TGA. If it is both unexpected and serious, it needs to be reported to the TGA within 7 days (fatal or life threatening) or 15 days (other).

2.13 Ethical considerations

2.13.1 General ethical considerations

The study will be conducted according to the declaration of Helsinki, the NHMRC criteria for the ethical conduct of research in humans and the principles of Good Clinical Practice [12].
All therapeutic agents in this study are registered for use in Australia and New Zealand. LPV/r has proven safe in the HIV setting. Hydroxychloroquine is widely used for autoimmune conditions. Chloroquine is widely used as an anti-malarial agent. Written informed consent will be sought from all participants. Approval will be sought from relevant human research ethics committees (HRECs) for all sites.
The study protocol, information statements, consent forms, and any other documents required for ethics approval will be submitted to the relevant HRECs for approval before the study commences. Each HREC reviewing the protocol must be properly constituted according to NHMRC requirements and have the capacity to review the study. Approvals must specify the study title, version numbers, and identify all documents reviewed and state the date of review. No amendments to, or deviations from, the protocol must be initiated without prior written approval from the relevant HREC. The exceptions to this are:

- administrative aspects that have no bearing on subjects;
- the need to address regulatory requirements; and/or,
- the need to eliminate immediate hazards to the subjects.

The investigator will inform the HREC of the following:

- all protocol amendments, informed consent changes or revisions of other documents originally submitted for review;
- serious and/or unexpected adverse events
- new information that may affect the safety of the subjects or the proper conduct of the trial;
- annual updates of study progress
- termination of the study including provision of a final study report.

2.13.2 Informed consent

See Section 2.5.3.

2.13.3 Drug shortages

In the event of shortages of either of the trial drugs LPV/r and hydroxychloroquine at participating trial sites, then treatment arms involving that drug will be suspended at those sites. Randomisation to standard of care or monotherapy with the remaining drug will continue. If both drugs are not available at participating trial sites, then the trial will be suspended at those sites.

The trial steering committee will liaise closely with drug providers to secure drug supply during the course of the study.

2.14 Regulatory approvals

Although LPV/r and hydroxychloroquine are licensed for use in Australia and New Zealand, they will be used outside their approved indications. Hence a Clinical Trials Notification (CTN) will be lodged with the Therapeutic Goods Administration (TGA) for all Australian sites.

2.15 Data harmonisation, access and sharing

2.15.1 Data harmonisation

Given the importance of data sharing with other studies being concurrently conducted, data collection and protocols are being harmonised with:

- WHO Master Protocol: https://www.who.int/blueprint/priority-diseases/key-action/multicenter-adaptive-RCT-of-investigational-therapeutics-for-COVID-19.pdf
- ISARIC (International Severe Acute Respiratory and Emerging Infection Consortium) WHO case Record Form: https://isaric.tghn.org/covid-19-clinical-research-resources/
- REMAP-CAP (A Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia): https://www.remapcap.org/

2.15.2 Data Access

The trial steering committee will be the custodians of the final trial dataset. No-one outside the trial steering committee will be given access to the data without the permission of the trial steering committee. No identifying data will be given to any third parties at any stage. Following study close out and locking of the database, it will be stored on the servers of the sponsor.

2.15.3 Data sharing

2.15.3.1 *Global datasets*

Harmonisation of data collection as detailed in 2.15.1 should facilitate data sharing. The study will have an ethos of appropriate sharing of data to contribute towards global datasets.

2.15.3.2 *Communication with REMAP-CAP*

At study sites where REMAP-CAP is open for recruitment, participants enrolled in ASCOT and progressing to ICU admission or need for invasive and non-invasive ventilation will be identified to REMAP-CAP study staff as being enrolled in ASCOT. The ASCOT unique study number will be communicated to REMAP-CAP to allow linkage of data.

2.15.3.3 *Communication with SPRINT-SARI*

At study sites where SPRINT-SARI is collecting observational data, data from participants enrolled in ASCOT will be shared with SPRINT-SARI. No identifiable data will be provided.

2.15.3.4 *Communication with participating sites and clinical community*

Data collected may be shared in aggregate form in real time to inform the clinical community and facilitate discussion of clinical management of patients. These data will only be presented for all participants in total without identification of allocated treatments. Examples of such data will be baseline characteristics, investigation results, hospitalisation and ICU status, need for invasive or non-invasive ventilation, and mortality.

2.16 Dissemination policy

The trial results will be communicated to all site investigators by teleconference prior to publication or presentation. The trial results will also be submitted for presentation at national and international meetings and publications submitted to a peer reviewed scientific journal, irrespective of the results. A plain-language summary of the trial results will be made available to individual participants upon request.

Primary and senior authorship will be determined by the study steering committee. The authorship of the paper will include all of the Steering Committee who meet ICJME criteria for authorship. Hospitals contributing at least one case for analysis will nominate a locally determined coordinating investigator for inclusion, in order of number of participants enrolled. All hospitals and participating organisations with protocols enacted will be listed as 'ASCOT study group'. The ASCOT study group will consist of all named site investigators and will be listed in the collaborators section of the paper. The author byline will include 'for the ASID Clinical Research Network'.

3. Appendices

3.1. Trial sites

See Appendix 1 for list of trial sites and site principal investigators.

3.2. Plans for biological specimens

There will be 3 tiers for collection of data and samples (see 2.5.7). The *Core* data only includes recording of clinical, outcome, treatment data and results from laboratory testing and does not involve storage of samples.

The *Enhanced biological* and *Research biological* data and samples includes the collection and storage of some biological samples. The collection, processing, storage and shipping of biological samples will follow local standard operating procedures and regulations for handling and transporting clinical specimens containing infectious materials. These details

will align with the Sentinel Travellers Research Preparedness Platform for Emerging Infectious Diseases (SETREP-ID) Biological Specimen Standard Operating Procedures. These samples and data collection will be dependent on site capacity and participant consent obtained for enhanced sample collection, storage and sharing.

3.3. Trial Governance

3.3.1. Trial Steering Committee

The trial will be overseen by the Trial Steering Committee that will include:
Steven Tong, Justin Denholm, Joshua Davis, David Paterson, representatives from each participating jurisdiction, the ASID CRN, and a biostatistician.

3.3.2. Trial Management Committee

The trial management committee will oversee the day to day aspects of the trial. This committee will include:
Steven Tong, Justin Denholm, Joshua Davis, clinical trial manager and project officers.

3.3.3. Funding arrangements

At the time of this protocol being completed, some seed funding has been obtained. Further funding is being sought. The appendix will be updated as funding sources are clarified and received.

4. References

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AustralaSian COVID-19 Trial

Study Title	***Australasian COVID-19 Trial (ASCOT) ADAptive Platform Trial***
Abbreviated Title	ASCOT ADAPT
Clinical trials registration	ACTRN12620000445976
Universal trial number	U1111-1250-5165
Protocol version/date	Version 6.0, 30 March 2022
Protocol number	ERM62646-A
Funding source	To date, funders for the ASCOT trial include • The Royal Brisbane and Women's Hospital Foundation • The Pratt family foundation • Minderoo • BHP • APPRISE network through the Doherty Institute • A New Zealand Health Research Council grant • Macquarie Group Foundation • Medical Research Future Fund (MRFF) Role of funders in study design, analysis and decision to publish: None
Overarching study sponsor	University of Melbourne
Sponsor for Australian sites	University of Melbourne
Sponsor for NZ sites	Middlemore Clinical Trials
Sponsor for Indian and Nepal sites	The George Institute for Global Health
Sponsor for Danish Sites	Centre of Research and Disruption of Infectious Diseases (CREDID)
Co-ordination	
Overarching Co-ordinating centre	The Peter Doherty Institute for Infection and Immunity (University of Melbourne)
ASCOT India and Nepal co-ordinating hub	The George Institute for Global Health India
NZ co-ordinating hub	Middlemore Clinical Trials
NSW/ACT co-ordinating hub	Hunter Medical Research Institute, Newcastle, NSW

QLD co-ordinating hub	University of Queensland Centre for Clinical Research
Collaborating bodies	The Australasian Society for Infectious Diseases Clinical Research Network (ASID CRN)
Investigators	
Co-ordinating Principal Investigators	A/Prof Steven Tong[1,2,3,] A/Prof Justin Denholm[1,2,4] Professor Joshua Davis[3,5] Professor Bala Venkatesh[6, 7, 8] Dr Susan Morpeth[9]
Chief Investigators	1. David Paterson[10] 2. David Price[1,4] 3. Matthew O'Sullivan[11,12,13] 4. Jason Roberts[10,14,15] 5. Megan Rees[2] 6. Vivek Jha[6,16,17] 7. Naomi Hammond[6] 8. Thomas Snelling[3, 18, 19, 20] 9. Asha Bowen[3,20,21] 10. Zoe McQuilten[22]
Coordinating and Chief Investigators' Affiliations	1. Peter Doherty Institute for Infection and Immunity, Victoria, 3000, Australia 2. Royal Melbourne Hospital, Melbourne Health, Victoria, 3050, Australia 3. Menzies School of Health Research, Casuarina NT 0811 4. University of Melbourne, Victoria, 3010, Australia 5. Hunter New England Health, Lookout Road, New Lambton Heights, NSW, 2305 6. The George Institute for Global Health, Sydney and New Delhi 7. Faculty of Medicine, University of New South Wales 8. Wesley and Princess Alexandra Hospitals, University of Queensland 9. Middlemore Hospital, 100 Hospital Road, Otahuhu, Auckland, NZ 10. Centre for Clinical Research, Faculty of Medicine, The University of Queensland, Level

	8, Building 71/918, UQCCR, RBWH Campus, Herston QLD 4029 11. Centre for Infectious Diseases and Microbiology, Westmead Hospital, Westmead, Australia 12. New South Wales Health Pathology – Institute for Clinical Pathology and Medical Research, Westmead, Australia 13. Marie Bashir Institute for Infectious Diseases and Biosecurity, University of Sydney, Australia 14. Departments of Pharmacy and Intensive Care Medicine, Royal Brisbane and Women's Hospital, Brisbane, Australia 15. Division of Anaesthesiology Critical Care Emergency and Pain Medicine, Nîmes University Hospital, University of Montpellier, Nîmes France 16. School of Public Health, Imperial College, London, UK 17. Manipal Academy of Higher Education, Manipal, India 18. Sydney School of Public Health, University of Sydney, Camperdown, NSW 19. Sydney Children's Hospital Network, Westmead, NSW 20. Wesfarmers Centre for Vaccines and Infectious Diseases, Telethon Kids Institute, University of Western Australia, WA 21. Department of Infectious Diseases, Perth Children's Hospital, WA 22. Department of Epidemiology and Preventive Medicine, Monash University, Victoria, 3001

Document history:

Version Number	Date	Summary of changes
1.0	23 March 2020	Final approved version submitted to HREC
2.0	1 April 2020	Updated post HREC review
3.0	18 May 2020	This version was not implemented at sites.
4.0	16 July 2020	Amendment to drop HCQ monotherapy and add convalescent plasma therapy

Version Number	Date	Summary of changes
ASCOT-ADAPT 1.0	10 Aug 2020	Transition to adaptive platform trial
ASCOT-ADAPT 2.0	30 Sep 2020	Updated following Investigator and HREC review.
ASCOT-ADAPT 3.0	30 October 2020	Minor amendments to provide clarity in various sections of the protocol.
ASCOT-ADAPT 4.0	30 April 2021	Minor amendments to provide clarity in various sections of the protocol.
ASCOT-ADAPT 5.0	05 Aug 2021	Minor amendments to clarify who will be unblinded to aggregate results.
ASCOT-ADAPT 6.0	30 Mar 2022	Minor amendments to include the use of Rapid Antigen Tests, incorporate changes to the statistical aspects of the study, and update some figures and formatting

Statement of Compliance

This clinical trial will be conducted in compliance with all stipulation of this protocol, the conditions of the ethics committee approval, the NHMRC National Statement on ethical Conduct in Human Research (2007 and all updates), the Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2), dated 9 November 2016 annotated with TGA comments and the NHMRC guidance Safety monitoring and reporting in clinical trials involving therapeutic goods (EH59, 2016).

ASCOT-ADAPT is a not-for-profit trial.

1. Table of Contents

ASCOT Study Synopsis

TITLE	Australasian COVID-19 Trial: An Adaptive Platform Trial (ASCOT-ADAPT). A multi-centre randomised adaptive platform clinical trial to assess clinical, virological and immunological outcomes in patients with SARS-CoV-2 infection (COVID-19)
BACKGROUND	The SARS-CoV-2 virus has caused over 1,000,000 deaths globally. The global response is working to accelerate diagnostics, vaccines and therapeutics. More effective therapies are needed.
CORE PRIMARY OUTCOME MEASURE	Death from any cause or requirement of new intensive respiratory support (invasive or non-invasive ventilation) or vasopressor/inotropic support in the 28 days after randomisation.
CORE SECONDARY OUTCOME MEASURES	1. Time to clinical recovery during the first 28 days after randomisation 2. WHO 8-point ordinal outcome scale at day 28 post randomisation 3. All-cause mortality at 28 and 90 days post randomisation 4. Days alive and free of hospital by 28 days post randomisation 5. Days alive and free of ventilation by 28 days post randomisation 6. Presence of patient reported outcome of shortness of breath at days 28 and 90 post randomisation 7. Quality of life as measured by EQ5D5L questionnaire at days 28 and 90 post randomisation
STUDY DOMAINS	1. Antiviral domain 2. Therapeutic antibody domain 3. Anticoagulation domain 4. Other domain (to be determined)
STUDY DURATION	November 2020 onwards
NUMBER OF PARTICIPANTS	Flexible (see statistical appendices for justification and details)
PLATFORM INCLUSION CRITERIA	1. Age ≥ 18 years 2. Admitted to an acute-care hospital 3. Confirmed SARS-CoV-2 by nucleic acid testing or rapid antigen testing in the 14 days prior to randomisation 4. Able to be randomised within 14 days of symptom onset 5. At least one symptom or sign attributable to SARS-CoV-2 infection
PLATFORM EXCLUSION CRITERIA	1. Currently receiving acute intensive respiratory support (invasive or non-invasive ventilation) or vasopressor/inotropic support. Note, participants already on community based non-invasive ventilation (either CPAP or BiPAP) can still be recruited. Humidified high flow nasal oxygen will not be considered an exclusion criterion. 2. Previous participation in the trial 3. Treating team deems enrolment in the study is not in the best interest of the patient

	4. Death is deemed to be imminent and inevitable within the next 24 hours 5. Either the patient or their primary treating clinician are not committed to active treatment
BLINDING	This will be an open-label study. Only specified members of the statistical analytical team, DSMB and data co-ordinator will have access to unblinded results and data, with other trial investigators and staff remaining blinded to the aggregate results until completion of final analysis for a domain.

Investigator Agreement

Note that this protocol can be virtually signed via the eISF (SiteDocs), in which case this page does not require a PI signature.

I have read the protocol entitled Australasian COVID-19 Trial (ASCOT- ADAPT).

By signing this protocol, I agree to conduct the clinical trial, after approval by a Human Research Ethics Committee or Institutional Review Board, in accordance with the protocol and the principles laid down in the Declaration of Helsinki and Good Clinical Practice [Guideline for Good Clinical Practice E6 (R2), dated 9 November 2016].

With the exception of medical emergencies, changes to the protocol will only be implemented after written approval is received from the relevant Human Research Ethics Committee or Institutional Review Board.

I will ensure that my trial staff fully understand and follow the protocol and evidence of their training is documented on the trial training log.

Name of Site	Name of PI	Signature and date (dd-mmm-yyyy format)

Contributions

Name	Summary of contribution
A/Prof Steven Tong	- initiated study design, protocol development
A/Prof Justin Denholm	- initiated study design, protocol development
Prof Joshua Davis	- initiated study design, protocol development
Prof Bala Venkatesh	- protocol development, development of international collaborations
Dr Susan Morpeth	- protocol development, site investigator, New Zealand lead
Prof David Paterson	- protocol development, site investigator, Queensland lead
Dr David Price	- provided statistical expertise on the clinical trial design
Dr Matthew O'Sullivan	- protocol development, site investigator
Prof Jason Roberts	- protocol development, pharmacokinetic expertise and lead
Dr Megan Rees	- protocol development
Prof Vivek Jha	- protocol development, development of international collaborations
Dr Naomi Hammond	- protocol development, development of international collaborations
Prof Thomas Snelling	- provided statistical expertise on the clinical trial design
Dr Asha Bowen	- chair of international trial steering committee
Dr Zoe McQuilten	- protocol development

1. Introduction

1.1 Abbreviations

AE	Adverse event
AR	Adverse reaction
ASC	ASCOT Sponsorship Committee
ASID CRN	The Australasian Society for Infectious Diseases Clinical Research Network
BIPAP	Bilevel positive airway pressure
CI	Chief Investigator – A researcher who contributes to the funding, planning, and running of the entire study
Co-I	Co-investigator (a clinician or research assistant who aids the PI at a site)
CPAP	Continuous positive airway pressure
CRF	Case Report Form
CRP	C-reactive protein
CTN	Clinical trial notification (to the Therapeutic Goods Administration)
DOB	Date of Birth
DSA	Domain Specific Appendix
DSMB	Data and safety monitoring board
DSWG	Domain Specific Working Group
eCRF	Electronic Case Report Form
EDC	Electronic data capture
eCRF	Electronic case report forms
GCP	Good clinical practice
GP	General practitioner
HRN	Hospital record number
HREC	Human research ethics committee
ICH	International Council for Harmonisation
ICU	Intensive care unit
ID	identification
ID physician	Infectious disease physician
ITSC	International Trial Steering Committee
NHMRC	National Health and Medical Research Council
NIV	Non-invasive ventilation
pCRF	Paper Case Report Form
PI	Principal Investigator (the clinician with overall responsibly at each site)
RC	Research co-ordinator (responsible for multiple sites)
RCT	Randomised control trial
RSA	Region Specific Appendix
RSWG	Region Specific Working Group
SAE	Serious adverse event

SAR	Serious Adverse Reaction
SSI	Significant safety issue
SOP	Standard Operating Procedure
SUSAR	Suspected unexpected serious adverse reaction
TAC	Therapeutic Advisory Committee
TGA	Therapeutic Goods Administration
USM	Urgent safety measure

1.2 Background and Rationale

1.2.1 Overview

In December 2019, a novel coronavirus emerged from Wuhan China as the cause of a pneumonia syndrome. This SARS-CoV-2 is a beta-coronavirus and related to SARS. Since December 2019, there have been hundreds of millions of cases worldwide, and millions of deaths.

Thousands of clinical trials have been registered and are ongoing for COVID treatments. At the time of writing, the only effective treatments are corticosteroid therapy[1-5], interleukin-6 receptor antagonists (IL-6 RA) such as tocilizumab[6], and possibly remdesivir.

Ongoing clinical trials are needed to identify individual treatments and/or treatment combinations that have the greatest beneficial potential for patients with moderate COVID-19, and to allow access to emerging and experimental therapeutics for patients in the participating regions.

1.2.2 Bayesian adaptive platform trials

Adaptive Platform Trials are an innovative trials methodology[7-9] now established for oncology trials[10] and recently funded for infectious diseases syndromes of community-acquired pneumonia (REMAP-CAP, NHMRC #1101719, CIA Webb), cystic fibrosis (BEAT-CF, NHMRC #1152376, CIA Snelling) and *S. aureus* bacteremia (SNAP, NHMRC #1184238, CIA Tong).

Conventional RCTs, at the time of design, make assumptions about plausible effect size, incidence of the primary outcome, and sample size, holding these assumptions constant until trial completion. Adaptive Platform Trials incorporate multiple statistical and design features that are not reliant on these types of pre-trial assumptions. Platform trials allow multiple questions to be evaluated simultaneously and sequentially as data accrues, and can evaluate interactions between different treatment options. They typically have the joint goals of optimising treatment for participants in the trial and also identifying the effects of treatment combinations for a disease as rapidly as possible. The move from ASCOT (conventional RCT) to ASCOT-ADAPT enables the benefit of the critical design features described below.

Critical design features of ASCOT-ADAPT that will contribute substantially to enhanced trial efficiency and rapid implementation of trial findings include:

First, the trial is highly **pragmatic and embedded** within routine care. The inclusion criteria are easily identified and exclusion criteria minimal. Wherever possible, routine clinical and administrative data will be used for data collection.

Second, we will implement a **universal trial master protocol** (known for this trial as the Core Protocol) with several domains. By addressing multiple questions in parallel and evaluating

interactions between interventions, the platform will reduce the time, cost and sample size required to reach definitive conclusions on optimal therapy.

Third, **frequent interim analyses** will be used so that questions are concluded as soon as there is robust statistical confidence, not when a pre-specified sample size has been recruited. This allows the platform to match the size of any observed treatment effect, including no effect, to conclude superiority and / or non-inferiority (within a pre-specified delta) as soon as warranted by accrued data. Regular interim analyses will be undertaken using a Bayesian Hierarchical Model[11] that estimates the probability of effectiveness and futility relative to pre-defined reference levels and superiority and inferiority relative to all other treatments for all interventions being evaluated. The results from each interim analysis will be reviewed by an independent DSMB responsible for recommending actions based on the analysis of accumulating data. Pre-specified stopping rules, informed by pre-trial simulations, will be provided to the DSMB. Details of simulations are provided in the Statistical Simulations Report.

Fourth, we will implement **response adaptive randomisation** (RAR), which involves updating allocation probabilities based on the results from each interim analysis. Under RAR, the proportion of patients randomised to different treatments will progressively reflect the relative benefit of these treatments up to that point in the trial. Therefore, while treatments are randomised, the participants will be preferentially allocated to those that the data indicate are more likely to be the most effective treatments.

1.2.3 Objectives

The overarching objective of ASCOT-ADAPT is to identify the regimen (combination of interventions) associated with the highest chance of survival free of advanced respiratory support or vasopressor / inotropic support at 28 days after randomisation, in adults hospitalised with COVID-19 but not requiring ICU-level care at baseline.

1.3 Protocol structure

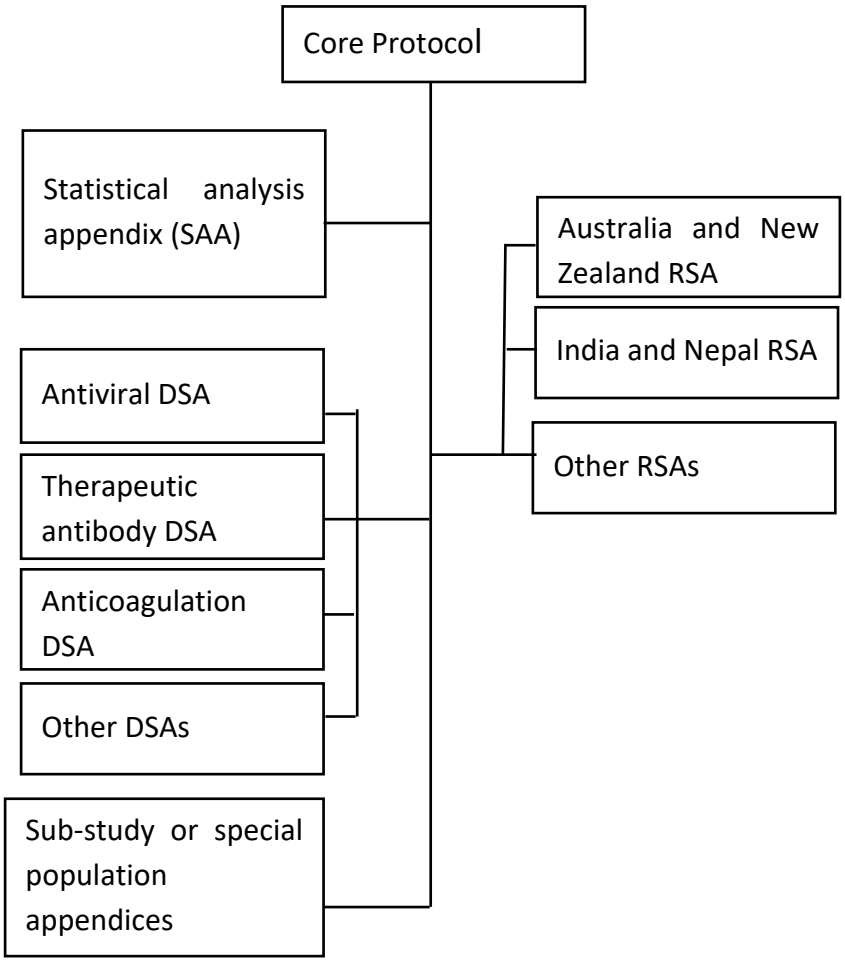


Figure 1: protocol structure. The protocol will include Domain Specific Appendices (DSA) and Regional Specific Appendices (RSA)

1.3.1 Core protocol

The Core Protocol (this document) contains all information relevant to trial processes and applies to all regions and to all domains for the duration of the trial. The Core Protocol is anticipated to require only rare modification. It contains the following information:

- The background and rationale for studying COVID as a problem of public health interest
- The rationale for the use of an adaptive platform trial structure
- The trial design, including eligibility criteria for entry into trial platform, randomisation and treatment allocation procedures, trial endpoints, methods to control bias, general principles of the statistical analysis of data, and criteria for termination of the trial
- The trial conduct, including methods of recruitment, site-specific timelines, data collection and management, and procedures related to participant safety and monitoring
- The international trial governance structures

Note that the eligibility criteria, data collection, and secondary outcomes in the core protocol are a subset of those in the DSAs. Each domain generally has additional eligibility criteria, data points and secondary outcome measures. Hence the DSA needs to be read in conjunction with the core protocol and selected other appendices (e.g. statistical, regional) in order to approximate a typical full trial protocol.

1.3.2 Statistical Documentation

The primary statistical documents for the trial are the Statistical Analysis Appendix (SAA), a Trial Simulations Report (TSR) and the Statistical Implementation Guide (SIG). Both the SAA and the TSR are designed to be generic documents largely unaffected by the introduction of new interventions and domains. Both the TSR and the SIG are operational documents that are intended to be revised as the trial progresses. An overview of the purpose and indicative contents of these documents are presented below.

1.3.2.2 Statistical Analysis

The SAA specifies the general statistical framework used in the trial. This includes, but is not limited to model specifications, definition of statistical quantities of interest, trial adaptations, decision criteria and approaches to reporting. As the SAA is a generic document it will be amended infrequently and will typically not need revision when new interventions or domains are added.

1.3.2.3 Trial Simulations Report

The TSR specifies the methods and results from the Monte Carlo simulations used to characterise the trial operating characteristics. These were run across a range of plausible assumptions regarding outcomes, treatment effects, and interactions between interventions in different domains. The cumulative probability of declaring effectiveness, superiority, inferiority and futility are evaluated using these simulations, which can be interpreted in terms of statistical power and the probability of false positives occurring. The expected sample size by treatment arm is evaluated to provide an indication of the number of participants allocated per treatment arm. The TSR will be maintained as an **operational document** that will be updated over the course of the trial, but conclusions from simulations will be included in protocol documents, which will be amended as required.

1.3.2.4 Statistical Implementation Guide

The SIG is an operational document that provides information on the trial status and low-level explanation and implementation details for statistical models and analyses based on the evolving state of the trial. Where necessary, that is where changes have occurred, a release of the SIG is made for each interim analysis. Unlike the SAA and the TSR, the SIG is not intervention agnostic and as such it contains details on treatment domains and interventions.

1.3.3 Region-specific appendices (RSAs)

ASCOT ADAPT will be conducted in multiple countries around the world with varying legislative, ethical and governance requirements. Each RSA contains information specific to the conduct of the trial in that region, including:

- The definition of the region
- The governance structure within a region
- Ethical and governance issues relevant to a region not covered in the Core Protocol
- The availability of trial domains and interventions within a region
- Region-specific treatment allocation and data management procedures

1.3.4 Domain-specific appendices (DSAs)

Each intervention examined within ASCOT ADAPT will be fully described within a DSA. Domains will evolve over time, with the potential for progressive additions and removals of both interventions within domains and entire domains as outcome data are accrued. DSAs contain the following information relevant to a domain:

- The background and rationale for each intervention examined
- Domain-specific eligibility criteria
- A description of the interventions and procedures for their delivery
- Domain-specific data and endpoints not included in the Core Protocol
- Domain-specific ethical considerations
- Domain-specific organisational considerations

1.3.5 Sub-study, biological specimens and special population appendices

Sub-studies will also be fully described within appendices. These will contain the following information relevant to a sub-study:

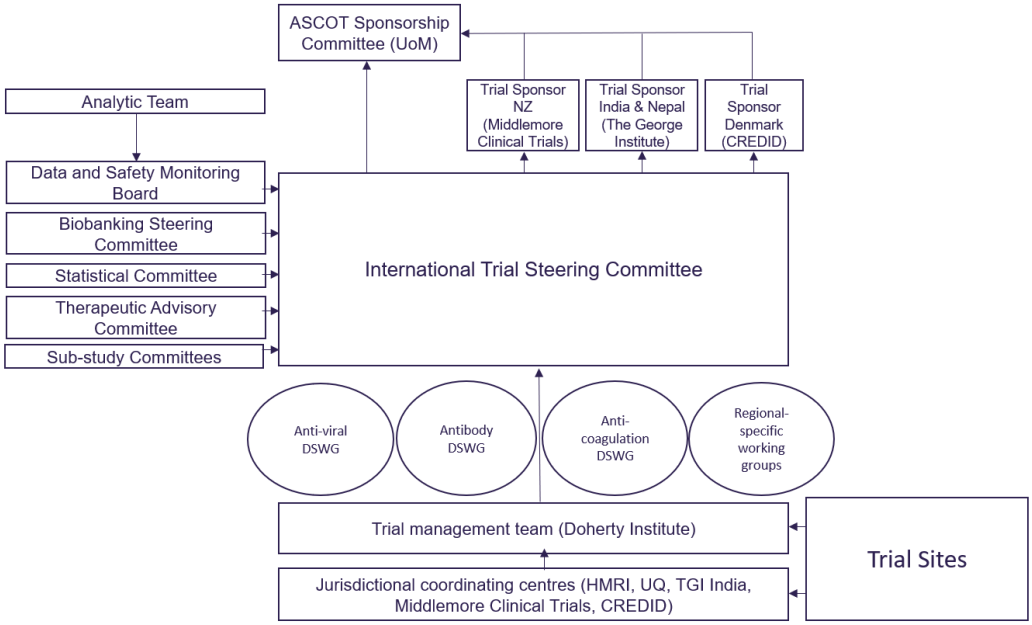
- Background and rationale for the sub-study
- Sub-study eligibility criteria
- Description of the procedures required for conduct of the sub-study

Appendices may also be required for special populations (e.g. pregnant women, patients with end stage renal disease, patients with active malignancy). For these special populations, appendices will include any additional exclusion criteria, data collection and ethical/legal considerations which are not already included in the core protocol.

A Biological Specimens appendix will contain details on any optional biospecimen collection not described in the core protocol or domain-specific appendices, including timing and type of collection, transport, storage and planned use of these specimens.

1.4 Study governance

Figure 2. Study administration and governance structure



1.4.1 International Trial Steering Committee (ITSC)

The intent of the ITSC is to have both theoretical and practical experience and knowledge regarding overall design, domain-specific expertise, and regional-specific expertise. As such, the ITSC will include clinical trialists, biostatisticians, regional lead investigators, domain lead investigators and project manager(s).

The responsibilities of the ITSC are:

- Development and amendment of the Core Protocol
- Recruitment and approval of new regions to the platform
- Liaison with the DSMB including, where appropriate, decisions regarding Platform Conclusions
- Consideration of requests and approval of the addition of domains and their nested interventions to the platform including prioritization of new domains, new interventions within a domain or both
- In conjunction with DSWGs, the analysis and reporting of results from domains
- Approval of manuscripts reporting results that are submitted by DSWGs
- Obtaining funding for the platform
- Determine the strategic direction of the platform

1.4.2 Regional Specific Working Group (RSWG)

The operation of the platform in each region is undertaken by that region's RSWG, the composition of which is to be determined by investigators in each region with membership listed in each RSA. Cross-representation between RSWGs is strongly encouraged.

The responsibilities of each RSWG are:

- Development and amendment of the RSA for that region
- Identification and management of sites in that region
- Liaison with regional funding bodies
- Consideration of the feasibility and suitability of interventions (and domains) for that region

1.4.3 Domain-Specific Working Groups (DSWG)

Each active and future planned domain (or closely related set of domains) will be administered by a DSWG.

The responsibilities of each DSWG are:

- Development and amendment of the DSA
- Proposal and development of new interventions within a domain
- In conjunction with the ITSC, analysing and reporting results from the domain
- Obtaining funding to support the domain, with a requirement that, if such funds are obtained, that an appropriate contribution to the conduct of the platform is also made.

Membership of each DSWG is set out in the corresponding DSA but should comprise individuals that provide broad international representation, content knowledge of the domain, expertise of trial conduct and design. Membership selection should take into account gender, geographical and craft group (infectious diseases, respiratory, biostatistics, haematology etc) equity and diversity.

1.4.4 Independent Data Safety and Monitoring Board (DSMB)

An independent DSMB will review the progress of the study and monitor adherence to the protocol, participant recruitment, outcomes, complications, accuracy and completeness of data capture and other issues related to participant safety. They will also monitor the assumptions underlying sample size calculations for the study and alert the investigators if they see substantial departures as the data accumulate. A copy of recommendations from the DSMB will be sent to respective HRECs.

The DSMB will be composed of international experts in infectious diseases, biostatistics, clinical trials, virology and immunology. The DSMB members will all be independent of the investigators (none of them will be chief investigators or site investigators).

The DSMB will make recommendations as to whether the study should continue or be terminated, consider participant safety or other circumstances as grounds for early termination, including either compelling internal or external evidence of treatment differences or feasibility of addressing the study hypotheses (e.g. poor participant enrolment, poor adherence).

The DSMB will operate under the rules of an approved charter that will be written by the ITSC and study staff and reviewed at the organisational meeting of the DSMB.

1.4.5 ASCOT Sponsorship Committee (ASC)

The ASC is a delegated sub-committee of the University of Melbourne Sponsorship Committee and is responsible for ensuring that the University's obligations as trial Sponsor are met. The committee will be composed of an independent chair, a representative of the ASCOT International Trial Steering Committee, members representing the major funding organisations, members with regulatory, HREC and research directorate experience, and legal counsel.

1.4.6 Therapeutic Advisory Committee (TAC)

An independent TAC will review any new potential therapies to be included into the ASCOT ADAPT domains. The committee will be composed of infectious diseases, virology and respiratory experts, a biostatistician, and other expertise as needed. The committee will meet on a regular basis and complete a documented review of proposals received from external sponsors. The TAC will report directly to the ITSC and operate under the rules of an approved charter.

1.4.7 ASCOT Biobanking Committee (ABC).

The ABC will oversee sample collection, storage and applications for sample access related to biological research undertaken through the ASCOT ADAPT platform. The committee will be composed of clinical and laboratory researchers, representatives from DSWG and RSWG, and other expertise as required. The ABC will meet regularly, report directly to the ITSC, and operate under the rules of an approved charter.

1.4.8 Statistical Committee

The Statistical Committee is responsible for the development of the statistical analysis plan and provide recommendations for the analysis and handling of outcome data. They will remain blinded to aggregated data and results until completion of final analysis for a domain.

1.4.9 Analytic Team

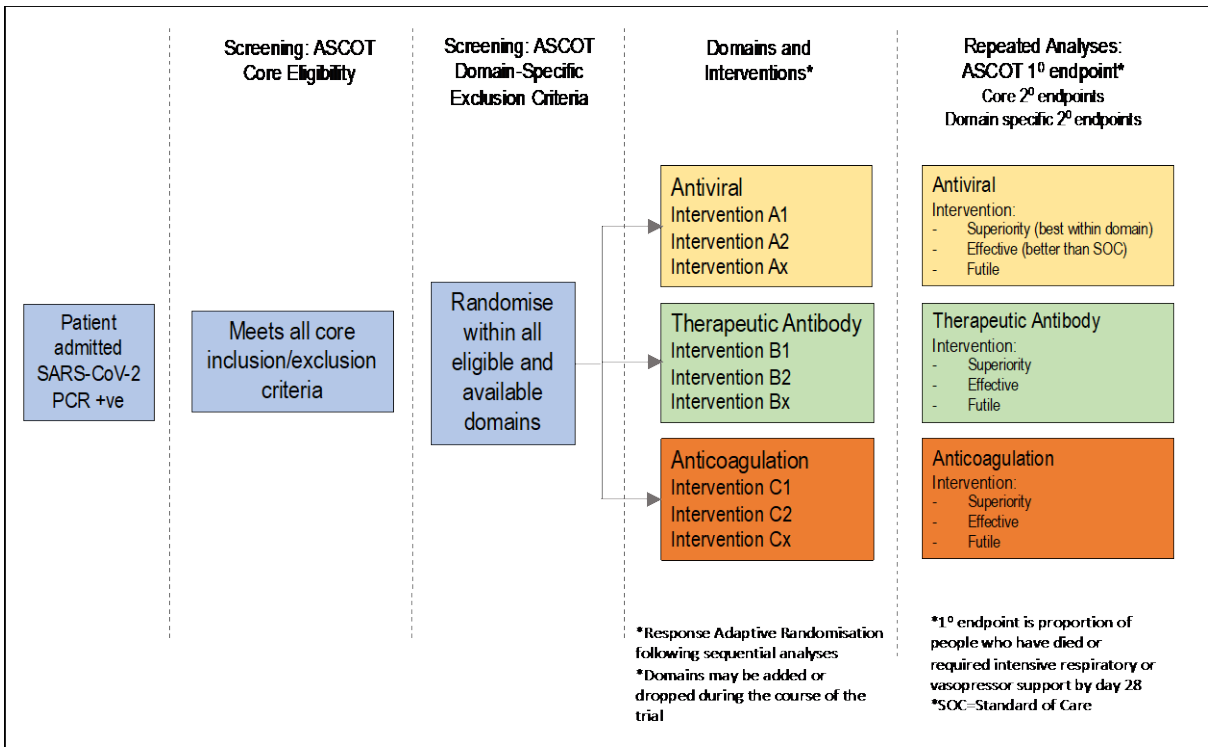
The analytical team is responsible for the conduct of the planned interim analyses in the trial by running predetermined statistical models at each adaptive analysis and providing this output to the DSMB. The analytic team will be unblinded to aggregate data and are therefore not permitted to contribute to variations in the design of the trial.

1.5 Trial design

ASCOT ADAPT is an investigator-initiated, multi-centre, open-label, randomised controlled Bayesian adaptive platform trial. The study design will allow harmonisation with existing frameworks such as the Randomized, embedded, multifactorial adaptive platform trial for community-acquired pneumonia (REMAP-CAP) study and biobanking initiatives. Patients enrolled in ASCOT ADAPT and who progress to requiring invasive or non-invasive ventilation can be enrolled in REMAP-CAP (follow-up data will still be collected from these patients for ASCOT).

There will be a core dataset collected for all patients at all sites and enhanced and research data and biological samples for sites with capacity (detailed in the Biological Specimens appendix). Data will be harmonised with outcome measures for COVID-19 clinical research[12].

Figure 3 – Overview of trial design



Domain structure at the initiation of the trial (as an illustration of study design)

Antiviral Domain	Therapeutic Antibody Domain	Anticoagulation Domain	Other domain(s)
1. Antiviral A 2. Antiviral B 3. Antiviral C 4. Antiviral D	1. Antibody A 2. Antibody B	1. Anticoagulation A 2. Anticoagulation B 3. Anticoagulation C	To be determined. May be added based on emerging data and drug availability.

Standard of care will vary between regions and sites, and over the course of the trial. At the time of writing, it is likely to include low-dose dexamethasone (6mg daily IV or PO for 10 days) in all patients requiring supplemental oxygen, and remdesivir in those regions/sites where it is available, again for patients requiring supplemental oxygen. Standard of care is not dictated by the core protocol, but data will be collected on any agents used as standard and adjusted for in the statistical model.

2. Methods

2.1 Study setting

We are aiming to recruit from international sites, including but not limited to Australia, NZ, Denmark and India. Sites will be selected on the basis of:

i. Capacity to randomise COVID-19 cases to the trial if there is an outbreak in the region;

ii. The availability of a committed and competent principal investigator (and site research team where appropriate);
iii. After satisfactory completion of a study feasibility questionnaire to determine the availability of resources and staff to conduct the ASCOT ADAPT trial.

2.2 Eligibility criteria

2.2.1 Participant inclusion criteria

1. Age ≥ 18 years
2. Admitted to an acute-care hospital
3. Confirmed SARS-CoV-2 by nucleic acid testing or rapid antigen testing in the past 14 days
4. Able to be randomised within 14 days of symptom onset
5. At least one symptom or sign attributable to SARS-CoV-2 infection

2.2.2 Participant exclusion criteria

1. Currently receiving acute intensive respiratory support (invasive or non-invasive mechanical ventilation) or vasopressor/inotropic support. Note, participants already on community based non-invasive ventilation (either CPAP or BiPAP) can still be recruited. Humidified high flow nasal oxygen will not be considered an exclusion criterion.
2. Previous participation in the trial
3. Treating team deems enrolment in the study is not in the best interests of the patient
4. Death is deemed to be imminent and inevitable within the next 24 hours
5. Either the patient or their primary treating clinician are not committed to active treatment.

This criterion seeks to exclude those patients where supportive comfort measures only are being provided. Patients who are planned for active ward management with a clear aim to improve survival, even if intensive care unit level support is not being offered, should still be included.

2.2.3 Strategies to improve adherence to protocol

2.2.3.1 Principal Investigator (PI) training

All site PIs will be trained in the study protocol, SOPs and their reporting requirements by the project manager, or a study chief investigator, prior to the site being opened for recruitment. All site PIs should complete an accredited Good Clinical Practice training course.

The project manager or their delegate will have regular contact with all enrolling site investigators, including after the enrolment of participants number 1, 2 and 5 at each site, and every 10 participants thereafter. This contact may be via telephone, email or in the format of group sessions involving more than one site at a time.

2.2.3.2 Documentation in patient's medical record and bedside chart

An ASCOT ADAPT sticker* will be placed in the patient's medical record (one on the progress notes on the day of randomisation, and one in the front inside cover of the medical record ["old note"] if one exists). This sticker will alert clinicians that the patient has been randomised to the ASCOT ADAPT study, with a brief explanation of the study.

A copy of the study synopsis will be placed in the bedside chart (observations and drug chart) of the patient. A checklist of study procedures will also be placed in the bedside chart.
*For sites with electronic medical records and/or prescribing, an electronic "sticker" may be used, and appropriate annotations will be made to the electronic drug chart, or as per local institutional guidelines.

2.2.3.3Checking of drug charts

The medication chart (be it paper or electronic) will be checked each business day by the PI or their delegate (registrar or research nurse) as long as the patient remains on at least one protocol-determined intervention, and whilst they remain an inpatient to ensure adherence to the study protocol. In the event of a SAR requiring treatment, the drug chart will continue to be checked until the treatment for the SAR is discontinued and/or the SAR has resolved.

2.3 Outcomes

2.3.1 Primary outcome

Death from any cause or requirement of new intensive respiratory support (invasive or non-invasive ventilation) or vasopressor/inotropic support in the 28 days after randomisation. This includes any participant who receives non-invasive mechanical ventilation (either CPAP or BIPAP, apart from the below considerations) any time after enrolment even if not transferred to ICU. It does NOT include the use of humidified high-flow nasal prong oxygen.

Participants on pre-existing home BiPAP or CPAP will not be considered to have met the primary outcome unless they have either

i. required invasive mechanical ventilation (i.e. intubation), or
ii. graduated from CPAP only whilst asleep to BiPAP at any time, or
iii. graduated from BiPAP only whilst asleep to BiPAP for >12 hours/day, or
iv. died by day 28

This endpoint applies across all domains.

There may be cases where a patient has been assessed as requiring intensive respiratory support (invasive or non-invasive ventilation) or vasopressor/inotropic support, but the patient or family declined treatment and the patient was discharged home. If attempts to obtain 28-day data are unsuccessful or not possible, and the investigator had deemed at the time of discharge that the patient would be highly likely to die within 28 days from randomisation, these participants will be deemed to have met the primary outcome.

2.3.2 Core secondary outcome measures

1. Time to clinical recovery during the first 28 days after enrolment
   1.1. Time to clinical recovery is defined as the first day, during the 28 days after enrolment, on which a patient satisfies categories 1, 2, or 3 on the WHO eight-point ordinal outcome scale. For the purposes of this outcome measure, it will be

assumed that the participant is not hospitalised on the first day following discharge.

2. WHO 8-point ordinal outcome scale at day 28 after randomisation
   2.1. The ordinal score is:
   1. Not hospitalised, no limitations on activities
   2. Not hospitalised, limitation on activities
   3. Hospitalised, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalization was extended for infection control purposes)
   4. Hospitalised, not requiring supplemental oxygen but requiring ongoing medical care (COVID-19 related or other medical conditions)
   5. Hospitalised, requiring supplemental oxygen
   6. Hospitalised, on non-invasive ventilation or high flow oxygen devices (refer to 2.3.1 for definition of non-invasive ventilation)
   7. Hospitalised, on invasive mechanical ventilation or ECMO
   8. Death.
   2.2. Admission to a Hospital in the Home unit is not counted as hospitalisation for the purposes of this ordinal scale. Patients who have been admitted to hospital and transferred to a Hospital in the Home unit will be assessed as either ordinal score 1 or 2.
3. All-cause mortality at 28 and 90 days after randomisation
4. Days alive and free of hospital by 28 days after randomisation
   4.1. Days spent in a Hospital in the Home unit will not be counted as days in hospital as hospital means 'acute-care hospital' for the purposes of this endpoint.
5. Days alive and free of invasive or non-invasive ventilation by 28 days after randomisation
6. Presence of patient reported outcome of shortness of breath at days 28 and 90
   6.1. Dichotomous comparison of a subjective measure of shortness of breath such as: "Are you currently experiencing shortness of breath that you didn't have before you got COVID, or which is worse now than before you got COVID?"
   6.2. Ordinal comparison of the modified Medical Research Council (mMRC) breathlessness scale:

Modified Medical Research Council (mMRC) Dyspnoea Scale for grading the severity of breathlessness during daily activities:

Grade	Symptom complex
0	I only get breathless with strenuous exercise
1	I get short of breath when hurrying on level ground or walking up a slight hill
2	On level ground, I walk slower than people of the same age because of breathlessness, or I have to stop for breath when walking at my own pace on the level

3	I stop for breath after walking about 100 metres or after a few minutes on level ground
4	I am too breathless to leave the house or I am breathless when dressing or undressing

7. Quality of life as measured by EQ-5D-5L[13] questionnaire at days 28 and 90.

Note that safety and virological secondary outcome measures will be included in the relevant domain specific appendices.

2.3.3 Rationale for these outcome measures

The study outcomes have been chosen for their clinical importance. As an open label study, the choice of objective primary outcomes (need for intensive organ support and mortality) also minimises bias.

The primary outcome captures a worsening in clinical status from enrolment. However, it is expected that most patients will improve over time and this will be captured by the secondary outcome of time to recovery.

2.4 Trial Procedures

2.4.1 Participant timeline

See Figure 3 and Table 1.

Table 1. Schedule of visits, data collection and follow-up.

Visit Day	Day 0 (-3 to 0)	Day 1	Day 2 till d/c[1]	Day 28	Day 90
Check eligibility	X				
Informed consent		X			
Demographic data		X			
Clinical details		X			
Randomise		X			
Clinical observations[1]		X	X		
Review of study and related treatments		X	X		
Vital and ICU status (WHO ordinal scale)		X	X	X	
MRC breathlessness scale				X	X
EQ-5D-5L				X	X
Urea, CRP[1,2]		X			

1. While in hospital only
2. If obtained during usual routine clinical care, record the highest value in the 24h prior to randomisation.

2.4.2 Screening

Patients will be screened against the eligibility criteria outlined in this core protocol, as well as eligibility criteria outlined in each domain-specific appendix for the domains the site is participating in. All patients with a positive nucleic acid or rapid antigen detection for SARS-CoV-2 and admitted to hospital will be referred by the pathology laboratory or the treating doctor to the site investigator or their delegate (sub-investigator or properly qualified research nurse), as soon as identified. The following information will be transcribed onto a screening log by a member of the study team at the time of referral: the hospital identification number, name & date of birth (DOB) of the patient and date the referral was received. The site investigator or their delegate will approach the doctors of the treating team and ask permission to approach the patient for potential recruitment onto the study and record their response in the screening log. To determine eligibility a screening CRF containing only de-identified data, will be completed for all potentially eligible participants. The site investigator will do this using information gathered from the medical record and the patient's treating clinician. If the patient is eligible, the investigator will document this in the medical records. Following screening, only patients who are eligible will be approached for an informed consent discussion. For ineligible patients and for patients who decline to participate, data may be able to be collected for observational studies (e.g. analysis of the population characteristics of those screened).

2.4.3 Informed Consent

Informed consent will be obtained from the participant prior to performing any study-related procedures (except for screening). The consent procedure will only be performed by personnel who have been delegated the responsibility of obtaining informed consent at the site. All consent procedures will accord with local jurisdictional requirements, which are detailed in the region-specific appendices and additional SOPs, where relevant.

Due to the stringent measures in infection control in hospitals, verbal consent may be obtained in place of written consent in jurisdictions where this is permitted. If the patient is unable to provide consent themselves, surrogate consent may be obtained in jurisdictions where this is permitted. The procedures for these methods of consent are outlined in the region-specific documentation.

2.4.4 Randomisation and blinding

To randomise the participant the PI or their delegate will log onto the ASCOT ADAPT database and enter the details required before randomisation and assignment of the regimen (combination of treatments) for that participant. Minimal compulsory fields required prior to randomisation include screening number, confirmation of eligibility, age, confirmation of consent, baseline therapies given or planned as part of standard of care, and eligibility criteria for each available domain at the site.

Participants will be randomised using response adaptive randomisation, that is the ratio of randomisation to each intervention will be proportional to the posterior probability that it is the best intervention within that domain at the most recent data examination. The initial randomisation ratios will be equal across all regimens; in other words no assumptions will be

made about the relative efficacy of each intervention prior to the first examination of the accumulating data.
As this is an open-label study, no unblinding procedures will be necessary in the event of a medical emergency.

2.4.5 Study Visit Day Details

2.4.5.1 Day 0/Screening (-3 to 0 days)

Screening activity, to evaluate eligibility will be undertaken as described in section 2.4.2 and will be undertaken whilst the patient is in hospital.
It is possible that Day 0 and Day 1 activities may be undertaken on the same day.
The activities undertaken at this visit are:

- Review of inclusion/exclusion criteria and determine eligibility for the platform, and for all domains available at that site

2.4.5.2 Day 1

The activities will occur on the calendar day of randomisation.
Once eligibility has been confirmed, and assuming informed consent has been obtained, the patient will be randomised. The allocated treatment regimen will be initiated as soon as practically possible after randomisation.
Informed consent must be documented in the participant's medical history (2.4.3).
Any activities that are listed below and which were taken as part of routine care within 2 days of randomisation can be used and does not need to be repeated specifically for this study. Most information will be available from the Hospital Medical Record. The evaluations that will be performed include:

- Informed consent
- Demographic information (date of birth, age, sex, ethnicity);
- Medical history including symptoms, signs and comorbidities
- Review medications history
- WHO ordinal scale
- Review of routine clinical blood test results including urea and CRP, highest value within 24 hours prior to randomisation to be recorded.

2.4.5.3 Day 2 till hospital discharge

These activities will be performed whilst the participant is in hospital:

- WHO scale and need for inotropes
- Review of domain specific treatments, adverse events, and outcomes

2.4.5.4 Day 28±2, 90±7

These activities will be performed in addition to those listed above:

- EQ5D5L questionnaire
- mMRC breathlessness scale
- WHO scale and treatment with inotropic medication (Day 28 only)

- Questions about days of hospitalisation and need for intensive respiratory support since the index hospitalisation episode

If the participant has been discharged, these procedures will be conducted by telephone contact with the participant or their GP. Prior to contacting the patient, the site PI or their delegate will make every effort to ascertain the patient's vital status on day 28 and day 90 (e.g. from hospital records) and will not ring the patient's family if they are known to have died. Data for Day 28 and Day 90 may be collected retrospectively (e.g. due to weekends/public holidays).

2.4.6 Data and sample collection

CRFs will be completed as soon as practicable and ideally within 48 hours of the relevant day. So the day 1 CRF should be filled out by day 3, day 3 by day 5 and day 7 by day 9. A site handbook will contain step by step details on how to recruit patients and collect data. Delayed collection of data will not be considered protocol deviations.

There will be several tiers for collection of samples and associated data. All sites will need to collect core clinical data. Sites may, in addition, opt-in to different parts of the enhanced, research and domain-specific biospecimen collection tiers.

Where appropriate consent has been obtained, stored samples may be used for future research related to COVID-19 and related research including, but not limited to, presence of biomarkers, genetic and immunological testing.

2.4.7 Discontinuation/withdrawal of participants from trial treatment

The participants have the right to choose to withdraw from the study at any time and the investigator may discontinue a participant from the study or from treatment if deemed appropriate at any time. Reasons why a participant may be withdrawn from the study include, but are not limited to:

- Participant (or person responsible) request
- primary treating clinician's request
- participant was enrolled and is ineligible

Participants will not automatically be withdrawn due to adverse events (in this case study treatment may be ceased, but data collection will continue). The decision to withdraw a participant from the study must be discussed with the coordinating investigators.

If the participant withdraws consent from participating in the study and also withdraws consent for disclosure of future information, no further evaluations will be performed, and no additional data will be collected. The co-ordinating investigators may retain and continue to use any data or samples collected before such withdrawal of consent. Participants who leave against medical advice will continue to be followed until the end of the trial to avoid missing data. If they did not complete treatment their data will be used in the intention-to-treat analysis. If they completed treatment their data will be used in the as per protocol analysis. For participants who are lost to follow-up, if the participant completed treatment their data will be used in the as per protocol analysis. Participants withdrawn from the treatment by the treating clinicians will continue to be followed up to the end of the trial to avoid missing data and will be used in the intention-to-treat analysis. If a patient is enrolled and later found to be ineligible, study treatment will be ceased but data will continue to be

collected and used in the intention-to-treat analysis. If a patient was enrolled in error, the patient will be withdrawn and their data will not be used in the intention-to-treat analysis.
If a participant is withdrawn the reason will be recorded in the database.
The study treatment the participant is randomised to will be discontinued if a participant chooses to withdraw from the study. Participants may opt to withdraw from study treatment but continue to provide data for follow-up.

2.5 End of trial

This is an open-ended study given the uncertainties of the epidemiological course of SARS-CoV-2. The international trial steering committee will continually assess the epidemiological situation, trial progress and interim results, and emerging external evidence of efficacy of the study and other interventional agents. The trial protocol may be adapted as the situation changes. Over time, individual interventions, or entire domains, may be removed from or added to the platform.

2.6 Study timeline

A simple frequentist design of ASCOT opened for recruitment at the first Australian site in April 2020. ASCOT ADAPT supersedes ASCOT and will include all data, participants and specimens already collected as part of ASCOT. Recruitment in ASCOT ADAPT is perpetual until a conclusion can be made for all study interventions and there are no new interventions to be investigated, or the condition itself is no longer prevalent.

2.7 Sample size

As of late October 2020, there is great uncertainty at this stage of the epidemic, with few cases in Australia and New Zealand, and large numbers in India. Until further information becomes available there is not sufficient data to predict likely numbers of patients presenting with COVID-19 during the study timeframe.

The aim of the platform itself is for perpetual recruitment until a conclusion can be made for all interventions under consideration and there are no new interventions to be investigated, or the condition itself is no longer prevalent. Frequent analyses are undertaken to assess hypotheses for interventions under evaluation and participants will be randomised to these interventions until there is sufficient evidence of superiority, inferiority or futility of the intervention. Evidence from external trials may also result in the closure of treatment arms if the ITSC and the relevant domain-specific working group judge the evidence to be sufficient to warrant closure.

On average, fewer participants will be required to reach a platform conclusion in domains with fewer interventions, and for interventions which have large effect sizes. The advantage of frequent analyses is that a decision can be made as soon as sufficient evidence exists, rather than waiting until a fixed and largely arbitrary sample size has been attained.

Due to the adaptive platform trial design, there is no simple formulaic method for determining power or Type I error. Instead, trial simulations are used to characterise the trial design and

select decision criteria. Complete details are provided in the Statistical Analysis Appendix and the Simulations Supporting Document.

2.7.1 Primary outcome

Estimated rates of need for ventilation among hospitalised patients have varied. In an early report from China of 1099 hospitalised cases, 5% required ICU admission with 2.3% undergoing invasive ventilation[14]. In Italy, ICU admissions (n=556) represented 16% of all patients (n=3420) who tested positive for COVID-19[15]. An observational study involving 208 UK hospitals reported that 17% of patients (n=3001) were admitted to critical care, and 10% (n=1658) received invasive ventilation[16]. In the New York City area, 14.2% of patients who were discharged or died, were treated in the ICU, and 12.2% received invasive mechanical ventilation[17].

During the first wave in Australia, up to June 21 2020, there had been 7,491 SARS-CoV-2 notifications in Australia, with 1,136 hospitalised (15%). Of those hospitalised, 213 (19%) were admitted to intensive care and 59 (5%) ventilated. Of those in ICU, 29 died (14%) and of those hospitalised overall, 83 (7%) have died. Assuming approximately 50% of those admitted to ICU were admitted to ICU at presentation, that leaves approximately 100 patients moving from initial hospitalisation to ICU admission and 54 dying outside of ICU. Therefore, an estimated 100 + 54 = 154 of those hospitalised but outside of ICU at presentation would have met the primary endpoint, from a denominator of 1,136 – 113 = 1023. This is 154/1023 = 15.1%.

For indicative purposes, in simulations assuming a baseline probability of death or invasive respiratory support of 20% at day 28, and a domain of four alternative interventions (including standard of care alone), a lone effective intervention which reduces the odds of death or invasive respiratory support by 50% had probability > 90% of triggering a decision for superiority of that intervention by 1,600 participants enrolled. In a domain with two interventions (including standard of care alone), a similarly effective intervention triggers a decision for superiority with probability > 90% by 800 participants enrolled into the trial.

2.8 Assignment of interventions

2.8.1 Allocation

Eligible participants will be allocated to a treatment regimen consisting of one intervention from each of the available domains (not all domains may be available at all sites/regions). Initially, all interventions within a domain will be allocated with equal probability to the regimen (for example, 1:1:1:1 in a domain with four interventions). Following the first and subsequent interim analyses the allocation ratios of regimens will be updated to be proportional to the probability the regimen is best in terms of maximising the probability of survival without requiring intensive respiratory support or vasopressor/inotropic support by 28 days. Unless an intervention has been explicitly dropped from the trial following an interim analysis (for inferiority or futility), we will enforce a domain specific minimal probability of allocation to all active interventions within a domain.

Full details of the RAR implementation are presented in the Statistical Analysis Appendix and the Simulations Supporting Document.

2.8.2 Allocation concealment

The algorithm that produces the randomised allocation will be stored in the database and will not be available to any investigators or member of study staff.

2.8.3 Implementation

The allocation sequence will be generated by an algorithm that will be updated by a statistician not involved in the day to day trial procedures. Participants will be enrolled by PIs or their delegates (research nurse or co-investigator). The person enrolling the participant will, following obtaining informed consent, obtain the treatment allocation by logging onto the electronic data capture system and completing the required fields before the system will allow randomisation and subsequent treatment allocation.

2.8.4 Blinding

This is an open-label study, but researchers assessing the laboratory outcomes will be blinded to treatment allocation. For the overall data and results, only specified members of the statistical analytical team, DSMB and the data co-ordinator will have access to unblinded results, with other trial investigators and staff remaining blinded to the aggregate results until completion of final analysis for a domain.

2.9 Data Management and Quality Assurance

2.9.1 Source data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include but are not limited to, hospital records both electronic and paper (which will include medical history, previous and current medications, any relevant radiography test, blood test results, haemodynamic parameters, medication charts and medical correspondence) and electronic clinic records (which will include vital status, recent medical history and relevant blood culture results). A further data source will be through telephone conversations with the study participant or GP.

Storage and archiving of study documents (pCRF's and consent forms) will be the responsibility of the PI and will remain at the site of recruitment and retained for 15 years. All study participants will be allocated a unique number at time of screening (screening number), this screening number will be added to all the CRF's for that participant. The date and time will be captured on the CRF for all telephone conversations with study participants or GP.

2.9.2 Protocol Deviations and Serious Breaches

The following protocol deviations will be documented and reported in the eCRF for this study:

- Randomisation or any study procedures (apart from screening) have occurred prior to informed consent having been obtained.

- Incorrect dosing of study drug/wrongly prescribed study drug or treatment administration.
- Randomising a patient who does not meet eligibility criteria.

A serious breach of GCP or the protocol is a breach that is likely to affect to a significant degree: a) The safety or rights of a trial participant, or b) The reliability and robustness of the data generated in the clinical trial.

As a pragmatic study, it is unlikely that any serious breaches will occur. However, if a suspected serious breach is identified at the site, the PI or their delegate should e-mail details to the regional sponsor within 72 hours of becoming aware of the suspected breach. The sponsor will then assess the report. Whether a reported breach meets the definition of a serious breach will depend on many factors. For example, where the breach significantly impacts on the quality of key analysis parameters and excluding those data from the analysis significantly impacts the trial, a serious breach may be confirmed. The sponsor will report all serious breaches to the ethics board / institutional review board within 7 days and conduct a root cause analysis and implement any corrective and preventative actions (this may be delegated to the site). The PI or their delegate should report any confirmed serious breach to their governance office within 72 hours.
Where protocol deviations or serious breaches identify protocol-related issues, the protocol will be reviewed and, where indicated, amended.

2.9.3 Data Recording and Record Keeping
Data for this study will be recorded via a secure, Electronic Data Capture (EDC) web-based system using the eCRFs. It can be transcribed by the PI or their delegate from the paper CRFs onto the eCRF (in no case is the paper CRF to be considered as source data for this trial). Data will be stored in a re-identifiable manner in the database, using a unique screening number for each patient.
The database will contain validation ranges for each variable to minimise the chance of data entry errors. An audit trail will maintain a record of initial entries and changes made; reasons for change; time and date of entry; and username of person who made the change. Data queries will be raised by the project manager and study monitor, and missing data or suspected errors will be raised as data queries and resolved prior to database lock and analysis. The database will contain in-line capability so that these queries and answers are logged as part of the audit trail.
For each potential participant screened (even those who are found not to be eligible on screening), the screening eCRF will be completed by the site PI or their delegate. For each participant enrolled, eCRFs must be completed. This also applies to records for those patients who fail to complete the study. The site PI should ensure the accuracy, completeness and timeliness of the data reported to the sponsor in the eCRFs and in all required reports. A comprehensive validation check program will verify the data and automatically generate discrepancies for resolution by the investigator. Manual discrepancies can also be raised if necessary.

In addition, accurate and reliable data collection will be assured by verification of the eCRFs against the investigator's records by the study monitor (source document verification), and the maintenance of medication/intervention compliance will be captured in the CRF's from the participant's medication chart, blood product prescription form, or other appropriate source document by the investigator.

Storage and archiving of hard-copy study documents (pCRFs and consent forms) will be the responsibility of the PI at each site and will remain at the site of recruitment following local security guidelines. Hard-copy study documents will be kept for a minimum of 15 years and confidentially destroyed at the end of this period only with the express consent of the study sponsor.

2.9.4 Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, research staff, and the sponsoring institution and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests (where consent has been provided) in addition to the clinical information relating to participating participants.

The trial protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the trial or the data will be released to any unauthorised third party, without prior written approval of the sponsoring institution. Authorised representatives of the sponsoring institution may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic or hospital) and pharmacy records for the participants in this trial. The clinical trial site will permit access to such records.

All laboratory specimens, evaluation forms, reports and other records that leave the site will be identified only by the Participant Identification Number to maintain participant confidentiality. The study database (eCRFs) will contain date of birth (added at screening) and participant initials (added following consent). No other identifiable information will be added to the eCRFs.

Clinical information will not be released without written permission of the participant, except as necessary for monitoring by HREC or regulatory agencies.

2.10 Statistical methods

2.10.1 Statistical analysis plan

Statistical inference will be based on the analysis of accumulated trial data using pre-specified Bayesian models at regularly scheduled analyses. The models will incorporate trial design features by accounting for potential heterogeneity by region, site, and time of enrolment (cohort). The primary model will be logistic regression on the primary outcome and incorporate model parameters which represent the effect of interventions assigned to participants from within each domain. Secondary models will investigate interaction effects between interventions across different domains as well as pre-specified sub-group effect heterogeneity.

These models will be used to calculate the posterior probabilities of hypotheses of interest, including, but not-necessarily limited to effectiveness, futility, superiority, and inferiority of the interventions. These probabilities, in addition to informing the RAR, will be assessed against decision specific thresholds which will inform platform conclusions and trial adaptations such as dropping of less effective interventions. These thresholds will be selected by examining trial simulations under various scenarios.

Full details of the statistical models, hypotheses, and decision thresholds are presented in the Statistical Analysis Appendix and the Trial Simulation Report.

2.11 Study monitoring

Study monitoring will be provided by the responsible monitor(s) or their delegate(s) in accordance with the Monitoring Plan and principles of ICH GCP. The monitoring plan will be developed and will likely mainly rely on central monitoring with limited site visits depending on resources, number of sites, and travel restrictions.

2.12 Safety Monitoring and Reporting

2.12.1 Definitions (for medicinal products)

Term	Description
Adverse Event (AE)	Any untoward medical occurrence in a patient/trial participant administered a medicinal product, and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the product.
Adverse Reaction (AR)	Any untoward and unintended response to a medicinal product related to any dose administered. **Comment**: All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product would qualify as adverse reactions. The expression 'reasonable causal relationship' means to convey, in general, that there is evidence or argument to suggest a causal relationship.
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the Reference Safety Information (RSI). **Note:** The RSI should be contained in the investigator's brochure for an unapproved medicinal product or Product Information (or another country's equivalent of the Product Information) for an approved medicinal product.

Reference Safety Information (RSI)	The information contained in an approved Australian Product Information (or other country equivalent) that contains the information used to determine what adverse reactions are to be considered expected adverse reactions and on the frequency and nature of those adverse reactions.
Serious Adverse Event (SAE)	An SAE is any adverse event that: ○ Results in death ○ Is life-threatening The term "life threatening" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically may have caused death, if it were more serious. ○ Results in unexpected prolongation of existing hospitalisation ○ Results in persistent or significant disability/incapacity ○ Is a medically important event or reaction **Note**: Medical and scientific judgement should be exercised in deciding whether an adverse event/reaction should be classified as serious in other situations. Important medical events that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.
Serious Adverse Reaction (SAR)	A SAE judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to an investigational product
Suspected Unexpected Serious Adverse Reaction (SUSAR)	Any SAE that is both unexpected (i.e. its nature or severity is not consistent with the Approved Product Information) and suspected to be related to the medicinal product (i.e. there is a reasonable causal relationship with that medicinal product).
Significant Safety Issue (SSI)	A safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial.
Urgent Safety Measure (USM)	A measure required to be taken to eliminate an immediate hazard to a participant's health or safety. (A subset of significant safety issues). **Note**: This type of significant safety issue can be instigated by either the investigator or sponsor and can be implemented before seeking approval from HRECs or institutions.

2.12.2 Assessment of Adverse Events (AEs)

Each adverse event must be evaluated for:

1) **Seriousness**: An assessment of whether the AE meets the definition of a Serious Adverse Event (SAE).
2) **Causality (relatedness):** A clinical assessment of whether there is a reasonable causal relationship between the AE and the trial treatment.

The PI (or medically qualified delegate) will make a judgement as to whether an AE has a *reasonable causal relationship* with the allocated treatment(s). The degree of certainty with

which an AE is attributable to treatment or an alternative cause will be determined by how well the event can be understood in terms of:

- Temporal relationship with the administration of the treatment or cessation of treatment
- Reactions of a similar nature previously observed in the individual or others following treatment

The PI or delegate's opinion of the relationship between the AE and the trial treatment will be specified as follows:

Not related	There is not a causal relationship.
Unlikely	The temporal association between treatment and the adverse event is such that treatment is not likely to have any reasonable association.
Possibly	The AE could have been caused by treatment.
Probably	The AE follows a temporal sequence from the time of treatment and cannot be reasonably explained by the known characteristics of the participant's clinical presentation/history.
Definitely	The AE follows a reasonable temporal sequence from the time of treatment or reappears when the treatment is repeated.

3) **Expectedness:** An assessment against the AEs/SAEs listed in the trial's Reference Safety Information (the relevant Australian Production Information or other country equivalent) as expected occurrences (considering the nature and frequency of the event).

2.12.3 Site responsibilities

The PI or their delegate should:

a. assess all AEs (note that not all AEs require recording on the CRF or reporting to the sponsor). Only specific AEs will be collected/recorded for this study, sites are not required to record all AEs. Events which are to be recorded are specified in the relevant domain-specific appendix. Recording and reporting procedures are outlined in the ASCOT ADAPT safety SOP.
b. report to the sponsor within 24 hours of becoming aware of the event:
   - all SARs (**Severe adverse reactions**, i.e. serious adverse events (SAEs) thought to have a reasonable causal relationship with one or more protocol-determined intervention, occurring within 28 days of randomisation)
   - any occurrences of congenital anomaly/birth defect arising from any pregnancy of a participant (or partner)
c. review of all safety communications from the sponsor (e.g. significant safety issues identified by the DSMB) and ensure any implications for trial participants are managed appropriately.

d. report to their local governance office, within 72 hours of becoming aware of the event: i) all significant safety issues reported to the site by the sponsor and ii) any SUSARs arising from the local site (if required by local governance).

2.12.4 SAEs not needing expedited reporting

It is recognised that the patient population in ASCOT ADAPT will experience a number of aberrations in laboratory values, signs and symptoms due to the severity of the underlying disease, the impact of standard treatments, and the natural history of the disease. These will not necessarily be considered adverse reactions or serious adverse reactions unless they are considered to be related to study treatment or in the principal investigator's clinical judgement are not recognised events consistent with the participants underlying critical illness and/or chronic diseases and expected clinical course.

Reporting of adverse events will be restricted to events that are considered to be serious adverse reactions, that is serious adverse events related to study treatment (possibly, probably or definitely). Sites are not required to report to the sponsor SAEs which are not thought to be attributable to a protocol-determined intervention. Sites will follow region-specific procedures for any locally required reporting.

SARs should be followed up until the event has resolved or a final outcome has been reached, or until Day 90, whichever is earlier. Any change of condition or other follow-up information for the SAR should be sent as soon as it is available.
The site will report SARs by completing the Safety Reporting CRF. The minimum amount of information that the site investigator must complete in the initial report is:

- title of the event
- date the event started
- reason the event is considered a SAR
- causality relationship to investigational product

2.12.5 Sponsor Reporting Procedures:

The Sponsor will assess and report SARs in accordance with the safety SOP, in accordance with the *NHMRC Guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods* (2016) and any additional requirements of the approving ethics committee / institutional review board. All SARs assigned by the site (or following central review) as both **related** to study treatment and **unexpected** will be classified as SUSARs and will be subject to expedited reporting to the Therapeutic Goods Administration (or regional equivalent) in accordance with the NHMRC Guidance and/or equivalent local regulations. SUSARs will also be reported to the medicine license holder/supplier of the investigational product.

The Sponsor will report all Significant Safety Issues (SSIs)* to sites (as well as the HREC(s), the TGA and national regulatory bodies in each participating country):

- SSIs that meet the definition of a USM *within 72 hours* of becoming aware of the issue.
- All other SSIs *within 15 calendar* days or becoming aware of the issue.

* SSIs result in a change – either to the protocol (amendment) or a temporary or permanent halt to the trial comparison arm(s). SSIs may be single case events (e.g. certain SUSARs) or events that arise from an aggregate analyses of safety reports (e.g. increases in frequency or severity of known events). The sponsor will action all SSIs in accordance with the NHMRC Guidance.

2.13 General ethical considerations

The study will be conducted according to the Declaration of Helsinki, the NHMRC criteria for the ethical conduct of research in humans and the principles of Good Clinical Practice [18].

The study protocol, information sheets, consent forms, and any other documents required for ethics approval will be submitted to the relevant HRECs for approval before the study commences. Each HREC reviewing the protocol must be properly constituted according to NHMRC requirements or as per local IRB policies and have the capacity to review the study. Approvals must specify the study title, version numbers, and identify all documents reviewed and state the date of review. No intentional amendments to, or deviations from, the protocol must be initiated without prior written approval from the relevant HREC. The exceptions to this are:

- administrative aspects that have no bearing on participants
- the need to address regulatory requirements; and/or
- the need to eliminate immediate hazards to the participants

The investigator will inform the HREC of the following:

- all protocol amendments, informed consent changes or revisions of other documents originally submitted for review
- serious and/or unexpected adverse events
- new information that may affect the safety of the participants or the proper conduct of the trial
- annual updates of study progress
- termination of the study including provision of a final study report.

2.14 Data harmonisation, access and sharing

2.14.1 Data harmonisation

Given the importance of data sharing with other studies being concurrently conducted, data collection and protocols are being harmonised with:

- WHO Master Protocol: https://www.who.int/blueprint/priority-diseases/key-action/multicenter-adaptive-RCT-of-investigational-therapeutics-for-COVID-19.pdf
- ISARIC (International Severe Acute Respiratory and Emerging Infection Consortium) WHO case Record Form: https://isaric.tghn.org/covid-19-clinical-research-resources/
- REMAP-CAP (A Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia): https://www.remapcap.org/

2.14.2 Data Access

The international trial steering committee will be the custodians of the final trial dataset. No-one outside the international trial steering committee will be given access to the data without the permission of the ITSC. No identifying data will be given to any third parties at any stage. Following study close out and locking of the database, it will be stored on the servers of the sponsor.

2.14.3 Data sharing

2.14.3.1 Global datasets

Harmonisation of data collection as detailed in 2.14.1 should facilitate data sharing. The study will have an ethos of appropriate sharing of data to contribute towards global datasets.

2.14.3.2 Communication with REMAP-CAP

At study sites where REMAP-CAP is open for recruitment, participants enrolled in ASCOT ADAPT and progressing to ICU admission or need for invasive and non-invasive ventilation will be identified to REMAP-CAP study staff as being enrolled in ASCOT ADAPT. The ASCOT ADAPT unique study number will be communicated to REMAP-CAP to allow linkage of data. Follow-up data will continue to be collected from the participant for ASCOT ADAPT if they are enrolled in REMAP-CAP.

2.14.3.3 Communication with participating sites and clinical community

Data collected may be shared in aggregate form in real time to inform the clinical community and facilitate discussion of clinical management of patients. These data will only be presented for all participants in total without identification of allocated treatments. Examples of such data will be baseline characteristics, investigation results, hospitalisation and ICU status, need for invasive or non-invasive ventilation, and mortality.

2.15 Dissemination policy

The trial results will be communicated to all site investigators by teleconference prior to publication or presentation. The trial results will also be submitted for presentation at national and international meetings and publications submitted to a peer reviewed scientific journal, irrespective of the results. The ITSC may decide to communicate results via media releases and pre-print submissions. A plain-language summary of the trial results will be made available to individual participants upon request.

Primary and senior authorship will be determined by the ITSC. The authorship of the paper will include all of the ITSC who meet ICJME criteria for authorship. Hospitals contributing at least one case for analysis will nominate a locally determined coordinating investigator for inclusion, in order of number of participants enrolled. All hospitals and participating organisations with protocols enacted will be listed as 'The ASCOT study group'. The ASCOT study group will consist of all named chief and site investigators and selected others who have contributed to protocol development, study design or analysis or participant recruitment, and

will be listed in the collaborators section of the paper. The author byline will include 'for the ASID Clinical Research Network'.

2.16 Collaborative agreements

The ASCOT ADAPT ITSC will be open to collaborative agreements with other investigators and sponsors. These will be on a case by case basis, but with the principals of:

- A willingness to share in the infrastructure developed by ASCOT
- Sharing of the intellectual property and outputs. For example, investigators and sponsors collaborating under the ASCOT umbrella can retain leadership of the direction of their domain / interventions and the resulting outputs.
- Written agreements specifying these and other aspects relating to the collaboration will be entered into prior to commencement of collaborative trial activities

3. References

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Trial Name:	Australasian COVID-19 Trial (ASCOT) ADAptive Platform Trial
Registration	ACTRN12620000445976 NCT04483960

The ASCOT trial has undergone the following major amendments:

Protocol	Date	Major Change
ASCOT v1.0	23 March 2020	Initial submission to HREC. Interventions of Lopinavir/Ritonavir (LPV/r), Hydroxychloroquine (HCQ), LPV/r + HCQ, or Standard of Care (SOC). No participants recruited
ASCOT v2.0	01 April 2020	Updated following review and comments from HREC. No participants recruited
ASCOT v3.0	18 May 2020	Clarification added to study design, drug preparation and exclusion criteria. No participants recruited
ASCOT v4.0	16 July 2020	Amendment to drop HCQ and LPV/r therapy and add convalescent plasma therapy
ASCOT ADAPT v1.0	12 August 2020	Transition to adaptive platform trial. Completely new protocol. Interventions of convalescent plasma, interferon, interferon + ribavirin, standard dose anticoagulation, intermediate dose anticoagulation and standard dose anticoagulation + aspirin. No participants recruited.
ASCOT ADAPT v2.0	30 September 2020	Updated following review and comments from HREC, and addition of nafamostat. No participants recruited.
ASCOT ADAPT v3.0	30 October 2020	Removal of convalescent plasma therapy, interferon and interferon + ribavirin arms.
ASCOT ADAPT v4.0	30 April 2021	Addition of therapeutic anticoagulation.
ASCOT ADAPT v5.0	05 August 2021	Removal of standard dose anticoagulation + aspirin.
ASCOT ADAPT v6.0	30 March 2022	Minor formatting and operational changes to add clarification to aspects of the study design.

Each detailed change to the protocol is provided in full in the tables below.

ASCOT
AustralaSian COVID-19 Trial

ASCOT PROTOCOL VERSION 2.0 TO VERSION 3.0				
Section number and title in version 2	**Section number and title in amendment (version 3)**	**Original text**	**Changed to**	**Rationale**
All document	All document	Footer: Version 2, April 1, 2020	Footer: Version 3, May 5, 2020	Updated to reflect new version
		N/A	N/A	Table of contents updated to reflect the modifications in the protocol
		N/A	N/A	Minor administrative changes including pagination, formatting changes.
Coverpage	Coverpage	Clinical trials registration: tbc	Clinical trials registration: ACTRN1262000044597	Trial was registered on the ACTRN website prior to study opening to recruitment
		Universal trial number:	Universal trial number: U1111-1250-5165	Trial was registered with WHO post initial HREC approval
		Protocol version/date: Version 2 / dated April 1 2020	Protocol version/date: Version 3 / dated May 5 2020	Updated version and date of protocol to reflect the amendment
		Chief Investigators: 14. Kristy Crooks	Chief investigators: -	Removed from version 3.
		Chief Investigators: -	Chief Investigators: 16. Emily Rowe 17. Sandy Hodge 18. Megan Rees	Addition of 3 chief investigators (numbers 16-18) who were inadvertently left off in the original protocol
		Coordinating and Chief Investigators' Affiliations: 21 listed	Coordinating and Chief Investigators' Affiliations: 23 listed	Addition of 2 new Affiliations which are linked to new Chief Investigators named
Study Synopsis	Study Synopsis	Various fields	Various fields	Fields amended/updated to reflect the modifications in the body of the protocol.
		Kristy Crooks	-	Removed from listing

ASCOT PROTOCOL VERSION 2.0 TO VERSION 3.0				
Section number and title in version 2	**Section number and title in amendment (version 3)**	**Original text**	**Changed to**	**Rationale**
Contributorship	Contributorship	Indigenous Australian Lead		
		-	Emily Rowe: Protocol development, site investigator Megan Rees Protocol development, respiratory lead Sandra Hodge Protocol development	New Chief Investigator contributorships added
2.2.2. Participant Exclusion Criteria	2.2.2. Participant Exclusion Criteria	Exclusion criteria: 1. Currently admitted to an Intensive Care Unit (ICU)	Exclusion criteria: 1. Currently admitted to an Intensive Care Unit (ICU) or a hospital that is functioning as an ICU	Amended to reflect acknowledgement that some hospitals were transformed to act as an ICU hospital in the current pandemic
		Exclusion criteria: 2. Currently receiving intensive respiratory support (*invasive or non-invasive ventilation or high flow nasal oxygen therapy)*	Exclusion criteria: 2. Currently receiving acute intensive respiratory support (*invasive or non-invasive ventilation).* Note that participants already on Non-invasive ventilation (either CPAP or BiPAP) in the community can still be recruited if they are continuing on their usual degree of NIV. Humidified high flow nasal oxygen will not be considered an exclusion critieron.	Acknowledgement by the Trial Steering Committee that there may be participants enrolled into the trial who use BiPAP or CPAP non-invasive ventilation at home.
		Exclusion criteria: 12. Unable to provide consent	-	Point removed from exclusion criteria list, after consultation with an independent consumer advisory panel who suggested that this exclusion criterion was discriminatory. By removing this exclusion criterion, this would enable participants who

ASCOT PROTOCOL VERSION 2.0 TO VERSION 3.0				
Section number and title in version 2	**Section number and title in amendment (version 3)**	**Original text**	**Changed to**	**Rationale**
				may have an intellectual disability, dementia re delirium to participate if appropriate surrogate consent was obtained through the medical decision treatment maker /person responsible. Therefore, a new section (2.5.3.1) has been added to the study protocol around surrogate consenting procedures, as well as the addition of a new Master PICF.
2.3 Treatment of study participants	Treatment of study participants	-	New paragraphs (3rd, 4th and table added) For participants who are enrolled into ASCOT AND who are taking an agent that is not on the contraindicated list (table 1) ***but*** that is potentially QT prolonging (table 2), clinical judgement is required. Consideration should be given to: 1. The relative importance of that medication; a. Could the medication be easily replaced with something else? b. Is there any harm in stopping the medication for 7-10 days? 2. Other patient-specific risk factors, such as; a. electrolyte disturbance, or presence of diarrhoea or use of diuretics that might predispose to electrolyte disturbance b. ischaemic heart disease or cardiomyopathy, history of ventricular arrhythmia 3. Recent use of QT prolonging agents with a long half-life, such as amiodarone	Acknowledgement by the ASCOT Trial Steering Committee that there are a number of medications that may potentially interact with COVID-19 medications and prolong QT interval have been listed. Instructions to site investigators to ensure to review the list of medications the participant is prescribed. 20 medications which are QT prolonging agents that may be most commonly used by participants have been listed. For a more comprehensive list, a link to a website has been added.

<table>
<tr><th colspan="5">ASCOT PROTOCOL VERSION 2.0 TO VERSION 3.0</th></tr>
<tr><th>Section number and title in version 2</th><th>Section number and title in amendment (version 3)</th><th>Original text</th><th>Changed to</th><th>Rationale</th></tr>
<tr><td></td><td></td><td></td><td>
4. The number of potentially QT prolonging agents the patient is taking
5. The QTc interval on the patient's ECG; if it is <470ms for males and <480 for females while on the medication/s then it is not a requirement to stop the medication/s in question in order to prescribe the trial antiviral agents.
Note Azithromycin is not a contraindication to enrolment in ASCOT and use of hydroxychloroquine and/or lopinavir-ritonavir, but the considerations above should be thought through by the participant's clinical team.
Table 2: Example of Drugs which are known QT prolonging agents
<table>
<tr><th>Drug Name</th><th></th></tr>
<tr><td>Amitriptyline</td><td>Use with caution</td></tr>
<tr><td>Azithromycin</td><td>Use with caution</td></tr>
<tr><td>Ciprofloxacin</td><td>Use with caution</td></tr>
<tr><td>Citalopram</td><td>Use with caution</td></tr>
<tr><td>Clozapine</td><td>Use with caution</td></tr>
<tr><td>Domperidone</td><td>Contraindicated</td></tr>
<tr><td>Escitalopram</td><td>Use with caution</td></tr>
<tr><td>Flecainide</td><td>Contraindicated</td></tr>
<tr><td>Haloperidol</td><td>Use with caution</td></tr>
<tr><td>Lithium</td><td>Use with caution</td></tr>
<tr><td>Methadone</td><td>Use with caution</td></tr>
<tr><td>Mirtazapine</td><td>Use with caution</td></tr>
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</td><td></td></tr>
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ASCOT PROTOCOL VERSION 2.0 TO VERSION 3.0				
Section number and title in version 2	**Section number and title in amendment (version 3)**	**Original text**	**Changed to**	**Rationale**
			Moxifloxacin — Use with caution Nortriptyline — Use with caution Ondansetron — Use with caution Propofol — Use with caution Tacrolimus — Use with caution Tamoxifen — Use with caution Tramadol — Use with caution Venlafaxine — Use with caution	
2.3.2 Active treatment factorial arm	2.3.2 Active treatment factorial arm	Paragraph 1: For participants who are unable to take medications by mouth, the LPV/r (400 lopinavir mg / 100 mg ritonavir) will be administered as a 5-ml suspension every 12 h via a pre-existing or newly placed nasogastric tube. Hydroxychloroquine can be suspended and administered with the same dose and schedule as the tablet formulation	Paragraph 1: Hydroxychloroquine can be suspended and administered with the same dose and schedule as the tablet formulation. For participants who are unable to take medications by mouth, the LPV/r (400 lopinavir mg / 100 mg ritonavir) will be administered as a 5-ml suspension every 12 h via a pre-existing or newly placed nasogastric tube. The Sponsor has been able to secure a limited stock of oral lopinavir/ritonavir solution. If during the study, the oral suspension is no longer available from the Sponsor, then the sites will be required to prescribe and administer study drug oral solutions as per the standard clinical pathways from their existing institutional stocks, otherwise refer to Appendix 3.4 for instructions on how to prepare oral suspensions.	Additional information to sites regarding administering study drug as oral solutions, and to clarify that if the sponsor is unable to supply this formulation, it will be prescribed from local stock.

ASCOT PROTOCOL VERSION 2.0 TO VERSION 3.0				
Section number and title in version 2	Section number and title in amendment (version 3)	Original text	Changed to	Rationale
		Paragraph 2: The dose of LPV/r is the standard dosing used for treatment of HIV. If oral solution is used, it should be administered with food to increase absorption (there is no recommendation for used with food for the tablets) Because LPV/r oral solution contains ethanol and propylene glycol, it is not recommended for use with polyurethane feeding tubes due to potential incompatibility. Feeding tubes that are compatible with ethanol and propylene glycol, such as silicone and polyvinyl chloride (PVC) feeding tubes, can be used	Paragraph 2: The dose of LPV/r is the standard dosing used for treatment of HIV. Because LPV/r oral solution contains ethanol and propylene glycol, it is not recommended for use with polyurethane feeding tubes due to potential incompatibility. Feeding tubes that are compatible with ethanol and propylene glycol, such as silicone and polyvinyl chloride (PVC) feeding tubes, can be used	Second sentence removed as it is not possible to administer oral solution of study drug with food

ASCOT PROTOCOL VERSION 2.0 TO VERSION 3.0				
Section number and title in version 2	Section number and title in amendment (version 3)	Original text	Changed to	Rationale
			New paragraph 5: For participants who have renal impairment, but not on dialysis, there will be no alteration in the hydroxychloroquine dosing schedule. Participants who are on dialysis (both haemodialysis or Peritoneal Dialysis) will have their dosing schedule changed to hydroxychloroquine 800mg twice on Day 1 followed by 400mg once daily for 6 days.	Added after consultation with the Australian Kidney Trials Network (AKTN)
2.3.3 study drugs	2.3.3 study drugs	Paragraph 1: There will be two routes by which study drugs will end up being provided. We have sourced study drugs from Abbvie and Mylan for lopinavir/ritonavir and from Sanofi for hydroxychloroquine. These will be delivered to and stored at the Royal Brisbane and Women's Hospital (RBWH) pharmacy. RBHW pharmacy is currently holds a	Paragraph 1: There will be two routes by which study drugs will end up being provided. We have sourced study drugs from Mylan for lopinavir/ritonavir (oral tablet), National Medical Stockpile (Australian Government) for Kaletra [lopinavir/ritonavir] (oral solution) and from Sanofi for hydroxychloroquine. These will be delivered to and stored at the Royal Brisbane and Women's Hospital (RBWH) pharmacy. RBHW pharmacy is currently holds a cGMP license and has been accredited by the TGA as a COVID-19 central facility and will act as the central and distribution warehouse for the ASCOT trial.	The Study was unable to secure lopinavir/ritonavir oral tablets from Abbvie. Mylan brand of lopinavir/ritonavir is not approved in Australia, and therefore no product information documentation is available. Mylan lopinavir/ritonavir oral tablets are approved by the European Medicines Agency https://www.ema.europa.eu/en/medicines/human/EPAR/lopinavirritonavir-mylan Mylan lopinavir/ritonavir oral tablets have an FDA New Drug Application [210540] and were still awaiting final FDA approval as of 30 March 2020: https://www.accessdata.fda.gov/drugsatfda_docs/pepfar/079074PI.pdf. The study has been available to secure small doses of the Abbvie brand Kaletra (lopinavir/ritonavir) oral solution from the Australian National Stockpile.

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		cGMP license and has been accredited by the TGA as a COVID-19 central facility and will act as the central and distribution warehouse for the ASCOT trial.		
		Paragraph 2: As there is still some unpredictability to this supply and distribution chain, during the early phase of the study sites will be able to prescribe and administer study drugs as per the standard clinical pathways from their existing institutional stocks. All study sites have clinical pharmacies that provide clinical dispensing to hospitalised patients.	Paragraph 2: During the early phase of the study sites will be able to prescribe and administer study drugs as per the standard clinical pathways from their existing institutional stocks. All study sites have clinical pharmacies that provide clinical dispensing to hospitalised patients.	Removal of the first part of sentence 1, as the study has secured study drug and there is currently no unpredictability to the study drug supply.

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		Paragraph 3: There will be a separate specific Trial Pharmacy Manual	Paragraph 3: There will be a separate IMP management plan	Change in name of the document
2.4.1 Primary outcome	2.4.1 Primary outcome	Proportion of participants alive and not having required intensive respiratory support (invasive or non-invasive ventilation or humidified high flow oxygen therapy) at 15 days after enrolment.	Proportion of participants alive and not having new required intensive respiratory support (invasive or non-invasive ventilation) at 15 days after enrolment. This includes any participant who receives non-invasive mechanical ventilation (either CPAP or BIPAP) on the ward any time after enrolment even if not transferred to ICU. It does NOT include the use of humidified high-flow nasal prong oxygen. Participants on pre-existing home BiPAP or CPAP will not be considered to have met the primary endpoint unless they have either required invasive mechanical ventilation (i.e. intubation) or died by day 15.	When ASCOT was designed, it seemed that there would be no aerosol generating procedures undertaken outside of the ICU setting (including humidified high flow oxygen therapy, and Non-invasive ventilation). This is no longer the case. Humidified high flow oxygen therapy may be given to participants and may be provided for the greater comfort of the patient, rather than a hard endpoint. Additionally, there are members of the community who currently use BiPAP or CPAP at home and would have met the end point on enrolment. Therefore, this endpoint has been amended in consultation and collaboration with respiratory physicians.
2.4.2.1 Clinical	2.4.2.1 Clinical	-	New point: 14. Safety. Acute Kidney Injury (AKI) based on the modified Kidney Disease Improving Global Outcomes (KDIGO) criteria (increases by creatinine by ≥ 26.5μmol/L within 48hrs, OR to ≥ 1.5 times baseline, known or presumed to have occurred within the 7 prior days.	New Secondary Outcome Measure added after consultation and collaboration with *Australasian Kidney Trials Network (AKTN)*, who lobbied to include participants with acute kidney injury to be included in the trial.
2.4.3 Rationale for	2.4.3 Rationale for	Paragraph 3:	Paragraph 3:	Addition of the link to the WHO Master Protocol outcomes

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these outcome measures	these outcome measures	To allow harmonisation with these WHO Master Protocol outcomes, the components for the ordinal scale will be part of the data collection. The ASCOT investigator group decided that analysis of these ordinal outcomes is complicated and a large sample size would be needed to evaluate any distinguishable/meaningful differences amongst these categories. We have preferred a binary primary endpoint	To allow harmonisation with these WHO Master Protocol outcomes (https://www.who.int/blueprint/priority-diseases/key-action/COVID -19_Treatment Trial Design Master Protocol synopsis_Final_18022020. pdf), the components for the ordinal scale will be part of the data collection. The ASCOT investigator group decided that analysis of these ordinal outcomes is complicated to evaluate any distinguishable/meaningful differences amongst these categories, and thus we have opted for a dichotomous primary endpoint	
2.5.1 Participant timeline	2.5.1 Participant timeline			Changes to Table 4 are in alignment with updated information added to sections 2.5.5.1 – 2.5.5.12 of the study protocol
-	2.5.3.1 Surrogate	-	If the inclusion/exclusion criteria are confirmed, and the potential participant is unable to provide consent, then the person	This section has been included as the TSC and an independent community consumer advisory group noted that it was

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	informed Consent		responsible/medical treatment decision maker (from this point referred to as person responsible) will be approached. At this time the most senior member of the research team (investigator) will assess the competency of the person responsible before approaching them and inviting them to consider enrolling the potential patient into the ASCOT trial. If agreeable, the person responsible will be provided with further information about the study, both verbally and in written format. This will include a description of: ❖ The purpose of the study, ❖ Study procedures, ❖ Possible risks/benefits ❖ Rights and responsibilities of the potential participant, and ❖ Alternatives to participation. The person responsible will be invited to ask questions which will be answered by investigator, and they will be provided with contact details if they have any further questions subsequently. If the person responsible agrees that the potential patient should participate in the study, they will be asked to sign the informed Consent Form. A copy of the form will be given to them to keep. If the person responsible is indecisive about enrolment, they will be given 24 hours to	discriminatory to exclude people because they were unable to provide their own consent.

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			consider the study and will be approached once more the following day. The ASCOT managing trial centre recognises that different state jurisdictions have different requirements regarding surrogate consenting procedures. It is up to each site to consider whether they will submit the person responsible/medical treatment decision maker PICF to their HREC/RGO office.	
2.5.5.2 Day 1	2.5.5.2 Day 1	3rd paragraph: • Verbal informed consent; • Demographic information (date of birth, age, sex, ethnicity); • Medical history including symptoms, comorbidities; • Travel history (if applicable) in the previous 14 days; • Review medications history (including any over-the-	3rd paragraph: • Verbal informed consent; • Demographic information (date of birth, age, sex, ethnicity); • Chest imaging. A CXR or CT chest is not mandated investigation, and data will only be collected if this has been performed as part of routine care on day 1 or results from the preceding 24-hour period; • Medical history including symptoms, comorbidities, BCG vaccination; • Travel history (if applicable) in the previous 14 days; • Review medications history (including any over-the-counter medications); • Vital signs (blood pressure, heart rate, temperature);	- Addition of the chest imaging as a part of the Day 1 activities (bullet point 3). This investigation inadvertently left off in the original approved protocol. Explanation that chest imaging is not a mandated study specific investigation and only results will be collected for the study if any imaging has been performed as part of routine care. - Addition of BCG vaccination as part of medical history (bullet point 4). While not clearly established, several epidemiological studies have now suggested that BCG vaccination may be protective against COVID-19, and a randomised controlled trial is underway to use BCG vaccination as an intervention against COVID-19. We feel it would be straightforward and prudent to collect this information as part of our overall risk factors for what might predict more significant disease. - Minor administrative and clarification information added to bullet point 9.

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		counter medications); • Vital signs (blood pressure, heart rate, temperature); • Review of routine clinical blood test results including full blood examination (FBE), biochemistry (i.e. EUC, LFTs, CRP); • Clinical blood test, not mandated but recommended Mg++, lactate, D-dimer, LDH, ferritin, troponin, BNP; • 12 lead ECG;	• Review of routine clinical blood test results including full blood examination (FBE), biochemistry (i.e. EUC, LFTs, CRP); • Clinical blood test, not mandated but recommended including, K+, Mg2+, lactate, D-dimer, LDH, coagulation studies, troponin, BNP. *If K+ or Mg2+ are abnormal, then they should be corrected*; • 12 lead ECG;	
		4th paragraph: Once eligibility has been confirmed the participant will be randomized. Prior to first dosing the	4th paragraph: Once eligibility has been confirmed the participant will be randomized. Prior to first dosing the following study specific activities will be undertaken: • GP will be notified;	- clarification and realignment of which samples are collected for research sample tiers; - addition that GP will be notified of the participant's involvement in the study. This activity now aligns with both the Schedule of Events and PICF;

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		following study specific activities will be undertaken: • *For sites involved in the enhanced biological component:* o Research blood sample (1x9mL SST blood tube); o Rectal swab sample; • *For sites involved in the research biological component:* o Research blood samples (5x9mL sodium heparin tubes; o Availability of respiratory tract samples from routine clinical care for biobanking	• *For sites involved in the enhanced biological component (tier 1):* o Research blood sample (1x9mL SST and 1x5mL EDTA blood tubes); o Stool sample; o Availability of respiratory tract samples from routine clinical care for biobanking from Day 0 and Day 1 OR Study specific nasopharyngeal and throat swab for biobanking • *For sites involved in the research biological component (tier 2):* Research blood samples (3x9mL sodium heparin tubes and 2x9mL ACD tubes);	- Addition of an extra 1x5mL EDTA blood tube to the tier 1 research blood sample collection; - Stool samples are now being collected instead of rectal swabs for biobanking; - change in the type of blood tubes, not volume, used to collect blood for isolating PBMCs

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		from Day 0 and Day 1;		
		Paragraphs 6-8	Paragraphs 6-8	Clarification of tests required at 4 and 8 hours post study drug administration
2.5.5.3 Day 2	2.5.5.3 Day 2	Paragraph 1: These activities will be performed whilst the participant is in hospital and prior to study drug dosing: • Vital signs; • Review of clinical observations, including any adverse events; • ICU status; • Prior to the 3rd dose of study drug the 24hour ECG post initial dose should be performed; • Review of routine clinical blood test results including full blood examination (FBE),	Paragraph 1: These activities will be performed whilst the participant is in hospital and prior to study drug dosing: • Vital signs; • Review of clinical observations, including any adverse events; • ICU status; • Prior to the 3rd dose of study drug the 24hour ECG post initial dose should be performed; • A blood glucose level check via a finger prick to be performed prior to the 24hour ECG; • Review of routine clinical blood test results including full blood examination (FBE), biochemistry (i.e. EUC, LFTs, CRP); • Clinical blood test, not mandated but recommended, K+ and Mg2+. *If K+ or Mg2+ are abnormal, then they should be corrected* Study drug administration doses and times recorded.	Alignment with the Schedule of Events table *Monitoring for h*ypoglycaemia was not initially included, since it generally occurs only with acute overdose of hydroxychloroquine. The TSC accepted the rationale for adding it, as advised by the AKTN, especially for End-stage Kidney disease patients. Therefore, a blood glucose level check was added as a safety investigation at the 24 hour time point for all participants.

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		biochemistry (i.e. EUC, LFTs, CRP); • Clinical blood test, not mandated but recommended, Mg2+. • Study drug administration doses and times recorded.		
		2nd paragraph: If the participant is discharged either today or any time during the study after this time point, then the site PI or their delegate will contact the participant by phone as per the schedule of visits as outlined in the Schedule of events (table 4) with the exception of weekends and public holidays. The purpose of this contact is to check compliance	2nd paragraph: If the participant is discharged either today or any time during the study after this time point, then the site PI or their delegate will contact the participant by phone on days 8, 11, 16 and 28 as outlined in the Schedule of events (table 4) with the exception of weekends and public holidays. The purpose of this contact is to check compliance with the protocol in terms of study drug prescribing and recording any adverse events.	Alignment with the Schedule of Events table (table 4)

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		with the protocol in terms of study drug prescribing and recording any adverse events.		
2.5.5.5 Day 4, 5, 6, 8, 9	2.5.5.5 Days 4, 5, 6, 8, 9	-	2nd paragraph: If the participant was discharged before Day 7, then the PI or their delegate will contact the participant by phone on ***Day 8*** and check: • Current health status; • Number of study drug tablets left; • Targeted side effects (i.e. diarrhoea, nausea, vomiting); • Any shortness of breath experienced.	New paragraph. Provides instructions on what information site staff are to collect if participants have been discharged from hospital before Days 7/8
2.5.7.8 Days 11-14	2.5.5.8 Days 11-14	-	2nd paragraph: If the participant was discharged before Day 10, then the PI or their delegate will contact the participant by phone on ***Day 11*** and check: • Current health status; • Number of study drug tablets left; • Targeted side effects (i.e. diarrhoea, nausea, vomiting); • Any shortness of breath experienced.	Amendment of section number New paragraph. Provides instructions on what information site staff are to collect if participants have been discharged from hospital before Days 10/11
2.5.7.10 Day 15	2.5.5.9 Day 15	-	2nd paragraph: If the participant was discharged before Day 15, then the PI or their delegate will contact the participant by phone on ***Day 16*** and check:	Amendment of section number

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Section number and title in version 2	Section number and title in amendment (version 3)	Original text	Changed to	Rationale
			• Current health status; • Targeted side effects (i.e. diarrhoea, nausea, vomiting); • Any shortness of breath experienced.	New paragraph. Provides instructions on what information site staff are to collect if participants have been discharged from hospital before Days 15/16
2.5.7.11 Day 28 ± 3 days	2.5.5.10 Day 28 + 3 days	-	2nd paragraph: If the participant was discharged before Day 28, then the PI or their delegate will contact the participant by phone on ***Day 28*** and check: • Current health status; • Targeted side effects (i.e. diarrhoea, nausea, vomiting).	Amendment of section number New paragraph. Provides instructions on what information site staff are to collect if participants have been discharged from hospital before Day 28
-	2.5.5.11 Day 90 + 14 days	-	These activities will be performed if the participant is in hospital: • Clinical observations, including any adverse events; • Current oxygen therapy; • Participant status. If the participant has been discharged prior to Day 90, then the site staff will review hospital medical records and/or contact the participant (or GP) on ***Day 90 or later*** to record the following information: • Participant status – alive or dead; • Date of death (if applicable); • Current oxygen therapy (if applicable	New section. Omitted from initial protocol

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Section number and title in version 2	**Section number and title in amendment (version 3)**	**Original text**	**Changed to**	**Rationale**
2.5.6 Data and sample collection	2.5.6 Data and sample collection	1st paragraph: CRFs will be filled out within 48 hours of the relevant day. So, the day 1 CRF will be filled out on day 2–3, day 3 on day 4–5 and day 7 on days 8–9. Standard Operating Procedures (SOPs) will contain step by step details on how to recruit patients and collect data.	1st paragraph: CRFs will be filled out within 48 hours of the relevant day. For example, the day 1 CRF will be filled out on day 2–3, day 3 on day 4–5 and day 7 on days 8–9.	There are no SOPS on how to recruit patients and collect data – so this sentence has been removed in the new version of the study protocol.
2.5.6.1 Core	2.5.6.1 Core Data	These are the core clinical data that contribute to the primary endpoint, key secondary outcomes, and key potential confounders	These are the core clinical data that contribute to the primary endpoint, key secondary outcomes, and key potential confounders. The procedures/investigations undertaken and recorded as part of this clinical data set are part of routine care – except for the ECGs taken at 4hrs, 24hrs and day 4 post initial drug administration.	Additional explanation that the activities undertaken as part of the Core data set are part of routine clinical care (except for ECGs – for the first 100 participants)
2.5.6.2 Enhanced biological	2.5.6.2 Enhanced biological (tier 1)	Includes research blood sampling and rectal sampling	Includes research blood, stool and respiratory sampling. Blood and stool samples for the analysis of potential biomarker assays, immunological responses including but not limited to antibody	Additional explanation around the research activities undertaken as part of tier 1 sampling

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			levels, response to virus and genetic analysis including genome wide association study (GWAS). Genomics is increasingly informing researcher's understanding of disease pathobiology. Large-scale human GWAS studies require large collections of DNA from people exposed to, or infected with, SARS-CoV-2. To identify human genes related to susceptibility or disease outcome, this would require COVID-19 individuals with well-defined clinical phenotypes, as GWAS are case-control studies that compare phenotypes, i.e. mild disease vs severe disease, asymptomatic vs active disease, survivors vs non-survivors. To ensure large sample sizes of individuals with differing clinical phenotypes it is essential to collect DNA from multiple studies, with diverse study designs. For example, DNA from active COVID-19 cases from the ASCOT study and from asymptomatic exposed individuals from household or population studies.	
2.5.6.3 Research biological	2.5.6.3 Research biological (tier 2)	Includes additional blood sampling for PBMC isolation and PK analysis. Additionally, storage of primary respiratory	Includes additional blood sampling for PBMC isolation and biobanking. Sites that agree to participate in tier 2 sampling, should also have tier 1 samples collected	Clarification that sites who participate in tier 2 are required to also collect tier 1 research samples.

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		tract specimens included.		
-	2.5.6.4 PK sampling	-	Blood samples for measurements of serum concentrations of lopinavir/ritonavir and/or hydroxychloroquine will be collected at timepoints specified in Table 4. Sites can opt to be involved in PK sampling, without being involved in tiers 1 or 2 research sampling or be involved in addition to tiers 1 and 2 research sampling.	Additional subsection added regarding PK sampling and clarification regarding when sites can participate.
2.5.7		Paragraph 6: If a participant is admitted to ICU due to progressive disease, the treating clinician can continue treatment using the allocated study drug for a total of 10 days	Paragraph 6: If a participant is admitted to ICU due to progressive disease, the treating clinician can continue treatment using the allocated study drug for a total of 10 days. At the time of ICU admission, ASCOT participants meet the study primary endpoint, and may thereafter be enrolled in other clinical trials if eligible, including randomisation to other interventions or continuation of ASCOT study drugs according to study investigators	Clarification around ASCOT participants who are admitted into ICU, meet the study primary endpoint and can be enrolled into other clinical trials, or continue on ASCOT study medication.
-	2.9.4 Confidentiality	-	Participant confidentiality is strictly held in trust by the participating investigators, research staff, and the sponsoring institution and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in	Addition of a section to the protocol which details how personal information from potential and enrolled participants will be collected, shared and maintained in order to protect confidentiality before, during and after the trial.

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			addition to the clinical information relating to participating participants. The trial protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the trial or the data will be released to any unauthorised third party, without prior written approval of the sponsoring institution. Authorised representatives of the sponsoring institution may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic or hospital) and pharmacy records for the participants in this trial. The clinical trial site will permit access to such records. All laboratory specimens, evaluation forms, reports and other records that leave the site will be identified only by the Participant Identification Number to maintain participant confidentiality. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by HREC or regulatory agencies	
2.10.1 Statistical analysis plan	2.10.1 Statistical analysis plan	-	Number point #6 *Those with end stage kidney disease (ESKD, meaning receipt of haemodialysis or peritoneal*	Additional secondary protocol analysis point added as requested by the AKTN

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			dialysis) at enrolment. The pharmacokinetics of hydroxychloroquine are uncertain in this population, the risk of drug-related adverse events may be higher, and the efficacy of the study drugs maybe either better (higher blood levels) or worse (underlying comorbidities leading to poor outcomes regardless of adjunctive therapies)	
		-	Number point #7 *Those who experienced acute kidney injury any time between randomisation and day 15.* The pharmacokinetics of hydroxychloroquine are uncertain in this population, the risk of drug-related adverse events may be higher, and the efficacy of the study drugs maybe either better (higher blood levels) or worse (underlying comorbidities leading to poor outcomes regardless of adjunctive therapies).	Additional secondary protocol analysis point added as requested by the AKTN
2.12.4 Serious adverse events (SAEs)	2.12.4 Serious adverse events (SAEs)	Paragraph #3 SAEs are monitored continuously and have special reporting. We are only collecting SAEs for any if the adverse events listed below for this study, if	Paragraph #3 SAEs are monitored continuously and have special reporting. Sites are not required to report SAEs which are considered to be consistent with COVID-19 and expected disease progression including: • Hypoxia; • increased requirement for supplemental oxygen;	Expanded and clarified the SAEs that ASCOT are not collecting. Paragraph 3 in version 2 has been split into paragraphs 3 & 4 in version 3. SAE are being collected for up to 30 days post last dose to align with the current reporting instructions in the study database.

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		thought to be attributable to one or more of the study drugs from randomisation up until Day 28.	• mechanical ventilation; • ICU admission or death due to respiratory failure; • venous thromboembolism; • chest pain; • shortness of breath; • fever or other features judged clinically to be consistent with COVID-19 disease progression. This study is only collecting SAEs for any of the adverse events listed below if thought to be attributable to one or more of the study drugs from randomisation up until 30 days post last study drug.	
-	3.4 Preparation of study oral solution.	-	**3.4. Preparation of Study Drug Oral Solution** **3.4.1 Hydroxychloroquine** **Hazard: Do not crush the tablet if you are pregnant. Consider local handling precautions for hazardous medicines** The following information has been provided by the REMAP-CAP group and is in line with their current practises. The information applies to 200mg tablets. 3.4.1.1 <u>For enteral feeding tubes:</u> 1. Give immediately after a bolus feed or stop the continuous feed.	Instructions regarding preparing oral solution for the study.

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			2. Flush the tube with 30 mL of water. 3. Crush the tablet to a fine powder using a mortar and pestle or a tablet crusher. 4. Add 10 mL of water to the powder and mix well (the tablet does not disperse easily). 5. Draw the mixture into the enteral syringe. 6. Rinse the crushing device with 10ml of water, then repeat with another 10ml (total of 20ml) and draw into the enteral syringe, to ensure that all of the medicine is removed. 7. Give the mixture (~30mL) immediately into the enteral feeding tube. 8. Rinse the enteral syringe with a further 10 mL of water to ensure the entire dose is given. 9. If other medicines are given, flush the tube with at least 5 mL of water between each medicine. 10. After the final medicine is given, flush the tube with 30 mL of water. 11. Restart the continuous feed immediately after dosing. Smaller volumes can be used to accommodate fluid-restriction. 3.4.1.2 <u>For swallowing difficulties:</u>	

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			1. Crush the tablet with a mortar and pestle or a tablet crusher. 2. Add 10 to 20 mL of water and mix well. 3. Draw the mixture into an oral dispenser/syringe. 4. Rinse the crushing device with 10ml of water, then repeat with another 10ml (total of 20ml) and draw into the oral dispenser/syringe, to ensure that all of the medicine is removed. 5. Give the mixture immediately. 6. Rinse the oral dispenser/syringe with a further 10mL of water and give to the patient, to ensure the entire dose is given. If the person cannot swallow thin fluids (i.e. is an aspiration risk) or the very bitter taste is unacceptable, crush the tablet and mix with a spoonful of yoghurt or apple puree. 3.4.2 Lopinavir / Ritonavir The Sponsor's first preference is to use commercia available oral suspension Lopinavir 80mg/Ritonavi 20mg per mL suspension. A limited number of lopinavir/ritonavir oral suspension stock has been secured from the National Medical Stockpile (Australian Government). Site access to this oral formulation is outlined in the IMP Management Plan. If during the study, the oral suspension is no	

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			longer available from the Sponsor, then we recommend sourcing the oral solution from local pharmacy. If there is no access for local sites to secure commercially available oral solution, then t Sponsor recommends crushing the lopinavir/ritonavir study tablets. Sites are to conta the Sponsor for further guidance and information regarding the crushing of lopinavir/ritonavir tablet <u>Swallowing difficulties:</u> 1. Administer 5mL of suspension orally The liquid has an unpleasant taste. The use of ice chips before and after the dose may numb the taste buds or mix the dose with chocolate syrup to mask the taste <u>Feeding tube:</u> 1. Give immediately after a bolus feed or stop the continuous feed 2. Flush the tube with 30 mL of water 3. Draw 5mL into an enteral syringe and dilute with at least an equal volume of water 4. Mix well and give via the nasogastric feeding tube 5. A white residue or cloudy solution may be seen but will not clog the tube 6. Flush the tube with 30 mL of water and restart the feed	

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			Due to the high content of propylene glycol and ethanol in the oral suspension, a PVC / silicone feeding tube should be used due to incompatibility with polyurethane. There is adequate absorption of lopinavir when the oral liquid is given through nasogastric or PEG tubes and reduced absorption when given through jejunal tubes.	

ASCOT PROTOCOL VERSION 3.0 TO VERSION 2.0				
Section number and title in version 3	**Section number and title in amendment (version 4)**	**Original text**	**Changed to**	**Rationale**
All document	All document	Footer: Version 3, May 18, 2020	Footer: Version 4, July 07, 2020	Updated to reflect new version
		N/A	N/A	Table of contents updated to reflect the modifications in the protocol
		N/A	N/A	Minor administrative changes including pagination; formatting; spelling corrections; grammatical corrections; reference list/number changes.
		N/A	- removal of monotherapy hydroxychloroquine arm; - addition of convalescent plasma domain;	This protocol amendment is considered a substantial amendment. There are substantial challenges with being able to organise clinical trials and appropriate treatment options given the rapid evolving disease under investigation. <u>Removal of hydroxychloroquine monotherapy.</u> The UK RECOVERY trial in late June 2020 released the

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				top-line results of the hydroxychloroquine (HCQ) part of their trial, showing no significant effect on mortality or hospital length of stay in 1,542 patients hospitalised with suspected or proven COVID-19 randomised to hydroxychloroquine compared with 3,132 randomised to usual care alone. https://www.recoverytrial.net/files/hcq-recovery-statement-050620-final-002.pdf Of note, the full results have not yet been published, but the protocol and SAP can be found on the above website. There was no clear safety concerns raised. Most other large HCQ trials have ceased recruitment into HCQ-containing arms (e.g. SOLIDARITY, the NIH trial, and Sanofi's trial), and

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				the US FDA has retracted their Emergency Use Authorisation for HCQ for COVID-19 in late June/early July. While the ASCOT TSC accept that ideally no decision should be made until all the data from RECOVERY has been reviewed, and even better from other RCTs as well, the TSC recognize that the clinician and community equipoise have been lost and it is not currently viable to continue to test hydroxychloroquine monotherapy arm. The study CPIs note that a probable lack of efficacy is the reason for all the trials ceasing: NOT evidence of harm. They believe that, given the complementary mechanisms of action, it is still feasible that the combination of HCQ plus

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				Lopinavir/r could be effective. Therefore, the decision was made by the TSC that the ASCOT study will continue with 3 arms: Lopinavir/r alone, Lopinavir/r plus HCQ or standard of care <u>Addition of Convalescent plasma as a treatment domain.</u> The use of convalescent plasma for the prevention and treatment of COVID-19 is a method that delivers passive immunity in patients when compared to active immunity that is induced by a vaccine. Convalescent plasma is not a new therapy and has been previously trialled in influenza, SARS-1 and Ebola virus infections. The National COVID-19 Health and Research Advisory Committee concluded that Australian research into the use of convalescent plasma

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				should be available as a treatment in the form of a controlled clinical trial. The ASCOT study provides such a platform to provide treatment to hospitalised COVID-19 patients who are at risk of developing more severe illness. Therefore, it was decided that a treatment domain be added to the study, where recruiting sites have the choice of randomising eligible participants to convalescent plasma versus standard of care.
Coverpage	Coverpage	Protocol version/date: Version 3 / dated May 18, 2020	Protocol version/date: Version 4 / dated July 07, 2020	Updated version and date of protocol to reflect the amendment
		Chief Investigators: 19. -	Chief investigators: 19. Zoe McQuilten	New chief investigator has joined the ASCOT team. Zoe McQuilten is leading the Convalescent domain.
		Coordinating and Chief Investigators' Affiliations: 24. -	Coordinating and Chief Investigators' Affiliations: 24. Department of Epidemiology and Preventative Medicine, Monash University, Victoria 3001	New Affiliation is linked to the new Chief Investigator Zoe McQuilten

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Section number and title in version 3	**Section number and title in amendment (version 4)**	**Original text**	**Changed to**	**Rationale**
		Document History:	Document History: 4.0 removal of the hydroxychloroquine monotherapy arm; addition of convalescent plasma as an intervention; primary outcome amended to day 28	Summary of the changes to the study protocol between version 3.0 and 4.0
Study Synopsis	Study Synopsis	Title: A multi-centre randomised clinical trial to assess the clinical, virologic and immunological outcomes in patients with SARS-CoV-2 infection (COVID-19) treated with lopinavir/ritonavir and/or hydroxychloroquine compared to standard of care.	Title: An International Multi-Centre Randomised Clinical Trial to Assess the Clinical, Virological and Immunological Outcomes in Patients Diagnosed with SARS-CoV-2 Infection (COVID-19)	Title has been amended to reflect the change in scope of the investigational products that are being trialled in the study, as part of version4 protocol amendment
		Various fields	Various fields	Fields amended/updated to reflect the modifications in the body of the protocol.
Contributorship	Contributorship	-	Zoe McQuilten: Protocol development	New Chief Investigator contributorship added
1.1 Abbreviation	1.1 Abbreviation	-	FFP: Fresh frozen plasma	New abbreviation added to the list
1.2.1 Overview	1.2.1 Overview	Paragraph 1: In December 2019 a novel coronavirus emerged from Wuhan China as the cause of a pneumonia syndrome. This SARS-CoV-2 is a betacoronavirus and related to SARS. At the time of writing (1/4/20) there were over	Paragraph 1: In December 2019 a novel coronavirus emerged from Wuhan China as the cause of a pneumonia syndrome. This SARS-CoV-2 is a betacoronavirus and related to SARS. At the time of writing (6/7/20) there	Updated to reflect the current COVID-19 statistics.

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		830,000 reported cases and >40,000 deaths globally with 4,559 cases and 19 deaths in Australia. The case fatality rate is still unknown but likely to be ~1%. By May 5, 2020, there were > 3.5 million cases and > 250,000 deaths globally, with 6,847 cases and 96 deaths in Australia.	were over 11 million reported cases and >500,000 deaths globally with 8,449 cases and 104 deaths in Australia. The case fatality rate is still unknown but likely to be ~1%.	
		Paragraph 2: There are no known effective therapeutic options at this stage. Clinical trials have begun for many agents including lopinavir/ritonavir (LPV/r) and hydroxychloroquine. While clinical trials in China initially provided an opportunity to assess the impact on clinical outcomes, there are now few reported cases in China. Clinical trials in Australia and New Zealand will have value in: 1) contributing to understanding of clinical efficacy in local healthcare settings; 2) allowing detailed assessments of virological and immunological outcomes in a blinded manner; 3) providing therapeutic options to Australian and New Zealand patients in the context of a clinical trial.	Paragraph 2: Clinical trials have begun for many agents including lopinavir/ritonavir (LPV/r), hydroxychloroquine and convalescent plasma. Clinical trials in Australia and New Zealand will have value in: 1) contributing to understanding of clinical efficacy in local healthcare settings; 2) allowing detailed assessments of virological and immunological outcomes in a blinded manner; 3) providing therapeutic options to Australian and New Zealand patients in the context of a clinical trial.	Updated the current status of COVID-19 clinical trials.
1.2.2 Clinical spectrum of disease	1.2.2 Clinical spectrum of disease	SARS-CoV-2 causes a clinically significant and transmissible respiratory tract infection. In a large case series patients commonly had fever, cough and evidence of pneumonia on chest xray[1].	SARS-CoV-2 causes a clinically significant and transmissible respiratory tract infection.	- More information about the disease is known, and has been simplified in this subsection; - reference 1 was deleted from the protocol

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Section number and title in version 3	**Section number and title in amendment (version 4)**	**Original text**	**Changed to**	**Rationale**
1.2.3 Therapeutic options	1.2.3 Therapeutic options	-	New Paragraph 1: Thousands of clinical trials have been registered and are ongoing for COVID treatments[1]. At the time of writing (6/07/2020), only two therapeutics have been shown to be of benefit in RCTs. Remdesivir, an intravenous viral RNA-dependant RNA polymerase inhibitor decreased the duration of symptoms in a single RCT, but reductions in mortality were not statistically significant[2]. Low-dose dexamethasone (6mg daily for up to 10 days) decreased 28-day mortality in patients with suspected or proven COVID-19 in the UK RECOVERY trial, but only in those requiring supplemental oxygen or ventilatory support[3]	- new paragraph 1 added to version4 of the study protocol; - new list of references added
		-	New paragraph 2: Ongoing clinical trials are needed to define the best treatment or combination of treatments for patients with moderate COVID-19, and to allow access to emerging and experimental therapeutics for patients in Australia, New Zealand, India, and other participating regions.	- new paragraph added to version4 of the study protocol; - outline of which countries the ASCOT study will be recruiting in.
		Paragraph 1: Several broad approaches to improving outcomes for severe viral infections can be considered, beyond optimal supportive care as appropriate. These approaches may include host immune modulation (for example, with the use of treatments such as	Paragraph 3: Several broad approaches to improving outcomes for severe viral infections can be considered, beyond optimal supportive care as appropriate. These approaches may include host immune modulation (for example, with the use of treatments such as	- minor amendment to the wording

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		steroids to reduce inflammation, or immune globulin against SARS-CoV-2 to enhance specific responses), or interventions which aim to interfere with viral activity.	steroids to reduce inflammation, or immunoglobulin against SARS-CoV-2 to enhance specific responses), or interventions which aim to interfere with viral activity.	
		Paragraphs 4 and 5: Several antiviral medications have been previously investigated in clinical and laboratory studies for Sudden Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), diseases caused by related coronaviruses (SARS-CoV and MERS CoV respectively). These have not established definite efficacy for these coronaviruses, but have suggested potential benefit from the use of LPV/r with or without interferon B[2-4]. Other antivirals, including ribavirin, appear to have been associated with increased mortality and are not considered suitable candidates for SARS-CoV-2. As SARS-CoV-2 is a novel viral pathogen, little clinical trial data on antiviral therapy and impact on outcomes exists. Laboratory studies have demonstrated that several agents, including chloroquine and LPV/r, have activity in vitro against SARS-CoV-2[5]. One recently published study reported improvement in time to clinical improvement in the group receiving LPV/r, but no statistically significant improvement in mortality[7]. However, the study was substantially underpowered to detect an effect, and a large randomised trial is needed to establish the	Paragraph 4: Several antiviral medications have been previously investigated in clinical and laboratory studies for Sudden Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), diseases caused by related coronaviruses (SARS-CoV and MERS CoV respectively). These have not established definite efficacy for these coronaviruses, but have suggested potential benefit from the use of LPV/r with or without interferon B[4-6]. One recently published study reported improvement in time to clinical improvement in the group receiving LPV/r, but no statistically significant improvement in mortality[7]. However, the study was substantially underpowered to detect an effect, and a large randomised trial is needed to establish the efficacy of LPV/r in hospitalised patients infected with SARS-CoV-2.	-paragraphs 4 & 5 in version3 of the study protocol were merged in version 4; - removal of a few outdated statements from version4 of the study protocol; - changes in the reference listing.

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Section number and title in version 3	Section number and title in amendment (version 4)	Original text	Changed to	Rationale
		efficacy of LPV/r in hospitalised patients infected with SARS-CoV-2		
		-	New paragraph 5: Regarding interventions targeted at immune modulation, there is experience using convalescent plasma (plasma collected from individuals who have recovered from specific infection) in previous epidemics and pandemics, including SARS and MERS.[8] These studies did not establish efficacy, but did suggest possible benefit. For SARS-CoV-2, to date there has been only one published RCT of convalescent plasma compared to standard of care, which was terminated early due to small case numbers and was therefore underpowered for the primary efficacy outcome[9].	- new paragraph added to version4 of the study protocol; - rationale to using convalescent plasma;
1.2.4 Rationale for selection of therapeutic agents	1.2.4 Rationale for selection of antiviral therapeutic agents	-	New paragraph 2: One recently published study reported improvement in time to clinical improvement in the group receiving LPV/r, but no statistically significant improvement in mortality[7]. However, the study was substantially underpowered to detect an effect, and a large randomised trial is needed to establish the efficacy of LPV/r in hospitalised patients infected with SARS-CoV-2. In a study from Hong Kong, the combination of LPV/r plus interferon-B 1b plus ribavirin led to more rapid viral clearance and earlier resolution of clinical symptoms and signs compared	- updated information around reported study results for lopinavir/ritonavir

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Section number and title in version 3	Section number and title in amendment (version 4)	Original text	Changed to	Rationale
			to LPV/r alone [11].	
	1.2.5 Rationale for selection of convalescent plasma as an intervention	-	New section added: Plasma collected from individuals who have recovered from COVID-19 represents a potential therapy that could be used immediately for treatment or prevention of disease. Hypothesised mechanism/s of action of passive antibody therapy in SARS-CoV-2 include viral neutralisation (by neutralising antibodies), antibody-dependent cellular cytotoxicity and/or phagocytosis.[14] Convalescent plasma is currently the only available source of antibodies directed at SARS-CoV-2, with monoclonal antibodies (mAb) under development but not yet available.[14] There is experience using convalescent plasma during previous epidemics and pandemics. A systematic review published in 2015 identified 32 studies of use of convalescent plasma or serum for SARS coronavirus infection and influenza.[8] An exploratory *post hoc* meta-analysis showed a significant reduction in the pooled odds of mortality following convalescent plasma therapy compared with placebo or no therapy.[8] However, included studies were of low or very low quality, lacked control groups and were at moderate to high risk of bias.[8] *Evidence for efficacy*	- new section added to version 4 of the study protocol; - previous section subsection numbering has changed; - rationale of why convalescent plasma has been chosen as a treatment therapy for the ASCOT study

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Section number and title in version 3	Section number and title in amendment (version 4)	Original text	Changed to	Rationale
			In the current SARS-CoV-2 pandemic, convalescent plasma is being administered for treatment of COVID-19. Small case series were reported in the early stages of the pandemic in China. The largest included 10 hospitalised patients with COVID-19 each given 200ml convalescent plasma with a neutralising antibody titre of >1:640 and described an improvement in clinical, laboratory and radiological parameters.[15] However, this study was not adequately controlled or powered to allow robust conclusions. Subsequently, an open-label, multi-centred randomised controlled trial comparing convalescent plasma with standard of care in 103 patients with severe COVID-19 has been reported.[9] There was no significant difference in the primary outcome of number of patients with clinical improvement at 28 days (51.9% in convalescent plasma group compared with 43.1% in the control group, hazard ratio 1.40 with 95% CI 0.79-2.49, p=0.26). In the sub-group with severe disease, clinical improvement occurred in 91.3% of the convalescent plasma group compared with 68.2% of the control group (HR 2.15, 95% CI 1.07-4.32, p=0.03); however, the p-value for interaction by disease severity was not significant (p=0.17). The study was terminated early due to insufficient case numbers, and therefore was underpowered to detect a clinically important benefit. Convalescent plasma treatment was associated with a higher rate	

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			of nasopharyngeal SARS-CoV-2 negativity at 72 hours (87.2% vs 37.5%, OR 11.39, 95% CI 3.91-33.18, p<0.001). *Potential adverse effects of convalescent plasma* Transfusion of clinical plasma has known risks, including transfusion-related lung injury (TRALI), circulatory overload (TACO), allergic reactions, and transfusion-transmitted infections. Given known respiratory complications of COVID-19, the risk of TRALI and TACO are of most concern. In the early case reports, six case series reporting the use of convalescent plasma in COVID-19 reported adverse events, including 26 participants. Of these, there were 2 adverse events – one moderate fever after convalescent plasma transfusion[16] and one severe anaphylactic shock.[17] Since then, convalescent plasma has now been given to more than 20,000 COVID-19 patients in the United States through an expanded access program. In an early report of the first 5,000 recipients, the incidence of serious adverse events in the first hours after transfusion was low at <1%, including mortality rate (0.3%).[18] Of the 36 reported SAEs, there were seven cases of TACO, 11 TRALI and 3 severe allergic transfusion reactions. However, only 2 were judged as definitely related to the convalescent plasma. There is also the theoretical risk of antibody-dependent enhancement of infection, whereby	

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			passive antibody administration worsens the infection.[14] Antibody-dependent enhancement (ADE) occurs when antibodies facilitate viral entry into host cells and enhance viral infection in these cells.[19] Potential toxicity associated with convalescent plasma has been of concern and this is very relevant to COVID patients who exhibit a spectrum of lung pathology from acute lung injury (ALI) to acute respiratory disease syndrome (ARDS) and death. In SARS-CoV-associated disease, antibodies may mediate pathology if they target a different serotype of the virus.[19,20] Furthermore, a novel mechanism for ADE where a neutralising antibody binding to the surface protein of coronavirus like a viral receptor triggers viral cell entry has been recently proposed. This ADE pathway was shown not only to be antibody dose dependent but also likely mediated by presence of non-neutralising antibodies. For these reasons, we plan to collect convalescent plasma at the earliest 28 days after recovery so that antibody response has matured in terms of titer and affinity. None of the studies describing transfusion of convalescent plasma to patients with COVID-19 to date have shown pulmonary injury or infection enhancement.	
1.3 Objectives and		We hypothesise that treatment with LPV/r ± hydroxychloroquine will lead to improved clinical	We hypothesise that treatment with LPV/r alone or LPV/r ± hydroxychloroquine will lead to improved clinical outcomes for hospitalised patients with	- amended the section to reflect the changes in investigational products

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Section number and title in version 3	**Section number and title in amendment (version 4)**	**Original text**	**Changed to**	**Rationale**
hypotheses	1.3 Objectives and hypotheses	outcomes for hospitalised patients with SARS-CoV-2 infection.	SARS-CoV-2 infection. We also hypothesise that treatment with convalescent plasma will lead to improved clinical outcomes for hospitalised patients with SARS-CoV-2 infection	that will be used in the new study protocol moving forward
		Primary Objective: To determine if LPV/r ± hydroxychloroquine will reduce the proportion of participants who survive without requiring invasive or non-invasive ventilation, 15 days after enrolment, in adult participants with non-critically ill SARS-CoV-2 infection.	Primary Objectives: i. To determine if LPV/r ± hydroxychloroquine will reduce the proportion of participants who survive without requiring invasive or non-invasive ventilation, 28 days after enrolment, in adult participants with non-critically ill SARS-CoV-2 infection. To determine if convalescent plasma will reduce the proportion of participants who survive without requiring invasive or non-invasive ventilation, 28 days after enrolment, in adult participants with non-critically ill SARS-CoV-2 infection	- updated the primary objectives to reflect the changes in investigational products that will be used in the study protocol; - Endpoint has been amended from 15 days to 28 days.
1.4 Trial design	1.4 Trial design	Paragraph 2: As it is too early to accurately predict the size and distribution of the SARS-CoV-2 epidemic the feasibility and sample size requirements of the study will be progressively considered. In the initial design, consented participants will be randomised 1:1:1:1 on day 1 to receive either i) standard of care without LPV/r or hydroxychloroquine, ii) LPV/r; iii) hydroxychloroquine, or	Paragraphs 2 – 5 As it is too early to accurately predict the size and distribution of the SARS-CoV-2 epidemic the feasibility and sample size requirements of the study will be progressively considered. In the initial design, consented participants will be randomised within two intervention domains: <u>Intervention domain 1 (antiviral):</u> Participants will be randomised 1:1:1 on day 1 to receive either	- paragraph 2 from version3 divided into 3 paragraphs in version4; - header added to the antiviral investigational intervention treatments; - removal of hydroxychloroquine monotherapy treatment arm;

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Section number and title in version 3	Section number and title in amendment (version 4)	Original text	Changed to	Rationale
		iv) LPV/r + hydroxychloroquine.	i) standard of care without LPV/r or hydroxychloroquine; or ii) LPV/r alone; or iii) LPV/r plus hydroxychloroquine. <u>Intervention domain 2 (antibody):</u> Participants will be randomised 1:1 on day 1 to receive either i) standard of care without convalescent plasma; or ii) convalescent plasma	- new paragraph added to version4 of the study protocol, which outlines the antibody interventional treatment options
		Paragraph 3: For patients that are clinically worsening at day 5 or beyond, the protocol allows for (but does not encourage) the treating clinician to commence LPV/r +/- hydroxychloroquine from day 5 onwards. Daily data will be collected for the first 15 days or until discharge, whichever is earlier. There will be a core dataset collected for all patients at all sites and enhanced and research data and biological samples for sites with capacity. Data will be harmonised with the ISARIC SARS-CoV-2 and REMAP-CAP protocols and CRFs (https://isaric.tghn.org/novel-coronavirus/). As long as the participant remains an inpatient, their medical records will be reviewed weekly until discharge or the 90-day time point, whichever occurs first.	Paragraph 6; Daily data will be collected for the first 15 days or until discharge, whichever is earlier. There will be a core dataset collected for all patients at all sites and enhanced and research data and biological samples for sites with capacity. As long as the participant remains an inpatient, their medical records will be reviewed weekly until discharge or the 90-day time point, whichever occurs first	- 1st sentence of version3 removed from version4 of the study protocol; - removal of the sentence which notes that the data will be harmonised with other infectious disease platforms.
		Figure 1: overview of trial design	Figure 1: overview of trial design	Updated the trial schematic

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Section number and title in version 3	**Section number and title in amendment (version 4)**	**Original text**	**Changed to**	**Rationale**
2.2.2 Participant exclusion criteria	2.2.2 Participant exclusion criteria	1. Currently admitted to an Intensive Care Unit (ICU) or a hospital area that is functioning as an ICU; 2. Currently receiving acute intensive respiratory support (invasive or non-invasive ventilation). Note, participants already on non-invasive ventilation (either CPAP or BiPAP) in the community can still be recruited if they are continuing on their usual degree of NIV. Humidified high flow nasal oxygen will not be considered an exclusion criterion. 3. Currently taking LPV/r OR hydroxychloroquine 4. Known allergy or hypersensitivity to LPV/r OR hydroxychloroquine 5. Use of medications that are contraindicated with LPV/r OR hydroxychloroquine that cannot be replaced or stopped during the study period. (see table 1 and https://www.covid19-druginteractions.org/) 6. Currently on other investigational agents with targeted antiviral effects 7. Known cirrhosis or ALT or AST > 5x upper limit of normal 8. Previous participation in the trial 9. Known pregnancy 10. Known HIV infection not on antiretroviral therapy (see note below*) 11. QTc ≥470ms for males, QTc ≥480ms for females	A. Overall exclusions: 1. Currently receiving acute intensive respiratory support (invasive or non-invasive ventilation) or vasopressor/inotropic support. Note, participants already on non-invasive ventilation (either CPAP or BiPAP) in the community can still be recruited if they are continuing on their usual degree of NIV. Humidified high flow nasal oxygen will not be considered an exclusion criterion. 2. Previous participation in the trial 3. Known pregnancy 4. Treating team deems enrolment in the study is not in the best interests of the patient 5. Death is deemed to be imminent and inevitable within the next 24 hours 6. Enrolment to other study protocols that do not allow co-enrolment in ASCOT B. Domain 1 (Antiviral) specific exclusions: 1. Currently taking LPV/r OR hydroxychloroquine 2. Known allergy or hypersensitivity to LPV/r OR hydroxychloroquine 3. Use of medications that are contraindicated with LPV/r OR hydroxychloroquine that cannot be replaced or stopped during the study period. (see table 1 and https://www.covid19-druginteractions.org/) 4. Known cirrhosis or ALT or AST > 5x upper limit of normal	- exclusion criteria have been divided into overall exclusions (core exclusions that apply to all participants enrolled into the study) and domain specific exclusions that apply only to the domain that the potential participant may potentially be enrolled into. If a potential participant is enrolled into both domains, then none of the eligibility criteria listed can be met

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Section number and title in version 3	Section number and title in amendment (version 4)	Original text	Changed to	Rationale
		12. Treating team deems enrolment in the study is not in the best interests of the patient 13. Death is deemed to be imminent and inevitable within the next 24 hours.	5. Known HIV infection not on antiretroviral therapy (see note below*) 6. QTc ≥470ms for males, QTc ≥480ms for females 7. Treating team deems enrolment in antiviral interventions is not in the best interests of the patient 8. LPV/r not available 9. Hydroxychloroquine not available C. <u>Domain 2 (Convalescent Plasma) specific exclusions:</u> 1. Convalescent plasma not available at trial site 2. Participant has already received treatment with non-trial prescribed COVID19-specific immunoglobulin therapy (convalescent plasma, hyperimmune globulin or monoclonal antibody) 3. Known previous history of transfusion-related acute lung injury 4. Know previous history of serious allergic reaction to blood product transfusion 5. Known religious objection to receiving blood products 6. Treating team deems enrolment in antibody interventions is not in the best interests of the patient.	
2.3 Treatment	2.3 Treatment of		New paragraph 1:	- instructions to recruiting site staff on how potential

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Section number and title in version 3	**Section number and title in amendment (version 4)**	**Original text**	**Changed to**	**Rationale**
of study participants	study participants		Participants will be assessed for eligibility for both intervention domains (antiviral and convalescent plasma). Participants who are eligible for both domains will be randomised within both domains concurrently. If participants are only eligible for the antiviral domain, then they will be randomised within antiviral domain (as outlined below) and NOT the convalescent plasma domain. If participants are only eligible for the convalescent plasma domain, then they will be randomised within the convalescent plasma domain (as outlined below) and NOT the antiviral domain.	participants can be recruited into the study
		Paragraph 4: Azithromycin is not a contraindication to enrolment in ASCOT and use of hydroxychloroquine and/or lopinavir-ritonavir, but the considerations above should be thought through by the participant's clinical team.	Paragraph 5: Azithromycin is not a contraindication to enrolment in ASCOT and use of lopinavir-ritonavir ± hydroxychloroquine, but the considerations above should be thought through by the participant's clinical team.	- reworded due to the removal of the hydroxychloroquine monotherapy arm
			New paragraph 6: *Participants eligible for convalescent plasma domain* **Participants eligible for this domain will be randomised 1:1 to** either the standard of care arm (2.3.1) or convalescent plasma arm (2.3.4). The day of randomisation is considered day 1 of treatment. Randomisation and allocation must occur within 12 days of index sample collection that detected SARS-CoV-2 and within 12 days of symptom onset. Those receiving convalescent plasma will receive a unit of	- information regarding participants eligible to be randomised into the convalescent plasma domain.

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			ABO compatible convalescent plasma as soon as it is available. If the patient has no serious adverse reactions to the transfusion, the second unit of convalescent plasma will be given. There must be a minimum of 12 hours between transfusions to allow appropriate assessment of adverse reactions to the initial transfusion. Both transfusions should be given within 48 hours from the start of the initial infusion	
2.3.1 standard of care arm	2.3.1 standard of care arm	Participants will receive usual medical care. The protocol does not allow the use of LPV/r or hydroxychloroquine in the first 5 days. If at day 5 the treating team decides to prescribe LPV/r or hydroxychloroquine, this will be permitted within the protocol and recorded. However, such action is not encouraged as: 1. There is no evidence to support either benefit or harm of antiviral agents in this setting; 2. The WHO has a clear statement that use of unproven therapeutic agents should occur in the context of a clinical trial; 3. In the setting of limited drug supplies, use should be prioritised to address clinical questions; 4. Study drug supplied by the Sponsor for the study will not be used in these cases. Sites will be required to acquire to LPV/r or hydroxychloroquine from their local institutional pharmacy through normal prescribing channels.	Participants will receive usual medical care. Use of corticosteroids such as dexamethasone will not be mandated as part of the protocol, but will be recorded. It is expected that for hypoxic patients, dexamethasone will be used in the majority of cases. Low-dose dexamethasone (6mg daily for up to 10 days) decreased 28-day mortality in patients with suspected or proven COVID-19 in the UK RECOVERY trial, but only in those requiring supplemental oxygen or ventilatory support [3]. Use of other potential therapies will also be discouraged but recorded if used. Antibiotic use will be recorded.	- information and interventions that can be used in the standard of care arm; - has been updated and in line with current available information from other COVID-19 studies; - investigators unlikely to use hydroxychloroquine or lopinavir/ritonavir outside of a clinical trial currently, so previous instructions removed.

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		If LPV/r and / or hydroxychloroquine are used, the reasons for this decision will be recorded on the CRF and specifically will be: 1. Development of severe disease as per American Thoracic Guidelines for community acquired pneumonia as detailed in Table 3 2. Impending need for intensive respiratory support (invasive or non-invasive ventilation or humidified high flow nasal oxygen therapy) Use of LPV/r or hydroxychloroquine outside of these reasons and if prior to day 5 will be considered protocol violations and a specific reason will be recorded. Use of corticosteroids is discouraged[10] but recorded if used. Use of other potential therapies will also be discouraged but recorded if used. Antibiotic use will be recorded. **Table 3: American Thoracic Society criteria for severe community acquired pneumonia** Either one major criterion or three or more minor criteria Minor criteria Respiratory rate≥30 breaths/min PaO2/FiO2 ratio≤250 New onset confusion/disorientation Uremia (blood urea nitrogen level≥7.14 mmol/L) Leukopenia* (white blood cell count<4,000 cells/μl) Thrombocytopenia (platelet count<100,000/μl)		

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Section number and title in version 3	Section number and title in amendment (version 4)	Original text	Changed to	Rationale
		Hypothermia (core temperature<36°C) Hypotension requiring aggressive fluid resuscitation Major criteria Septic shock with need for vasopressors Respiratory failure requiring mechanical ventilation *Note: Multilobar infiltrates has been removed as this is typical for COVID-19*		
-	2.3.4 Active convalescent plasma treatment arm	-	New section: Convalescent plasma will be collected in Australia by Australian Red Cross Lifeblood (ARCL) and in New Zealand by New Zealand Blood Service (NZBS) from donors who have recovered from confirmed or probable COVID-19 *Donor selection* Donors with prior COVID-19 infection, who meet eligibility criteria for acceptance of blood donors, and are at least 28 days from COVID-19 symptom resolution. We will use existing Lifeblood and NZBS TRALI risk mitigation strategies. In Australia, Lifeblood will only use convalescent plasma collected from male donors. In New Zealand, NZBS will only use convalescent plasma collected from male donors or female donors with negative HLA antibody testings. *Donor testing* Donor samples will also undergo routine blood group and infectious disease testing as for any fresh blood	- section 2.3.4 of version3 study protocol has been moved and is labelled as section 2.3.6 in version4 of the study protocol - new section 2.3.4 in version4 of the study protocol provides background, donor selection, donor testing and convalescent plasma collection and distribution

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			component by Lifeblood and NZBS. Testing for SARS-CoV-2 serology, including SARS-CoV-2 Spike binding ELISA and neutralising assay will be performed according to blood service protocols. In Australia, only collections that have measurable neutralising antibodies will be used for the trial. *Plasma manufacture* Convalescent plasma will be collected and processed in exactly the same pathway as clinical plasma. It will be preferentially collected by apheresis and the final product will be 250-310 mL volume, stored at or below minus 25 degrees Celsius, and will meet all regulatory requirements of use as clinical plasma. *Convalescent plasma dosing:* 2 units of (250-310ml) ABO compatible convalescent plasma given within 48 hours of commencement of initial infusion (minimum 12 hours between doses). *Duration of therapy* Those receiving plasma will receive a unit of ABO compatible convalescent plasma on the first day of the study. If the patient has no serious adverse reactions to the transfusion, the second unit of convalescent plasma will be given. There must be a minimum of 12 hours between transfusions to allow appropriate assessment of adverse reactions to the initial transfusion. Both transfusions should be given within 48 hours of commencement of initial infusion.	

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Section number and title in version 3	**Section number and title in amendment (version 4)**	**Original text**	**Changed to**	**Rationale**
-	2.3.5 Other therapeutic agents with antiviral effects	-	New section: Remdesivir may be co-administered during the trial and will be recorded. However, whether co-enrolment is allowed will depend on the pathway by which remdesivir is obtained and stipulations for access should be adhered to.	- new section in protocol version4; - advising study sites that other antiviral agents may be administered to ASCOT participants, and their use will be recorded.
2.4.1 Primary outcome	2.4.1 Primary outcome	Proportion of participants alive and not having new required intensive respiratory support (invasive or non-invasive ventilation) at 15 days after enrolment. This includes any participant who receives non-invasive mechanical ventilation (either CPAP or BIPAP) on the ward any time after enrolment even if not transferred to ICU. It does NOT include the use of humidified high-flow nasal prong oxygen. Participants on pre-existing home BiPAP or CPAP will not be considered to have met the primary endpoint unless they have either required invasive mechanical ventilation (i.e. intubation) or died by day 15.	Proportion of participants alive and not having required new intensive respiratory support (invasive or non-invasive ventilation) or vasopressor/inotropic support in the 28 days after randomisation. This includes any participant who receives non-invasive mechanical ventilation (either CPAP or BIPAP) any time after enrolment even if not transferred to ICU. It does NOT include the use of humidified high-flow nasal prong oxygen. Participants on pre-existing home BiPAP or CPAP will not be considered to have met the primary endpoint unless they have either: i) required invasive mechanical ventilation (i.e. intubation); ii) graduated from CPAP whilst asleep to BiPAP at any time; iii) graduated from BiPAP only whilst asleep to BiPAP for >12 hours/day; iv) died by day 28	- amended the endpoint from 15 to 28 days; - refined the primary endpoint for participants on pre-existing home BiPAP or CPAP ventilation units.
		Point 12:	Point 12:	- amended the secondary outcome point #12 to

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Section number and title in version 3	**Section number and title in amendment (version 4)**	**Original text**	**Changed to**	**Rationale**
2.4.2.1 Clinical	2.4.2.1 Clinical	12. Safety. Any of the following adverse events in first 10 days. See section on adverse events for definitions and applicable domain 12.1 Diarrhoea – grade 2 or greater 12.2 Nausea – grade 2 or greater 12.3 Vomiting – grade 2 or greater 12.4 Pancreatitis – grade 2 or greater 12.5 QTc prolongation (>500ms) 24 hours following initial dose of study drugs	13. Safety. Any of the following adverse events in first 10 days. See section on adverse events for definitions and applicable domain 13.1 Diarrhoea – grade 2 or greater 13.2 Nausea – grade 2 or greater 13.3 Vomiting – grade 2 or greater 13.4 Pancreatitis – grade 2 or greater 13.5 QTc prolongation (>500ms) 24 hours following initial dose of study drugs 13.6 Serious allergic reaction or anaphylaxis 13.7 Transfusion-related acute lung injury 13.8 Transfusion-associated circulatory overload	include adverse events that may be reported for participants randomised into the convalescent domain
		-	Point 15: Safety. Confirmed deep vein thrombosis, pulmonary embolus, ischemic cerebrovascular event, acute myocardial infarction or other thrombotic event during index hospitalisation	- new safety clinical outcome added to version4 of the study protocol; - previous point 15 in version3 *(Viral clearance. Proportion of patients with negative SARS-CoV-2 RT-PCR at day 3 and day 7 from upper or lower respiratory tract samples)* is renumbered as point 16 in version4 of the study protocol.
2.4.3 Rationale for these	2.4.3 Rationale for these	Paragraph 1: It is not clear at this stage how many patients will be suitable for enrolment. Therefore, there may not be sufficient patient numbers to power the study on	Paragraph 1: It is not clear at this stage how many patients will be suitable for enrolment. Therefore, there may not be sufficient patient numbers to power the study on	- statistical analysis has changed due to the change in interventions (removal of hydroxychloroquine as a

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outcome measures	outcome measures	clinical outcomes. If the case fatality rate is ~1%, the study will almost certainly not be powered for showing a difference in mortality. If the requirement for ventilation or mortality at 15 days is 5%, the study will require 2440 patients to demonstrate a difference of 2.5% in the primary endpoint. Nonetheless, the investigator group felt that the primary endpoint should be one of clinical significance. There is also value in conducting the study to assess virologic and immunologic outcomes. If viral clearance can be achieved more rapidly, in addition to potentially improving the clinical course, it would have implications for infection control and duration of hospitalisation	clinical outcomes. If the case fatality rate is ~1%, the study will almost certainly not be powered for showing a difference in mortality. To detect a reduction in the primary endpoint from 5% to 2.5% would require a sample size of 1,623. To detect a reduction in the primary endpoint from 15% to 7.5% (corresponding to the Lopinavir/ritonavir monotherapy arm) would require a sample size of 1,038. To detect a reduction in the primary endpoint from 20% to 10% would require a sample size of 744.. Nonetheless, the investigator group felt that the primary endpoint should be one of clinical significance. There is also value in conducting the study to assess virologic and immunologic outcomes. If viral clearance can be achieved more rapidly, in addition to potentially improving the clinical course, it would have implications for infection control and duration of hospitalisation	monotherapy and the introduction of convalescent plasma as another treatment option)
		Paragraph 3: To allow harmonisation with these WHO Master Protocol outcomes (https://www. who.int/blueprint/ priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf), the components for the ordinal scale will be part of the data collection. The ASCOT investigator group decided that analysis of these ordinal outcomes is complicated to evaluate any distinguishable/meaningful differences amongst	Paragraph 3: To allow harmonisation with these WHO Master Protocol outcomes (https://www. who.int/blueprint/ priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf), the components for the ordinal scale will be part of the data collection.	- simplification of why the WHO Master Protocol outcomes were used as part of ASCOT data collection;

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		these categories, and thus we have opted for a dichotomous primary endpoint.		
Table 4: Schedule of visits, data collection and follow-up	Table 3: Schedule of visits, data collection and follow-up	Refer to study protocol	Refer to study protocol	- table number amended in keeping with the removal of a table earlier in the version4 protocol (section 2.3.1); - updated to reflect the activities that will be undertaken in the study; - detailed information can be found in subsection 2.5.5, under the specific study visit; - footnote updated to explain the activities listed in the table
2.5.2 Screening	2.5.2 Screening	All patients with a positive nucleic acid detection for SARS-CoV-2 will be referred by the pathology laboratory to the site investigator or their delegate (sub-investigator or properly qualified research nurse), as soon as identified. The following information will be transcribed onto a screening log by a member of the study team at the time of referral: date and time the sample was collected, the hospital record number (HRN), name & date of birth (DOB) of the patient and date and time the referral	All patients with a positive nucleic acid detection for SARS-CoV-2 will be referred by the pathology laboratory to the site investigator or their delegate (sub-investigator or properly qualified research nurse), as soon as identified. The following information will be transcribed onto a screening log by a member of the study team at the time of referral: name & date of birth (DOB) of the patient and date the referral was received. The site investigator or their delegate will approach the	- removal of reference to hospital record number, and the date & time the sample was collected from the screening log;

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		was received. The site investigator or their delegate will approach the doctors of the treating team and ask permission to approach the patient for potential recruitment onto the study and record their response in the screening log. To determine eligibility a screening paper CRF (CRF1) will be completed for all potentially eligible participants. The site investigator will do this using information gathered from the medical record and the patient's treating clinician. If the patient is eligible, the investigator will document this in the medical records. Following completion of CRF1, only patients who are eligible will be approached for an informed consent discussion. For ineligible patients and for patients who decline to participate, data may be able to be collected for observational studies. No identifiable data captured on CRF1 will leave the recruiting site	doctors of the treating team and ask permission to approach the patient for potential recruitment onto the study and record their response in the screening log. To determine eligibility a screening paper CRF (CRF1) will be completed for all potentially eligible participants. The site investigator will do this using information gathered from the medical record and the patient's treating clinician. If the patient is eligible, the investigator will document this in the medical records. Following completion of CRF1, only patients who are eligible will be approached for an informed consent discussion. For ineligible patients and for patients who decline to participate, data may be able to be collected for observational studies. No identifiable data captured on CRF1 will leave the recruiting site	
2.5.3 Informed Consent	2.5.3 Informed Consent	Paragraph 4: If a form is not available in a person's own language, the form must be translated verbally by an interpreter. The interpreter should sign the consent form held outside the isolation room that such a verbal and literal translation has been given. Where an interpreter is required, the interpreter will need to use appropriate PPE and follow local hospital policy procedures.	Paragraph 4: If a form is not available in a person's own language, the form must be translated verbally by an interpreter. The interpreter should sign the consent form held outside the isolation room that such a verbal and literal translation has been given. Where an interpreter is required, the interpreter will need to use appropriate PPE and follow local hospital policy procedures. If an interpreter is only available by telephone, the investigator must document this on the consent form and medical records and	- procedures to site staff on how to document the involvement of an interpreter during the verbal consent process.

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			document the name and contact number of the interpreter. The investigator should also request that the interpreter provide email confirmation that translation was provided in full and the participant agreed to participate.	
2.5.3.1 Surrogate informed consent	2.5.3.1 Surrogate informed consent	Paragraph 3: -	Paragraph 3: If the person responsible/medical decision maker is unable to come into the hospital, the consent process may be completed over the telephone or by video call following approval by the sponsor. The person responsible will be asked to email the site team a confirmation of consent, and the site team will document this on the consent form, along with a contact number/email for the person responsible.	- documentation of consent for person responsible/medical decision maker if they are unable to physically be present in the hospital;
2.5.4 Randomisation and blinding	2.5.4 Randomisation and blinding	Paragraph 2: Participants will be randomised in a 1:1:1:1 ratio to the standard of care or treatment arms, where the randomisation schedule will be generated by an independent statistician. Randomisation will be stratified by site and will be in permuted blocks of variable block size. The randomised sequence allocation will only be accessible to the data management group and as outlined in the data management SOP. As this is an open-label study and in the event of medical emergency no unblinding procedures are necessary.	Paragraph 2: Participants will be randomised in a 1:1:1 ratio to the standard of care or treatment arms in the antiviral domain; and 1:1 to convalescent plasma or no convalescent plasma in the antibody domain, where the randomisation schedule will be generated by an independent statistician. Randomisation will be stratified by site and will be in permuted blocks of variable block size. The randomised sequence allocation will only be accessible to the data management group and as outlined in the data management SOP. As this is an open-label study and in the event of medical emergency no unblinding	- specification of the randomisation ratio of the antiviral domain; - addition of the randomisation ratio for the convalescent domain

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			procedures are necessary.	
2.5.5.2 Day 1	2.5.5.2 Day 1	Paragraph 3: Any activities that are listed below and which were taken as part of routine care within 2 days of randomisation can be used and does not need to be repeated specifically for this study. Most information will be available from the Hospital Medical History. The evaluations/results that will be performed/recorded: • Verbal informed consent; • Demographic information (date of birth, age, sex, ethnicity); • Chest imaging. A CXR or CT chest is not mandated investigation, and data will only be collected if this has been performed as part of routine care on day 1 or results from the preceding 24-hour period; • Medical history including symptoms, comorbidities, BCG vaccination; • Travel history (if applicable) in the previous 14 days; • Review medications history (including any over-the-counter medications); • Vital signs (blood pressure, heart rate, temperature); • Review of routine clinical blood test results including full blood examination (FBE), biochemistry (i.e. EUC, LFTs, CRP); • Clinical blood test not mandated but	Paragraph 3: Any activities that are listed below and which were taken as part of routine care within 2 days of randomisation can be used and does not need to be repeated specifically for this study. Most information will be available from the Hospital Medical History. The evaluations/results that will be performed/recorded: • Verbal informed consent; • Demographic information (date of birth, age, sex, ethnicity); • Chest imaging. A CXR or CT chest is not mandated investigation, and data will only be collected if this has been performed as part of routine care on day 1 or results from the preceding 24-hour period; • Medical history including symptoms, comorbidities, BCG vaccination; • Travel history (if applicable) in the previous 14 days; • Review medications history (including any over-the-counter medications); • Vital signs (blood pressure, heart rate, temperature); • Review of routine clinical blood test results including full blood examination (FBE), biochemistry (i.e. EUC, LFTs, CRP);	- confirmation that the 12-lead baseline ECG is only applicable to participants enrolled into Domain 1 (antivirals); - ABO blood grouping required for any participant randomised to Domain 2.

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		recommended including, K+, Mg2+, lactate, D-dimer, LDH, coagulation studies (APTT, INR, fibrinogen) troponin, BNP. *If K+ or Mg2+ are abnormal, then they should be corrected*; • 12 lead baseline ECG;	• Clinical blood test not mandated but recommended including, K+, Mg2+, lactate, D-dimer, LDH, coagulation studies (APTT, INR, fibrinogen) troponin, BNP. *If K+ or Mg2+ are abnormal, then they should be corrected*; • 12 lead baseline ECG (Domain 1 only); • ABO blood grouping (Domain 2 only)	
		Paragraph 5 subheading: -	Paragraph 5 subheading: Drug administration (Domain 1) antiviral	- confirmation that the activities listed below the subsection are only applicable to participants enrolled into Domain 1 (antiviral)
		Paragraph 6: -	Paragraph 6: *Treatment administration Domain 2 (convalescent plasma):* • Request ABO blood group and complete laboratory form for convalescent plasma • Once available, administer convalescent plasma first unit as per instructions (depending on time of delivery, this may not be possible until next day) • Monitor for safety (adverse) events related to transfusions	- information added specifically for Domain 2 for the new intervention convalescent plasma;
2.5.5.3 Day 2	2.5.5.3 Day 2	Paragraph 1:	Paragraph 1:	- activity list from version3 has been divided between paragraph 1 and paragraph

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		These activities will be performed whilst the participant is in hospital and prior to study drug dosing: • Vital signs; • Review of clinical observations, including any adverse events; • ICU status; • Prior to the 3rd dose of study drug the 24hour ECG post initial dose should be performed; • A blood glucose level check via a finger prick to be performed prior to the 24hour ECG; • Review of routine clinical blood test results including full blood examination (FBE), biochemistry (i.e. EUC, LFTs, CRP); • Clinical blood test, not mandated but recommended, K+ and Mg2+. *If K+ or Mg2+ are abnormal, then they should be corrected* • Study drug administration doses and times recorded.	These activities will be performed whilst the participant is in hospital and prior to study drug dosing: • Vital signs; • Review of clinical observations, including any adverse events; • ICU status; • Review of routine clinical blood test results including full blood examination (FBE), biochemistry (i.e. EUC, LFTs, CRP)	2 in version4 of the protocol; - all trial activity listed in paragraph 1 will be undertaken for all participants enrolled into the study, regardless of which Domain(s) they were randomised too;
		Paragraph 2: -	New subsection: paragraphs 2 - 4: *Domain 1 (antiviral) only:* • Prior to the 3rd dose of study drug, the 24hour ECG post initial dose should be performed; • A blood glucose level check via a finger prick to be performed prior to the 24hour ECG; • Clinical blood test not mandated but recommended, K+ and Mg2+. *If K+ or Mg2+ are*	- activity list from version3 has been divided between paragraphs 1 and 2 in version4 of the protocol; - this section in version4 of the protocol (paragraphs 2 -4) have been rearranged from version3, as the activities listed are

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			abnormal, then they should be corrected • Study drug administration doses and times recorded. After the 4th dose of study drug and only for sites involved in the PK component the following samples will be taken: o Research blood sample (1x5mL EDTA for hydroxychloroquine arm and / or 1x5mL lithium heparin blood tube for LPV/r arms) ***4 hours*** post 4th (or 5th) study dose; o Research blood sample (1x5mL EDTA for hydroxychloroquine arm and / or 1x5mL lithium heparin blood tube for LPV/r arms) ***8 hours*** post 4th (or 5th) dose; The PK samples may be taken on day 3 after the 5th dose of study drug, if more practicable for the site staff.	specifically related to the participants enrolled in the antiviral domain Paragraphs 3 & 4 have been moved in version4 of the study protocol (were previously paragraphs 3 & 4
		Paragraph 5: -	New paragraph 5: *Domain 2 (convalescent plasma) only:* • Convalescent plasma administration, dose and time recorded • Monitor for safety (adverse) events related to transfusions	- new paragraph in version4 of the protocol, as the tasks are specific to convalescent plasma (Domain 2);
2.5.5.4 Day 3	2.5.5.4 Day 3	Paragraph 2: -	Paragraph 2: *Domain 1 (antiviral) only:* • Study drug administration doses and times recorded.	- new paragraph which contains tasks listed previously in version3 of the study protocol, but

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			• *For sites involved in the enhanced biological component (tier 1):*
			  ○ Research blood sample (1x9mL SST blood tube);
			• *For sites involved in the research biological component (tier 2):*
			  ○ Research blood sample (3x9mL sodium heparin tubes and 2x9mL ACD tubes);
				have been split from paragraph 1 in version4 of the study protocol as tasks associated with participants enrolled in Domain 1 (antivirals)

2.5.5.5 Days 4, 5, 6, 8, 9	2.5.5.5 Days 4, 5, 6, 8, 9	Paragraph 2: -	Paragraph 2: *Domain 1 (antiviral) only:* • 12 lead ECG • Study drug administration doses and times recorded	- new paragraph which contains tasks listed previously in version3 of the study protocol, but have been split from paragraph 1 in version4 of the study protocol as tasks associated with participants enrolled in Domain 1 (antivirals)
2.5.5.6 Day 7	2.5.5.6 Day 7	Paragraph 2: -	Paragraph 2: *Domain 1 (antiviral) only:* • Study drug administration doses and times recorded. • *For sites involved in the enhanced biological component (tier 1):* ○ Research blood sample (1x9mL SST blood tube);	- new paragraph which contains tasks listed previously in version3 of the study protocol, but have been split from paragraph 1 in version4 of the study protocol as tasks associated with participants enrolled in Domain 1 (antivirals)

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Section number and title in version 3	Section number and title in amendment (version 4)	Original text	Changed to	Rationale
			• *For sites involved in the research biological component (tier 2):* Research blood sample (3x9mL sodium heparin tubes and 2x9mL ACD tubes);	
2.5.5.7 Day 10	2.5.5.7 Day 10	Paragraph 2: -	Paragraph 2: *Domain 1 (antiviral) only:* • Study drug administration doses and times recorded.	- new paragraph which contains tasks listed previously in version3 of the study protocol, but have been split from paragraph 1 in version4 of the study protocol as tasks associated with participants enrolled in Domain 1 (antivirals)
2.5.5.8 Days 11-14	2.5.5.8 Days 11-14	Paragraph 1: These activities will be performed if the participant is still in hospital: • Review of clinical observations, including any adverse events; • ICU status.	Paragraph 1: These activities will be performed if the participant is still in hospital: • Review of vital signs; • Review of clinical observations, including any adverse events; • ICU status.	- addition of a task that was omitted in version3 of the protocol;
2.5.5.9 Day 15	2.5.5.9 Day 15	Paragraph 1: These activities will be performed if the participant is still in hospital: • Review of clinical observations, including any adverse events;	Paragraph 1: These activities will be performed if the participant is still in hospital: • Review of vital signs;	- addition of a tasks that were omitted in version3 of the protocol;

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Section number and title in version 3	Section number and title in amendment (version 4)	Original text	Changed to	Rationale
		• ICU status; • Review of routine clinical blood test results including full blood examination (FBE), biochemistry (i.e. EUC, LFTs, CRP);	• Review of clinical observations, including any adverse events; • ICU status; • Review of routine clinical blood test results including full blood examination (FBE), biochemistry (i.e. EUC, LFTs, CRP);	
-	2.5.5.10 Days 16-27	-	New section: These activities will be performed if the participant is in hospital: • Review of vital signs and ICU status;	- section 2.5.5.10 in version3 of the protocol is now subsection 2.5.5.11 in version4; - new section has been added due to the new endpoint of Day 28, instead of Day 15;
2.5.2.10 Day 28 ± 3 days	2.5.2.11 Day 28 ± 3 days	Paragraph 1: These activities will be performed if the participant is in hospital: • Clinical observations, including any adverse events;	Paragraph 1: These activities will be performed if the participant is in hospital: • Review of vital signs and ICU status; • Clinical observations, including any adverse events;	- addition of a task that was omitted in version3 of the protocol;
2.7.1 Primary Endpoint	2.7.1 Primary Endpoint			This section has undergone a substantial change, due to the removal of a treatment arm (monotherapy hydroxychloroquine) and the addition of a new

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				domain (antibodies which includes convalescent plasma). Please refer to the tracked changes of the protocol for more details.
2.8.1 Allocation	2.8.1 Allocation	Participants will be randomized 1:1:1:1 ration to active treatment or standard of care, using a randomisation schedule generated by an independent statistician produced and uploaded into the database which is available 24 hours per day, 7 days per week	Eligible participants will be randomized 1:1:1 in intervention domain 1 (antiviral) and 1:1 in intervention domain 2 (antibody), using a randomisation schedule generated by an independent statistician produced and uploaded into the database which is available 24 hours per day, 7 days per week	- randomization information has been updated to reflect the change in interventional treatment arms.
2.9.1 Source data	2.9.1 Source data	Paragraph 2: Storage and archiving of study documents (CRFs and consent forms) will be the responsibility of the site principal investigator and will remain at the site of recruitment and retained for 15 years. All study participants will be allocated a unique number at time of screening (screening number), this screening number will be added to all the CRFs for that participant. The participants will also have their HRN recorded on the CRFs as this information will be required to ensure the correct medical record is accessed during medical record reviews. The date and time will be captured on the CRF for all telephone conversations with study participants or GP.	Paragraph 2: Storage and archiving of study documents (CRFs and consent forms) will be the responsibility of the site principal investigator and will remain at the site of recruitment and retained for 15 years. All study participants will be allocated a unique number at time of screening (screening number), this screening number will be added to all the CRFs for that participant. The date and time will be captured on the CRF for all telephone conversations with study participants or GP.	- removal of the requirement of sites recording HRN (hospital record number) on paper CRFs. Each CRF has room for the participants unique study ID to be inserted.

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Section number and title in version 3	**Section number and title in amendment (version 4)**	**Original text**	**Changed to**	**Rationale**
2.10.1 Statistical analysis plan	2.10.1 Statistical analysis plan	Paragraph 3: A ***secondary per-protocol analysis*** of all endpoints will be conducted. The per protocol population is defined as 1) for the control group: did not receive any LPV/r or hydroxychloroquine; 2) for the intervention group: received at least 80% of possible doses of study drug; 3) has available data	Paragraph 3: A ***secondary per-protocol analysis*** of all endpoints will be conducted. The per protocol population for intervention 1 (antiviral) is defined as 1) for the control group: did not receive any LPV/r or hydroxychloroquine; 2) for the intervention group: received at least 80% of possible doses of LPV/r +/- hydroxychloroquine; 3) has available data. The per protocol population for intervention 2 (antibody) is defined as 1) for the control group: did not receive any convalescent plasma; 2) for the intervention group: did receive at least one unit of convalescent plasma	- statistical analysis plan has been updated to reflect the changes in interventions (removal of hydroxychloroquine monotherapy; addition of convalescent plasma)
2.12.3 Safety critical adverse events	2.12.3 Safety critical adverse events	-	Table 5: definition of transfusion-related adverse events for intervention domain 2 (antibody)	Please refer to the tracked protocol for more information about the addition of this new table; - table 5 has been added due to inclusion of a new intervention: convalescent plasma;
2.12.4 Serious Adverse events (SAEs)	2.12.4 Serious Adverse events (SAEs)	-	Paragraph 6 <u>For convalescent plasma:</u> In addition to the ASCOT SAE reporting procedure, all transfusion reactions must also be reported to hospital blood bank/transfusion service as per usual local practice.	- new paragraph that outlines the SAE reporting procedures for convalescent plasma

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Section number and title in version 3	**Section number and title in amendment (version 4)**	**Original text**	**Changed to**	**Rationale**
2.13.1 General ethical considerations	2.13.1 General ethical considerations	-	New paragraph 4: Convalescent plasma will be collected and manufactured in accordance with and meet all regulatory requirements for clinical plasma	- additional information pertaining to convalescent plasma;
2.13.2 Summary of potential harms and risks to study participants	2.13.2 Summary of potential harms and risks to study participants	Both LPV/r and Hydroxychloroquine have been used in millions of people worldwide over decades and have established safety profiles. However, with both of these drugs there is a small risk of severe and possibly even fatal adverse events (see section 1.2.4 for more detail). We believe this small risk is justified because of the potential for benefit, and the context that the enrolled patients have a serious infection with has a 1.5%-7% chance of mortality (hundreds of times higher than the risk of severe AEs from the study drugs). Furthermore, eligibility criteria and monitoring mitigate the risk of severe AEs, and patients have provided informed consent, with the knowledge of the possibility of these AEs.	Both LPV/r and Hydroxychloroquine have been used in millions of people worldwide over decades and have established safety profiles. However, with both of these drugs there is a small risk of severe and possibly even fatal adverse events (see section 1.2.4 for more detail). We believe this small risk is justified because of the potential for benefit, and the context that the enrolled patients have a serious infection with has a 1.5%-7% chance of mortality (hundreds of times higher than the risk of severe AEs from the study drugs). Clinical plasma is a commonly administered blood component, with well-defined safety profile through our local and international haemovigilance networks. Convalescent plasma has now been given to thousands of patients with COVID-19 internationally, with a safety profile similar to clinical plasma and no evidence of additional adverse effects. Furthermore, eligibility criteria and monitoring mitigate the risk of severe AEs, and patients have provided informed consent, with the knowledge of the possibility of these AEs.	- specific information pertaining to convalescent plasma added;

ASCOT PROTOCOL VERSION 3.0 TO VERSION 2.0				
Section number and title in version 3	**Section number and title in amendment (version 4)**	**Original text**	**Changed to**	**Rationale**
2.14 Regulatory approvals	2.14 Regulatory approvals	Although LPV/r and hydroxychloroquine are licensed for use in Australia and New Zealand, they will be used outside their approved indications. Hence a Clinical Trials Notification (CTN) will be lodged with the Therapeutic Goods Administration (TGA) for all Australian sites for all three interventions	Although LPV/r and hydroxychloroquine are licensed for use in Australia and New Zealand, they will be used outside their approved indications. Convalescent plasma will be given outside its described indication in Australia. Hence a Clinical Trials Notification (CTN) will be lodged with the Therapeutic Goods Administration (TGA) for all Australian sites for all three interventions	- specific information pertaining to convalescent plasma added;
-	Appendix 3.5 Obtaining verbal consent via telephone from the Person Responsible/ Medical Treatment Decision Maker for participation in ASCOT		New section: Refer to study protocol	- procedures that are required to be followed related to obtaining consent by site staff from Person Responsible/Medical Treatment Decision Maker if that individual cannot be present to consent in-person.

ASCOT
AustralaSian COVID-19 Trial

ASCOT ADAPT CORE PROTOCOL VERSION 1.0 TO VERSION 2.0				
Section number and title in version 1	**Section number and title in amendment (version 2)**	**Original text**	**Changed to**	**Rationale**
All document	All document	Footer: Version 1.0, August 12, 2020	Footer: Version 2.0, September 30, 2020	Updated to reflect new version.
		N/A	N/A	Table of contents updated to reflect the modifications in the protocol.
Cover page	Cover page	Protocol number:	Protocol number: ERM62646-A	Protocol number added as this was omitted in error in version 1.0.
		Protocol version/date: Version 1.0, 12/08/2020	Protocol version/date: Version 2.0, 30 September 2020	Updated version and date of the protocol to reflect the amendment.
ASCOT Study Synopsis	ASCOT Study Synopsis	Various text	Various text	Updated to reflect the removal of day 14 secondary outcomes.
1.2.1 Overview	1.2.1 Overview	Various text	Various text	Updated to reflect the most recent case numbers worldwide.
2.3.2 Core secondary outcome measures	2.3.2 Core secondary outcome measures	2. WHO 8-point ordinal outcome scale at days 14 and 28 after randomisation 6. Presence of patient reported outcome of shortness of breath at days 14, 28 and 90	2. WHO 8-point ordinal outcome scale at day 28 after randomisation 6. Presence of patient reported outcome of shortness of breath at days 28 and 90	Day 14 has been removed as a timepoint for these secondary outcomes to reduce the burden of data collection on sites.
Table 1. Schedule of visits, data collection and follow-up.	Table 1. Schedule of visits, data collection and follow-up.	Day 0 (-14 to 0) mMRC breathlessness scale was indicated to be performed on Day 1 and Day 14. Included chest imaging. Included day 3 and day 7. Clinical observations were indicated to be performed on day 28 and day 90.	Day 0 (-3 to 0) mMRC breathlessness scale removed for Day 1 and Day 14, now only to be completed on Days 28 and 90. Chest imaging removed. Days 3 and 7 removed. Clinical observations removed from days 28 and 90. No reference to telephone contact.	Changed Day 0 from -14 to -3 as all test results to be used for eligibility must have been collected within the previous 3 days. The mMRC breathlessness scale asks questions relating to exercising including walking up hills etc. and is therefore not relevant to hospitalised patients. This will now only be collected at follow-up.

ASCOT ADAPT CORE PROTOCOL VERSION 1.0 TO VERSION 2.0				
Section number and title in version 1	Section number and title in amendment (version 2)	Original text	Changed to	Rationale
		If discharged, contact participant via telephone, GP or hospital database. FBC, EUC, LFTs, CRP, D-Dimer [1,2] Footnote: 1. While in hospital only 2. Results of investigations performed at any timepoint during usual routine clinical care to be recorded in the CRF. The protocol suggested timepoints at day 1, 3, 7, 14 and 28 for investigations are not considered mandatory.	Urea, CRP [1,2] Footnote: 1. While in hospital only 2. If obtained during usual routine clinical care, record the highest value in the 24h prior to randomisation.	Chest imaging is not required as it is not related to any of the primary or secondary outcomes, or safety. This has therefore been removed. Clinical observations are not required at days 28 and 90. Reference to telephone contact has been removed, as the method of contact is not relevant to the data collected on these days. Laboratory results are not related to any of the primary or secondary outcomes, or safety for the core protocol. Domain-specific required laboratory results will be included in the domain-specific appendices. Only urea and CRP will now be collected at baseline. As the laboratory results and chest imaging will no longer be collected, day 3 and day 7 have been removed as there are no additional procedures on these days.
2.4.3 Informed Consent	2.4.3 Informed Consent	-	** If the site infection control procedures allow for written consent then this may be obtained.*	The informed consent section of the protocol has been updated based on our experience from the first 25 participants enrolled in the trial. Some sites have indicated that their local infection control procedures allow for written consent to be obtained, therefore this has been added as an option in the protocol.
		** If phone facilities are available and visual contact can be made with the*	*** If phone facilities are available, and the PICF can be provided to the patient,*	The informed consent section of the protocol has been updated based on our experience from the first 25 participants enrolled in the trial. A number

ASCOT ADAPT CORE PROTOCOL VERSION 1.0 TO VERSION 2.0				
Section number and title in version 1	Section number and title in amendment (version 2)	Original text	Changed to	Rationale
		patient, and the PICF can be provided to the patient, verbal consent can be obtained without entering the room.	*verbal consent can be obtained without entering the room.*	of investigators have raised the issue that their patients are in isolated rooms with no window into the room. They are therefore unable to make visual contact with the patient.
		The following day, the investigator or clinical team will verbally confirm with the participant that they have consented to participate.	If there is a delay between obtaining consent and randomisation, the investigator or clinical team will verbally confirm with the participant that they have consented to participate prior to undertaking any further day 1 procedures.	The informed consent section of the protocol has been updated based on our experience from the first 25 participants enrolled in the trial. There was some confusion around this statement as the protocol allows for Day 0 and Day 1 procedures to be undertaken on the same day. Investigators were unsure whether if this was the case, they would still need to confirm consent on day 2. This has now been clarified to state that consent must be confirmed before day 1 procedures if there is a delay between consent and randomisation.
		There will be only a single consent discussion, covering all domains of the platform.	There will be only a single consent discussion, covering all domains of the platform available at the site.	The informed consent discussion will only cover the domains the site is participating in, this has been clarified.
		Coordinating and Chief Investigators' Affiliations: 21 listed	Coordinating and Chief Investigators' Affiliations: 23 listed	Addition of 2 new Affiliations which are linked to new Chief Investigators named
2.4.3.1 Surrogate Informed Consent	2.4.3.1 Surrogate Informed Consent	The person responsible will be invited to ask questions which will be answered by the investigator, and they will be provided with contact details if they have any further questions. If the person responsible agrees that the patient should participate in the study,	The person responsible will be invited to ask questions which will be answered by the investigator, and they will be provided with contact details if they have any further questions. If the person responsible agrees that the patient should participate in the study,	The possibility of obtaining verbal consent from the person responsible has been added. This is based on the experience of the clinicians obtaining consent thus far in the trial, and the inability of next of kin or person responsible being able to attend hospital due to infection control measures.

ASCOT ADAPT CORE PROTOCOL VERSION 1.0 TO VERSION 2.0				
Section number and title in version 1	Section number and title in amendment (version 2)	Original text	Changed to	Rationale
		the person responsible will be asked to sign the Consent Form.	the person responsible will be asked to sign the Consent Form. If written consent cannot be obtained, verbal consent will be acceptable (e.g. via telephone). In this case the person responsible will be provided with a copy of the consent form signed by the investigator, either by mail or email.	
		-	If the participant later becomes able to provide consent themselves, additional consent from the participant should be obtained either verbally or in writing depending on infection control procedures at the site. This additional informed consent process should be documented in the participant's medical notes and on a PICF for person providing own consent.	If participants later become able to provide consent themselves, then the full informed consent discussion should take place with them before they continue in the study.
2.4.5.2. Day 1	2.4.5.2. Day 1	The evaluations that will be performed include: • Informed consent • Demographic information (date of birth, age, sex, ethnicity); • Medical history including symptoms and comorbidities	The evaluations that will be performed include: • Informed consent • Demographic information (date of birth, age, sex, ethnicity);	The mMRC breathlessness scale asks questions relating to exercising including walking up hills etc. and is therefore not relevant to hospitalised patients. This will now only be collected at follow-up. Laboratory results and chest imaging are not relevant to any of the primary or secondary

ASCOT ADAPT CORE PROTOCOL VERSION 1.0 TO VERSION 2.0				
Section number and title in version 1	Section number and title in amendment (version 2)	Original text	Changed to	Rationale
		• Review medications history • Vital signs (blood pressure, heart rate, temperature, respiratory rate) • mMRC breathlessness scale • Review of routine clinical blood test results including full blood examination (FBE), biochemistry (i.e. EUC, LFTs, CRP, D-dimer) and chest imaging	• Medical history including symptoms, signs and comorbidities • Review medications history • WHO ordinal scale • Review of routine clinical blood test results including urea and CRP, highest value within 24 hours prior to randomisation to be recorded.	outcomes, or safety, these have therefore been removed.
2.4.5.3 Day 2 till hospital discharge	2.4.5.3 Day 2 till hospital discharge	These activities will be performed whilst the participant is in hospital: • Vital signs • Review of clinical observations, including any adverse events • ICU status • Review of study related and other specified treatments If the participant is discharged on this day or any time during the study after this time point, then the PI or their delegate will contact the participant by phone on days 14, 28 and 90 as outlined in the Schedule of events with the exception of weekends and public holidays. The purpose of this contact is	These activities will be performed whilst the participant is in hospital: • WHO scale and need for inotropes • Review of domain specific treatments, adverse events, and outcomes	Vital signs are not relevant to any of the primary or secondary outcomes, or safety, these have therefore been removed from these data collection points. The primary outcome will be ascertained by completion of the WHO scale and use of inotropes, rather than ICU status. The paragraph relating to follow-up after discharge has been removed as this is not relevant to this section of the protocol.

ASCOT ADAPT CORE PROTOCOL VERSION 1.0 TO VERSION 2.0				
Section number and title in version 1	Section number and title in amendment (version 2)	Original text	Changed to	Rationale
		to collect data for the primary outcome. Prior to doing this, the PI or their delegate will make every effort to ascertain the patient's vital status (e.g. from hospital records, usual general practitioner, death notices) and will not ring the patient's family if they are known to have died.		
2.4.5.4 Day 3, 7, 14±2, 28±2	-	In addition to activities noted for Day 2 till hospital discharge, the following will be reviewed if the participant remains in hospital: • Review of routine clinical blood test and radiology results (i.e. FBE, EUC, LFTs, CRP, D-dimer, CXR)	-	Laboratory results and chest imaging are not relevant to any of the primary or secondary outcomes, or safety, these have therefore been removed.
2.4.5.5 Day 14±2, 28±2, 90±7	2.4.5.4 Day 28±2, 90±7	These activities will be performed in addition to those listed above: • mMRC breathlessness scale • EQ5D5L questionnaire for days 28±2, 90±7	These activities will be performed in addition to those listed above: • EQ5D5L questionnaire • mMRC breathlessness scale • WHO scale • Questions about days of hospitalisation and need for intensive respiratory support since the index hospitalisation episode.	Day 14 has now been removed as a timepoint of interest. The WHO scale and additional questions have been added to follow-up procedures as these are important for addressing the primary and secondary outcomes.

ASCOT ADAPT CORE PROTOCOL VERSION 1.0 TO VERSION 2.0				
Section number and title in version 1	**Section number and title in amendment (version 2)**	**Original text**	**Changed to**	**Rationale**
2.9.4 Confidentiality	2.9.4 Confidentiality	-	The study database (eCRFs) will contain date of birth (added at screening) and participant initials (added following consent). No other identifiable information will be added to the eCRFs.	A statement has been added to clarify the identifiable information that will be recorded in the eCRFs.
2.12.3 Site responsibilities	2.12.3 Site responsibilities	The PI or their delegate should: a. capture and assess all AEs b. report to the sponsor within 24 hours of becoming aware of the event: – all SARs (**Severe adverse reactions**, i.e. serious adverse events (SAEs) thought to have a reasonable causal relationship with one or more protocol-determined intervention, occurring from randomisation up until 30 days post last dose of the intervention)	The PI or their delegate should: a. Assess all AEs (note that not all AEs require recording on the CRF or reporting to the sponsor). Only specific AEs will be collected/recorded for this study, sites are not required to record all AEs. Events which are to be recorded are specified in the relevant domain-specific appendix. Recording and reporting procedures are outlined in the ASCOT ADAPT safety SOP. b. report to the sponsor within 24 hours of becoming aware of the event: - all SARs (**Severe adverse reactions**, i.e. serious adverse events (SAEs) thought to have a reasonable causal relationship with one or more protocol-determined intervention, occurring within 28 days of randomisation)	It has now been clarified that not all AEs require recording on the CRF or reporting to the sponsor. This is to avoid confusion at sites as only SARs require reporting. The timeframe for capturing SARs has also been modified to align with the data collection timepoints, and SARs will now be collected up until 28 days after randomisation.
2.12.4 SAEs not needing	2.12.4 SAEs not needing	Sites are not required to report SAEs which are not thought to be	It is recognised that the patient population in ASCOT ADAPT will	Clarification regarding what constitutes a reportable SAR has been added to this section.

ASCOT ADAPT CORE PROTOCOL VERSION 1.0 TO VERSION 2.0				
Section number and title in version 1	Section number and title in amendment (version 2)	Original text	Changed to	Rationale
expedited reporting	expedited reporting	attributable to a protocol-determined intervention. SARs should be followed up until the event has resolved or a final outcome has been reached. Any change of condition or other follow-up information for the SAR should be sent as soon as it is available.	experience a number of aberrations in laboratory values, signs and symptoms due to the severity of the underlying disease, the impact of standard treatments, and the natural history of the disease. These will not necessarily be considered adverse reactions or serious adverse reactions unless they are considered to be related to study treatment or in the principal investigator's clinical judgement are not recognised events consistent with the participants underlying critical illness and/or chronic diseases and expected clinical course. In Australia, New Zealand and India, reporting of adverse events will be restricted to events that are considered to be serious adverse reactions, that is serious adverse events related to study treatment (possibly, probably or definitely). Sites are not required to report SAEs which are not thought to be attributable to a protocol-determined intervention. SARs should be followed up until the event has resolved or a final outcome	

ASCOT ADAPT CORE PROTOCOL VERSION 1.0 TO VERSION 2.0				
Section number and title in version 1	Section number and title in amendment (version 2)	Original text	Changed to	Rationale
			has been reached, or until Day 90, whichever is earlier. Any change of condition or other follow-up information for the SAR should be sent as soon as it is available.	

ASCOT ADAPT CORE PROTOCOL VERSION 2.0 TO VERSION 3.0				
Section number and title in version 2	**Section number and title in amendment (version 3)**	**Original text**	**Changed to**	**Rationale**
All document	All document	Footer: Version 2.0, September 30, 2020	Footer: Version 3.0, October 30, 2020	Updated to reflect new version.
		N/A	N/A	Table of contents updated to reflect the modifications in the protocol.
Cover page	Cover page	Protocol version/date: Version 2.0, 30 September 2020	Protocol version/date: Version 3.0, 30 October 2020	Updated version and date of the protocol to reflect the amendment.
		To date, funders for the ASCOT trial include • the Royal Brisbane and Women's Hospital Foundation have raised $2,000,000 • the Pratt family foundation have donated $1,000,000 • Minderoo have donated $1,000,000 • BHP have donated $1,000,000 • APPRISE network through the Doherty has provided a grant of $40,000	To date, funders for the ASCOT trial include • The Royal Brisbane and Women's Hospital Foundation • The Pratt family foundation • Minderoo • BHP • APPRISE network through the Doherty Institute • A New Zealand Health Research Council grant • Macquarie Group Foundation • Medical Research Future Fund (MRFF)	Reference to the specific amounts from funders removed as funding amount is varying and the amount is not relevant to the protocol.

ASCOT ADAPT CORE PROTOCOL VERSION 2.0 TO VERSION 3.0				
Section number and title in version 2	**Section number and title in amendment (version 3)**	**Original text**	**Changed to**	**Rationale**
		• A New Zealand Health Research Council grant of NZ$766,113 • Macquarie Group Foundation $1,000,000 • MRFF $350,000		
ASCOT Study Synopsis	ASCOT Study Synopsis	Various text	Various text	Fields amended/updated to reflect the amendments in the body of the core protocol
1.1 Abbreviations	1.1 Abbreviations	N/A	N/A	Updated to add and remove abbreviations relevant to the amendments in the body of the core protocol
1.2.1 Overview	1.2.1 Overview	Various text	Various text	Updated to reflect the most recent case numbers worldwide.
1.4.4 Independent Data Safety and Monitoring Board (DSMB)	1.4.4 Independent Data Safety and Monitoring Board (DSMB)	The DSMB will be composed of experts in infectious diseases, biostatistics, clinical trials, virology and immunology. The DSMB members will all be independent of the investigators (none of them will be chief investigators or site investigators).	The DSMB will be composed of international experts in infectious diseases, biostatistics, clinical trials, virology and immunology. The DSMB members will all be independent of the investigators (none of them will be chief investigators or site investigators).	Members of the DSMB contain international experts. Text was added to specify this.
1.5 Trial design	1.5 Trial design	ASCOT ADAPT is an investigator-initiated, multi-centre, open-label, randomised controlled Bayesian adaptive platform	ASCOT ADAPT is an investigator-initiated, multi-centre, open-label, randomised controlled Bayesian adaptive platform	Clarification added that data for ASCOT will continue to be collected if participant is enrolled into REMAP-CAP

ASCOT ADAPT CORE PROTOCOL VERSION 2.0 TO VERSION 3.0				
Section number and title in version 2	Section number and title in amendment (version 3)	Original text	Changed to	Rationale
		trial. The study design will allow harmonisation with existing frameworks such as the Randomized, embedded, multifactorial adaptive platform trial for community-acquired pneumonia (REMAP-CAP) study (CI Steve Webb) and biobanking initiatives. Patients enrolled in ASCOT ADAPT and who progress to requiring invasive or non-invasive ventilation can be enrolled in REMAP-CAP.	trial. The study design will allow harmonisation with existing frameworks such as the Randomized, embedded, multifactorial adaptive platform trial for community-acquired pneumonia (REMAP-CAP) study (CI Steve Webb) and biobanking initiatives. Patients enrolled in ASCOT ADAPT and who progress to requiring invasive or non-invasive ventilation can be enrolled in REMAP-CAP (follow-up data will still be collected from these patients for ASCOT).	
2.2.3.1 Principal Investigator (PI) training	2.2.3.1 Principal Investigator (PI) training	The project manager or their delegate will have regular contact with all enrolling site investigators, including after the enrolment of participants number 1, 2 and 5 at each site, and every 10 participants thereafter.	The project manager or their delegate will have regular contact with all enrolling site investigators, including after the enrolment of participants number 1, 2 and 5 at each site, and every 10 participants thereafter. This contact may be via telephone, email or in the format of group sessions involving more than one site at a time.	Specification added about how the project manager or their delegate can contact sites.
2.2.3.3 Checking of drug charts	2.2.3.3 Checking of drug charts	The medication chart (be it paper or electronic) will be checked each business day by	The medication chart (be it paper or electronic) will be checked each business day by	Text added to specify that drug charts will be checked in the event of an SAR

ASCOT ADAPT CORE PROTOCOL VERSION 2.0 TO VERSION 3.0				
Section number and title in version 2	**Section number and title in amendment (version 3)**	**Original text**	**Changed to**	**Rationale**
		the PI or their delegate (registrar or research nurse) as long as the patient remains on at least one protocol-determined intervention, and whilst they remain an inpatient to ensure adherence to the study protocol.	the PI or their delegate (registrar or research nurse) as long as the patient remains on at least one protocol-determined intervention, and whilst they remain an inpatient to ensure adherence to the study protocol. In the event of a SAR requiring treatment, the drug chart will continue to be checked until the treatment for the SAR is discontinued and/or the SAR has resolved.	requiring treatment, to align with recording requirements of SARs.
2.3.2 Core secondary outcome measures	2.3.2 Core secondary outcome measures	1. Time to clinical recovery during the first 28 days after enrolment 1.1. Time to clinical recovery is defined as the first day, during the 28 days after enrolment, on which a patient satisfies categories 1, 2, or 3 on the WHO eight-point ordinal outcome scale.	1. Time to clinical recovery during the first 28 days after randomisation 1.1. Time to clinical recovery is defined as the first day, during the 28 days after randomisation, on which a patient satisfies categories 1, 2, or 3 on the WHO eight-point ordinal outcome scale. For the	WHO ordinal scale 1 and 2 specifies patient is not hospitalised, therefore clarification of the day the participant is hospitalised and not hospitalised is needed. When discharged, the participant is in hospital for part of the day and therefore clarification was added to assume the day after discharge would be the first hospital free day. Clarification added that it is up to 28 days after randomisation, not enrolment.

ASCOT ADAPT CORE PROTOCOL VERSION 2.0 TO VERSION 3.0				
Section number and title in version 2	Section number and title in amendment (version 3)	Original text	Changed to	Rationale
			purposes of this outcome measure, it will be assumed that the participant is not hospitalised on the first day following discharge.	
		2. WHO 8-point ordinal outcome scale at day 28 after randomisation 2.1. The ordinal score is: … 6. Hospitalised, on non-invasive ventilation or high flow oxygen devices	2. WHO 8-point ordinal outcome scale at day 28 after randomisation 2.1. The ordinal score is: … 6. Hospitalised, on non-invasive ventilation or high flow oxygen devices (refer to 2.3.1 for definition of non-invasive ventilation)	Reference to the section of text that outlines the definition of non-invasive ventilation was added.
		6. Presence of patient reported outcome of shortness of breath at days 28 and 90	6. Presence of patient reported outcome of shortness of breath at days 28 and 90 after randomisation	Clarification added that this is at days 28 and 90 after randomisation.

ASCOT ADAPT CORE PROTOCOL VERSION 2.0 TO VERSION 3.0				
Section number and title in version 2	Section number and title in amendment (version 3)	Original text	Changed to	Rationale
		7.Quality of life as measured by EQ-5D-5L9 questionnaire at days 28 and 90	7.Quality of life as measured by EQ-5D-5L9 questionnaire at days 28 and 90 after randomisation.	
2.4.2 Screening	2.4.2 Screening	All patients with a positive nucleic acid detection for SARS-CoV-2 and admitted to hospital will be referred by the pathology laboratory or the treating doctor to the site investigator or their delegate (sub-investigator or properly qualified research nurse), as soon as identified. … Following screening, only patients who are eligible will be approached for an informed consent discussion. For ineligible patients and for patients who decline to participate, data may be able to be collected for observational studies	Patients will be screened against the eligibility criteria outlined in this core protocol, as well as eligibility criteria outlined in each domain-specific appendix for the domains the site is participating in. All patients with a positive nucleic acid detection for SARS-CoV-2 and admitted to hospital will be referred by the pathology laboratory or the treating doctor to the site investigator or their delegate (sub-investigator or properly qualified research nurse), as soon as identified. … Following screening, only patients who are eligible will be approached for an informed consent discussion. For ineligible patients and for patients who decline to participate, data may be able to be collected for observational studies (e.g.	Text added to specify eligibility will be assessed at screening. Examples added to further clarify observational studies

ASCOT ADAPT CORE PROTOCOL VERSION 2.0 TO VERSION 3.0				
Section number and title in version 2	Section number and title in amendment (version 3)	Original text	Changed to	Rationale
			analysis of the population characteristics of those screened).	
2.4.3 Informed Consent	2.4.3 Informed Consent	All consent procedures will accord with local jurisdictional requirements. Due to the stringent measures in infection control in hospitals, verbal consent may be obtained in place of written consent*. Considerations include: • Bringing a consent form and pen to the bedside and then removing them from the room may violate the infection control rules. • To minimise personal protective equipment use, it will be allowed that only one person will enter a room to discuss the study with the	Informed consent will be obtained from the participant prior to performing any study-related procedures (except for screening). The consent procedure will only be performed by personnel who have been delegated the responsibility of obtaining informed consent at the site. All consent procedures will accord with local jurisdictional requirements, which are detailed in the region-specific appendices and additional SOPs, where relevant. Due to the stringent measures in infection control in hospitals, verbal consent may be obtained in place of written consent in jurisdictions where this is permitted. If the patient is unable to provide consent themselves, surrogate consent may be obtained in jurisdictions where this is permitted. The procedures for	Addition to specify informed consent to occur before performing study procedures (except for screening) and by delegated personnel. As there are varying consent requirements in different regions and at different sites, specific instructions for consent have now been removed from the core protocol. Consent procedures will be in separate consent-specific SOPs and/or specified in region-specific appendices.

ASCOT ADAPT CORE PROTOCOL VERSION 2.0 TO VERSION 3.0				
Section number and title in version 2	Section number and title in amendment (version 3)	Original text	Changed to	Rationale
		patient**. In such cases, neither the next of kin nor a witness will be present. However, if an interpreter is required for the consent discussion, both the investigator and interpreter*** may enter the room together. A phone interpreter may also be used. • It is acceptable to take the Patient Information Sheet and Consent form (PICF) into the room for viewing by the patient, and for these documents to be left in the room.	these methods of consent are outlined in the region-specific documentation.	

ASCOT ADAPT CORE PROTOCOL VERSION 2.0 TO VERSION 3.0				
Section number and title in version 2	Section number and title in amendment (version 3)	Original text	Changed to	Rationale
		• Taking a photo of the signed consent form using site investigator staff digital phones or dedicated iPad (or equivalent devices) may be considered, as long as their use meets the local infection control requirements. ** If the site infection control procedures allow for written consent then this may be obtained.* *** If phone facilities are available, and the PICF can be provided to the patient, verbal consent can be obtained without entering the room. or a*		

ASCOT ADAPT CORE PROTOCOL VERSION 2.0 TO VERSION 3.0				
Section number and title in version 2	Section number and title in amendment (version 3)	Original text	Changed to	Rationale
		hospital email account. **** Where an interpreter is required in person, the interpreter will need to use appropriate PPE and follow local hospital policy or procedure.* The PI or their delegate will hold an informed consent discussion with each patient. The patient will be given a hard copy of the approved PICF and time to ask questions and consider whether to take part in the study. The PICF will remain in the patient's room, in accordance with infection control rules. The PI or their delegate (and when an interpreter was utilised, the interpreter) will confirm the patient's agreement to the information detailed in the consent form by signing a separate copy of the form		

ASCOT ADAPT CORE PROTOCOL VERSION 2.0 TO VERSION 3.0				
Section number and title in version 2	Section number and title in amendment (version 3)	Original text	Changed to	Rationale
		kept outside the isolation room. If there is a delay between obtaining consent and randomisation, the investigator or clinical team will verbally confirm with the participant that they have consented to participate prior to undertaking any further day 1 procedures. A copy of the signed consent form will be given to the participant either at discharge, via email or by post. Prior to proceeding with randomisation, the investigator who has conducted the consent discussion will document in the medical records a summary of the discussion that includes: a statement that consent was obtained, details of any questions asked and answered and if applicable, that an interpreter was involved. There will be only a single consent discussion, covering all domains of the platform available at the site.		

ASCOT ADAPT CORE PROTOCOL VERSION 2.0 TO VERSION 3.0				
Section number and title in version 2	**Section number and title in amendment (version 3)**	**Original text**	**Changed to**	**Rationale**
2.4.3.1 Surrogate Informed Consent	2.4.3.1 Surrogate Informed Consent	The ASCOT ADAPT managing trial centre recognises that different jurisdictions have different requirements regarding surrogate consenting procedures. It is up to each site to consider whether they will use this process; if they decide to do so, they must submit the person responsible/medical treatment decision maker PICF to their HREC/RGO office, and to ensure jurisdictional approval has been received if required in that jurisdiction.. If the inclusion/exclusion criteria are confirmed, and the potential participant is unable to provide consent, then the person responsible/medical treatment decision maker (from this point referred to as person responsible) will be approached. If agreeable, the person responsible will be provided with further information about the study, both verbally and in written format (PICF).	N/A	As there are varying consent requirements, including requirements for surrogate consent, in different regions and at different sites specific instructions for surrogate consent have now been removed from the core protocol. Consent procedures, including requirements for surrogate consent, will be in separate consent-specific SOPs and/or specified in region-specific appendices.

ASCOT ADAPT CORE PROTOCOL VERSION 2.0 TO VERSION 3.0				
Section number and title in version 2	Section number and title in amendment (version 3)	Original text	Changed to	Rationale
		The person responsible will be invited to ask questions which will be answered by the investigator, and they will be provided with contact details if they have any further questions. If the person responsible agrees that the patient should participate in the study, the person responsible will be asked to sign the Consent Form. If written consent cannot be obtained, verbal consent will be acceptable (e.g. via telephone). In this case the person responsible will be provided with a copy of the consent form signed by the investigator, either by mail or email. In some jurisdictions, the person responsible indicates what they think the patient would want, until the patient regains ability to provide consent, or dies. A copy of the form will be given to the person responsible to keep. If the person responsible is indecisive about enrolment, they will be given 24 hours to		

ASCOT ADAPT CORE PROTOCOL VERSION 2.0 TO VERSION 3.0				
Section number and title in version 2	Section number and title in amendment (version 3)	Original text	Changed to	Rationale
		consider the study and will be approached once more the following day. If the participant later becomes able to provide consent themselves, additional consent from the participant should be obtained either verbally or in writing depending on infection control procedures at the site. This additional informed consent process should be documented in the participant's medical notes and on a PICF for person providing own consent. The ASCOT ADAPT managing trial centre recognises that different jurisdictions have different requirements regarding surrogate consenting procedures. It is up to each site to consider whether they will submit the person responsible/medical treatment decision maker PICF to their HREC/RGO office, and to ensure jurisdictional approval has been received.		

ASCOT ADAPT CORE PROTOCOL VERSION 2.0 TO VERSION 3.0				
Section number and title in version 2	**Section number and title in amendment (version 3)**	**Original text**	**Changed to**	**Rationale**
2.4.5.1 Day 0/Screening (-3 to 0 days)	2.4.5.1 Day 0/Screening (-3 to 0 days)	• Confirmation of a positive SARS-CoV-2 test within the last 14 days	N/A	Removal of confirmation of a positive SARS-CoV-2 test on Day 0 as this is not a procedure required on -3 to 0 days, and is part of assessing eligibility.
2.4.5.4 Day 28±2, 90±7	2.4.5.4 Day 28±2, 90±7	-	Data for Day 28 and Day 90 may be collected retrospectively (e.g. due to weekends/public holidays).	For pragmatic reasons, Day 28 and Day 90 data can be collected retrospectively. Text to clarify this was added.
2.4.6 Data and sample collection	2.4.6 Data and sample collection	Stored samples may be used for future research related to COVID-19 and related research including, but not limited to, presence of biomarkers, genetic and immunological testing.	Where appropriate consent has been obtained, stored samples may be used for future research related to COVID-19 and related research including, but not limited to, presence of biomarkers, genetic and immunological testing.	PICF contains separate section for participant to indicate consent for use of samples in future studies. This sentence was added to clarify this consent must be obtained first before samples are used in future research.
2.4.7 Discontinuation/withdrawal of participants from trial treatment	2.4.7 Discontinuation/withdrawal of participants from trial treatment	Reasons why a participant may be withdrawn from the study include, but are not limited to: • Participant request	Reasons why a participant may be withdrawn from the study include, but are not limited to: • Participant (or person responsible) request	Addition to clarify person responsible can also withdraw participant.
		Participants will not automatically be withdrawn due to adverse events.	Participants will not automatically be withdrawn due to adverse events (in this case study treatment may be ceased, but data collection will continue).	Treatments can be ceased if they are contributing to an adverse event, but this does not mean the participant is withdrawn from the study. Text was added to clarify this.
		Participants who are lost to follow up will continue to be	N/A	This sentence was confusing as it is not possible to follow-up participants who are

ASCOT ADAPT CORE PROTOCOL VERSION 2.0 TO VERSION 3.0				
Section number and title in version 2	Section number and title in amendment (version 3)	Original text	Changed to	Rationale
		followed until the end of the trial to avoid missing data.		lost to follow-up. The sentence has therefore been removed.
		-	Participants may opt to withdraw from study treatment but continue to provide data for follow-up.	Specification added that cessation of treatment does not mean the participant has been fully withdrawn from the trial.
2.5 End of trial	2.5 End of trial	The trial steering committee will continually assess the epidemiological situation, trial progress and interim results, and emerging external evidence of efficacy of the study and other interventional agents.	The international trial steering committee will continually assess the epidemiological situation, trial progress and interim results, and emerging external evidence of efficacy of the study and other interventional agents	Members of the TSC contain international members. Text was added to specify this.
2.7 Sample size	2.7 Sample size	As of mid-July, there is great uncertainty at this stage of the epidemic, with few cases in Australia, and New Zealand, and large numbers in India.	As of late October 2020, there is great uncertainty at this stage of the epidemic, with few cases in Australia and New Zealand, and large numbers in India.	Updated to reflect more recent (since October) case numbers in Australia, and New Zealand.
2.8.1 Allocation	2.8.1 Allocation	Unless an intervention has been explicitly dropped from the trial following an interim analysis (for inferiority),	Unless an intervention has been explicitly dropped from the trial following an interim analysis (for inferiority or futility),	An intervention can be stopped due to futility. Text was added to specify this.
2.8.3 Implementation	2.8.3 Implementation	The person enrolling the participant will, following obtaining verbal informed consent, …	The person enrolling the participant will, following obtaining informed consent, …	Based on local infection control requirements, some sites do allow obtaining written consent (not just verbal), therefore reference to verbal consent only was removed.
2.9.2 Protocol Deviations and Serious Breaches	2.9.2 Protocol Deviations and Serious Breaches	The following protocol deviations will be documented	The following protocol deviations will be documented	For pragmatic reasons and because a deviation of this nature is unlikely to

ASCOT ADAPT CORE PROTOCOL VERSION 2.0 TO VERSION 3.0				
Section number and title in version 2	Section number and title in amendment (version 3)	Original text	Changed to	Rationale
		and reported in the eCRF for this study: ○ Missed visits as outlined in the Schedule of Events Table 4 ○ Incorrect dosing of study drug/wrongly prescribed study drug or treatment administration ○ Day 28 outcomes missing	and reported in the eCRF for this study: ○ Randomisation or any study procedures (apart from screening) have occurred prior to informed consent having been obtained ○ Incorrect dosing of study drug/wrongly prescribed study drug or treatment administration ○ Day 28 outcomes missing	greatly impact statistical outcomes, missed visits was removed as a protocol deviation. It will be evident that a visit was missed if no data are entered for that visit, therefore additional protocol deviation reporting is not required. Informed consent must occur before randomisation or any other study-related procedures (except consent), therefore this has been added as a reportable protocol deviation.
		The sponsor will report all serious breaches to the ethics board / institutional review board within 7 days and conduct a root cause analysis and implement any corrective and preventative actions	The sponsor will report all serious breaches to the ethics board / institutional review board within 7 days and conduct a root cause analysis and implement any corrective and preventative actions (this may be delegated to the site).	As this is an international trial, it is not always practical for sponsors to implement changes at sites to prevent future breaches. In most cases, sites are better positioned to implement changes in light of their own procedures and processes. Text was added to specify this.
2.9.3 Data Recording and Record Keeping	2.9.3 Data Recording and Record Keeping	In addition, accurate and reliable data collection will be assured by verification of the eCRFs against the investigator's records by the study monitor (source document verification), and the maintenance of	In addition, accurate and reliable data collection will be assured by verification of the eCRFs against the investigator's records by the study monitor (source document verification), and the maintenance of	Specification added: ○ Addition of 'intervention' compliance, as not all interventions are medications. ○ Addition of blood product prescription form, or other appropriate source document, as some interventions (e.g.

ASCOT ADAPT CORE PROTOCOL VERSION 2.0 TO VERSION 3.0				
Section number and title in version 2	Section number and title in amendment (version 3)	Original text	Changed to	Rationale
		medication compliance will be captured in the CRF's from the participant's medication chart (source document) by the investigator.	medication/intervention compliance will be captured in the CRF's from the participant's medication chart, blood product prescription form, or other appropriate source document by the investigator.	convalescent plasma) are not medications and therefore will not be recorded on medications charts.
2.9.4 Confidentiality	2.9.4 Confidentiality	This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participating participants.	This confidentiality is extended to cover testing of biological samples and genetic tests (where consent has been provided) in addition to the clinical information relating to participating participants.	PICF contains separate section for participant to indicate consent for collection and testing of their biological samples. A sentence was added to clarify this.
2.11 Study monitoring	2.11 Study monitoring	Study monitoring will be provided by the responsible monitor(s) in accordance with the Monitoring Plan and principles of ICH GCP	Study monitoring will be provided by the responsible monitor(s) or their delegate(s) in accordance with the Monitoring Plan and principles of ICH GCP	For pragmatic reasons, a delegate of the monitor can also conduct monitoring. Text was added to clarify this.
2.12.2 Assessment of Adverse Events (AEs)	2.12.2 Assessment of Adverse Events (AEs)	3) Expectedness: An assessment against the AEs/SAEs listed in the trial's Reference Safety Information (the relevant Australian Production Information) as expected occurrences (considering the nature and frequency of the event).	3) Expectedness: An assessment against the AEs/SAEs listed in the trial's Reference Safety Information (the relevant Australian Production Information or other country equivalent) as expected occurrences (considering the nature and frequency of the event).	Countries outside Australia will be a part of ASCOT and may have different safety reference information to refer to. Text was added to specify this.

ASCOT ADAPT CORE PROTOCOL VERSION 2.0 TO VERSION 3.0				
Section number and title in version 2	**Section number and title in amendment (version 3)**	**Original text**	**Changed to**	**Rationale**
2.12.5 Sponsor Reporting Procedures:	2.12.5 Sponsor Reporting Procedures:	All SARs assigned by the site (or following central review) as both related to study treatment and unexpected will be classified as SUSARs and will be subject to expedited reporting to the Therapeutic Goods Administration (or regional equivalent) in accordance with the NHMRC Guidance.	All SARs assigned by the site (or following central review) as both related to study treatment and unexpected will be classified as SUSARs and will be subject to expedited reporting to the Therapeutic Goods Administration (or regional equivalent) in accordance with the NHMRC Guidance and/or equivalent local regulations.	NHMRC is specific to Australia, and is not necessarily relevant to countries outside Australia who are participating in ASCOT. Reference to equivalent local regulations was therefore added to clarify this.
		-	SUSARs will also be reported to the medicine license holder/supplier of the investigational product.	Current contractual agreements with suppliers of the investigational product include reporting of SUSARs. A sentence was added to reflect this.
		The Sponsor will report all Significant Safety Issues (SSIs)* to sites (as well as the HREC(s), and the TGA)	The Sponsor will report all Significant Safety Issues (SSIs)* to sites (as well as the HREC(s), the TGA and national regulatory bodies in each participating country):	Multiple countries will be participating in ASCOT and need to abide by their own regulatory procedures. Text was amended to reflect this.
2.13 General ethical considerations	2.13 General ethical considerations	Each HREC reviewing the protocol must be properly constituted according to NHMRC requirements and have the capacity to review the study.	Each HREC reviewing the protocol must be properly constituted according to NHMRC requirements or as per local IRB policies and have the capacity to review the study.	Multiple countries will be participating in ASCOT and need to abide by their own regulatory board review procedures. Text was amended to reflect this.
		No amendments to, or deviations from, the protocol	No intentional amendments to, or deviations from, the	Protocol deviations that occur accidentally are common in clinical trials and we accept

ASCOT ADAPT CORE PROTOCOL VERSION 2.0 TO VERSION 3.0				
Section number and title in version 2	Section number and title in amendment (version 3)	Original text	Changed to	Rationale
		must be initiated without prior written approval from the relevant HREC. The exceptions to this are: • administrative aspects that have no bearing on participants • the need to address regulatory requirements; and/or • the need to eliminate immediate hazards to the participants	protocol must be initiated without prior written approval from the relevant HREC. The exceptions to this are: • administrative aspects that have no bearing on participants • the need to address regulatory requirements; and/or • the need to eliminate immediate hazards to the participants	that these may occur and should be reported on the protocol deviations form. We have therefore specified that no intentional deviations from the protocol should occur.
2.14.3 Data sharing	2.14.3 Data sharing	-	Follow-up data will continue to be collected from the participant for ASCOT ADAPT if they are enrolled in REMAP-CAP.	Clarification added that data for ASCOT will continue to be collected if participant is enrolled into REMAP-CAP
2.15 Dissemination policy	2.15 Dissemination policy	The ASCOT group will consist of all named site investigators and will be listed in the collaborators section of the paper.	The ASCOT study group will consist of all named chief and site investigators and selected others who have contributed to protocol development, study design or analysis or	Clarification added to specify who constitutes members of the ASCOT study group.

ASCOT ADAPT CORE PROTOCOL VERSION 2.0 TO VERSION 3.0				
Section number and title in version 2	Section number and title in amendment (version 3)	Original text	Changed to	Rationale
			participant recruitment, and will be listed in the collaborators section of the paper.	
2.16 Collaborative agreements	2.16 Collaborative agreements	The ASCOT TSC will be open to collaborative agreements with other investigators and sponsors.	The ASCOT ADAPT ITSC will be open to collaborative agreements with other investigators and sponsors.	Minor correction to study name and International Trial Steering Committee abbreviation.

ASCOT ADAPT CORE PROTOCOL VERSION 3.0 TO VERSION 4.0				
Section number and title in version 3	**Section number and title in amendment (version 4)**	**Original text**	**Changed to**	**Rationale**
All document	All document	Footer: Version 3.0, October 30, 2020	Footer: Version 4.0, 30 April, 2021	Updated to reflect new version.
		N/A	N/A	Table of contents updated to reflect the modifications in the protocol.
		N/A	N/A	Minor formatting, spelling/grammar and wording changes throughout document.
Cover page	Cover page	Protocol version/date: Version 3.0, 30 October 2020	Protocol version/date: Version 4.0, 30 April 2021	Updated version and date of the protocol to reflect the amendment.
		Listed Sponsors: University of Melbourne University of Melbourne Middlemore Clinical Trials The George Institute for Global Health	Listed sponsors: University of Melbourne University of Melbourne Middlemore Clinical Trials The George Institute for Global Health Centre of Research and Disruption of Infectious Diseases (CREDID)	The trial will be expanding into Denmark and CREDID will act as local sponsor within that country.
ASCOT Study Synopsis	ASCOT Study Synopsis	BACKGROUND The SARS-CoV-2 virus has caused over 1,000,000 deaths globally due to COVID-19 since its initial recognition in December 2019. The global response is working to accelerate diagnostics, vaccines and therapeutics. While remdesivir has been shown to accelerate time to recovery, and low-dose dexamethasone to decrease mortality, more effective therapies are needed.	BACKGROUND The SARS-CoV-2 virus has caused over 1,000,000 deaths globally. The global response is working to accelerate diagnostics, vaccines and therapeutics. More effective therapies are needed.	Simplified and shortened to remove reference to specific treatments to avoid continually updating when new information on treatments becomes available.

ASCOT ADAPT CORE PROTOCOL VERSION 3.0 TO VERSION 4.0				
Section number and title in version 3	**Section number and title in amendment (version 4)**	**Original text**	**Changed to**	**Rationale**
ASCOT Study Synopsis	ASCOT Study Synopsis	Platform exclusion criteria: 1. Currently receiving acute intensive respiratory support (invasive or non-invasive ventilation) or vasopressor/inotropic support.	Platform exclusion criteria: 1. Currently receiving acute intensive respiratory support (invasive or non-invasive ventilation) or vasopressor/inotropic support. Note, participants already on community based non-invasive ventilation (either CPAP or BiPAP) can still be recruited. Humidified high flow nasal oxygen will not be considered an exclusion criterion.	Added clarification on existing NIV to match wording in the body of the protocol.
1.2.1 Overview	1.2.1 Overview	Various text	Various text	Updated to reflect the most recent case numbers worldwide and most effective therapies.
-	1.4.7. ASCOT Biobanking Committee (ABC)	-	The ABC will oversee sample collection, storage and applications for sample access related to biological research undertaken through the ASCOT ADAPT platform. The committee will be composed of clinical and laboratory researchers, representatives from DSWG and RSWG, and other expertise as required. The ABC will meet regularly, report directly to the	The biobanking committee were not included in the previous version of the protocol and have been added for completeness.

ASCOT ADAPT CORE PROTOCOL VERSION 3.0 TO VERSION 4.0				
Section number and title in version 3	Section number and title in amendment (version 4)	Original text	Changed to	Rationale
			ITSC, and operate under the rules of an approved charter.	
2.1. Study Setting	2.1. Study setting	We are aiming to recruit from sites across Australia, NZ, India and potentially other countries.	We are aiming to recruit from international sites, including but not limited to Australia, NZ, Denmark and India.	Addition of Denmark as a participating country.
2.4.1. Participant Timeline	2.4.1. Participant Timeline	Schedule of visits (Table 1) showed Vital and ICU status (WHO scale) being collected at day 90.	WHO scale removed from day 90.	This measure is not required for any of the primary or secondary outcomes at this timepoint and has been removed.
2.4.5.4 Day 28±2, 90±7	2.4.5.4 Day 28±2, 90±7	WHO scale	WHO scale and treatment with inotropic medication (Day 28 only)	Treatment with inotropic medication is part of the primary outcome and it has been clarified that this will be collected. Also specified that this will only be collected at day 28 as this outcome is not relevant to day 90.
2.4.7 Discontinuation/withdrawal of participants from trial treatment	2.4.7 Discontinuation/withdrawal of participants from trial treatment	If the participant withdraws consent from participating in the study and also withdraws consent for disclosure of future information, no further evaluations will be performed, and no additional data will be collected. The co-ordinating investigators may retain and continue to use any data or samples collected before such withdrawal of consent. Participants who leave against	If the participant withdraws consent from participating in the study and also withdraws consent for disclosure of future information, no further evaluations will be performed, and no additional data will be collected. The co-ordinating investigators may retain and continue to use any data or samples collected before such withdrawal of consent. Participants who leave against	Clarifications around use of data for different scenarios of patient withdrawal.

ASCOT ADAPT CORE PROTOCOL VERSION 3.0 TO VERSION 4.0				
Section number and title in version 3	Section number and title in amendment (version 4)	Original text	Changed to	Rationale
		medical advice will continue to be followed until the end of the trial to avoid missing data. If they did not complete treatment their data will be used in the intention-to-treat analysis. If they completed treatment their data will be used in the per protocol analysis. If the participant completed treatment their data will be used in the as per protocol analysis. Participants withdrawn from the treatment by the treating clinicians will continue to be followed up to the end of the trial to avoid missing data and will be used in the intention-to-treat analysis.	medical advice will continue to be followed until the end of the trial to avoid missing data. If they did not complete treatment their data will be used in the intention-to-treat analysis. If they completed treatment their data will be used in the as per protocol analysis. For participants who are lost to follow-up, if the participant completed treatment their data will be used in the as per protocol analysis. Participants withdrawn from the treatment by the treating clinicians will continue to be followed up to the end of the trial to avoid missing data and will be used in the intention-to-treat analysis. If a patient is enrolled and later found to be ineligible, study treatment will be ceased but data will continue to be collected and used in the intention-to-treat analysis.	
2.7 Sample size	2.7 Sample size	The aim of the platform itself is for perpetual recruitment until a conclusion can be made for all interventions under	The aim of the platform itself is for perpetual recruitment until a conclusion can be made for all interventions under consideration	Addition of information that evidence from other trials may be sufficient to warrant closure of a treatment arm.

ASCOT ADAPT CORE PROTOCOL VERSION 3.0 TO VERSION 4.0				
Section number and title in version 3	Section number and title in amendment (version 4)	Original text	Changed to	Rationale
		consideration and there are no new interventions to be investigated, or the condition itself is no longer prevalent. Frequent analyses are undertaken to assess hypotheses for interventions under evaluation and participants will be randomised to these interventions until there is sufficient evidence of superiority, inferiority or futility of the intervention.	and there are no new interventions to be investigated, or the condition itself is no longer prevalent. Frequent analyses are undertaken to assess hypotheses for interventions under evaluation and participants will be randomised to these interventions until there is sufficient evidence of superiority, inferiority or futility of the intervention. Evidence from external trials may also result in the closure of treatment arms if the ITSC and the relevant domain-specific working group judge the evidence to be sufficient to warrant closure.	
2.12.1 Definitions (for medicinal products)	2.12.1 Definitions (for medicinal products)	-	Serious Adverse Reaction (SAR): A SAE judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to an investigational product	Added definition of SAR.
2.12.4 SAEs not needing expedited reporting	2.12.4 SAEs not needing expedited reporting	In Australia, New Zealand and India, reporting of adverse events will be restricted to events that are considered to be serious adverse reactions, that is serious adverse events related to study treatment (possibly, probably or definitely). Sites are	Reporting of adverse events will be restricted to events that are considered to be serious adverse reactions, that is serious adverse events related to study treatment (possibly, probably or definitely). Sites are not required to report to the sponsor SAEs which are not	Removal of reference to specific countries, as some SAE reporting requirements are region-specific.

ASCOT ADAPT CORE PROTOCOL VERSION 3.0 TO VERSION 4.0				
Section number and title in version 3	Section number and title in amendment (version 4)	Original text	Changed to	Rationale
		not required to report SAEs which are not thought to be attributable to a protocol-determined intervention.	thought to be attributable to a protocol-determined intervention. Sites will follow region-specific procedures for any locally required reporting.	

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ASCOT ADAPT CORE PROTOCOL VERSION 4.0 TO VERSION 5.0				
Section number and title in version 4.0	Section number and title in amendment (version 5.0)	Original text	Changed to	Rationale
All document	All document	Footer: Version 4.0, 30 April, 2021	Footer: Version 5.0, 05 August, 2021	Updated to reflect new version.
		N/A	N/A	Table of contents updated to reflect the modifications in the protocol.
		N/A	N/A	Minor formatting, spelling/grammar and wording changes throughout document.
Cover page	Cover page	Protocol version/date: Version 4.0, 30 April 2021	Protocol version/date: Version 5.0, 05 August, 2021	Updated version and date of the protocol to reflect the amendment.
Document History	Document History	-	New Row: ASCOT-ADAPT 5.0 05 August, 2021– Minor Amendments to clarify who will be unblinded to aggregate results	Updated to reflect new version.
ASCOT Study Synopsis – BLINDING	ASCOT Study Synopsis – BLINDING	This will be an open-label study.	This will be an open-label study. For the overall data and results, only specified members of the statistical analytical team, DSMB and data co-ordinator will have access to unblinded results, with other trial investigators and staff remaining blinded to the aggregate results until completion of final analysis for a domain.	Updated to provide clarification regarding blinding and unblinding.
Contributions	Contributions	Dr David Price - provided statistical expertise on the clinical trial design, - will conduct the primary statistical analysis	Dr David Price - provided statistical expertise on the clinical trial design Prof Thomas Snelling	Updated as Dr Price and Prof Snelling will not perform analysis on blinded data

ASCOT ADAPT CORE PROTOCOL VERSION 4.0 TO VERSION 5.0				
Section number and title in version 4.0	Section number and title in amendment (version 5.0)	Original text	Changed to	Rationale
		Prof Thomas Snelling - provided statistical expertise on the clinical trial design, - will conduct the primary statistical analysis	- provided statistical expertise on the clinical trial design	
Figure 2. Study administration and governance structure	Figure 2. Study administration and governance structure	-	Addition of sponsor in Denmark. Addition of analytic team.	Updated to specify relationship between analytic team and other ASCOT committees. Updated to add Denmark sponsor (CREDID)
-	1.4.8 Statistical Committee	-	The Statistical Committee is responsible for the development of the statistical analysis plan and provide recommendations for the analysis and handling of outcome data. They will remain blinded to aggregated data until completion of final analysis for a domain.	Updated to provide details regarding the statistical committee responsibilities.
-	1.4.9 Analytic Team	-	The analytical team is responsible for the conduct of the planned interim analyses in the trial by running predetermined statistical models at each adaptive analysis and providing this output to the DSMB. The analytic team will be unblinded to aggregate data.	Updated to provide details regarding the analytical team responsibilities
2.4.7 Discontinuation/withdrawal of participants from trial treatment	2.4.7 Discontinuation/withdrawal of participants from trial treatment	If a patient is enrolled and later found to be ineligible, study treatment will be ceased but data will continue to be collected and used in the intention-to-	If a patient is enrolled and later found to be ineligible, study treatment will be ceased but data will continue to be collected and used in the intention-to-treat	Updated to provide clarification on patient enrolment errors in ITT analysis.

ASCOT ADAPT CORE PROTOCOL VERSION 4.0 TO VERSION 5.0				
Section number and title in version 4.0	Section number and title in amendment (version 5.0)	Original text	Changed to	Rationale
		treat analysis. If a participant is withdrawn the reason will be recorded in the database.	analysis. If a patient was enrolled in error, the patient will be withdrawn and their data will not be used in the intention-to-treat analysis. If a participant is withdrawn the reason will be recorded in the database.	
2.8.4 Blinding	2.8.4 Blinding	This is an open-label study, but researchers assessing the laboratory outcomes will be blinded to treatment allocation. Although blinding was considered, the added complications and expense were deemed prohibitive.	This is an open-label study, but researchers assessing the laboratory outcomes will be blinded to treatment allocation. For the overall data and results, only specified members of the statistical analytical team, DSMB and the data co-ordinator will have access to unblinded results, with other trial investigators and staff remaining blinded to the aggregate results until completion of final analysis for a domain.	Updated to clarify who will be unblinded to aggregate results.

ASCOT ADAPT CORE PROTOCOL VERSION 5.0 TO VERSION 6.0				
Section number and title in version 5.0	Section number and title in version 6.0	Original text	Changed to	Rationale
Summary table	Summary table	Overarching study sponsor Sponsor for Australian sites Sponsor for NZ sites Sponsor for Indian sites Sponsor for Danish Sites	Overarching study sponsor Sponsor for Australian sites Sponsor for NZ sites Sponsor for Indian and Nepal sites Sponsor for Danish Sites	Add Nepal sites
		Overarching Co-ordinating centre ASCOT India co-ordinating hub NZ co-ordinating hub NSW/ACT co-ordinating hub QLD co-ordinating hub	Overarching Co-ordinating centre ASCOT India and Nepal co-ordinating hub NZ co-ordinating hub NSW/ACT co-ordinating hub QLD co-ordinating hub	Add Nepal co-ordinating hub
ASCOT Study Synopsis – Platform Inclusion Criteria	ASCOT Study Synopsis – Platform Inclusion Criteria	1. Age ≥ 18 years 2. Admitted to an acute-care hospital 3. Confirmed SARS-CoV-2 by nucleic acid testing in the 14 days prior to randomisation 4. Able to be randomised within 14 days of symptom onset 5. At least one symptom or sign attributable to SARS-CoV-2 infection	1. Age ≥ 18 years 2. Admitted to an acute-care hospital 3. Confirmed SARS-CoV-2 by nucleic acid testing or rapid antigen testing in the 14 days prior to randomisation 4. Able to be randomised within 14 days of symptom onset 5. At least one symptom or sign attributable to SARS-CoV-2 infection	To allow for the use of Rapid Antigen Testing for inclusion criteria
ASCOT Study Synopsis – Blinding	ASCOT Study Synopsis – Blinding	This will be an open-label study. For the overall data and results, only specified members of the statistical analytical team, DSMB and data co-ordinator will have access to unblinded results, with	This will be an open-label study. Only specified members of the statistical analytical team, DSMB and data co-ordinator will have access to unblinded results and data, with other trial investigators	Minor changes to align with the updated statistical appendix

ASCOT ADAPT CORE PROTOCOL VERSION 5.0 TO VERSION 6.0				
Section number and title in version 5.0	Section number and title in version 6.0	Original text	Changed to	Rationale
		other trial investigators and staff remaining blinded to the aggregate results until completion of final analysis for a domain.	and staff remaining blinded to the aggregate results until completion of final analysis for a domain.	
1.2.1 Overview	1.2.1 Overview	Ongoing clinical trials are needed to define the best treatment or combination of treatments for patients with moderate COVID-19, and to allow access to emerging and experimental therapeutics for patients in the participating regions.	Ongoing clinical trials are needed to identify individual treatments and/or treatment combinations that have the greatest beneficial potential for patients with moderate COVID-19, and to allow access to emerging and experimental therapeutics for patients in the participating regions.	Minor changes to align with the updated statistical appendix
1.2.2 Bayesian adaptive platform trials	1.2.2 Bayesian adaptive platform trials	Adaptive Platform Trials are an innovative trials methodology7-9 now established for oncology trials10 and recently funded for infectious diseases syndromes of community-acquired pneumonia (REMAP-CAP, NHMRC #1101719, CIA Webb), cystic fibrosis (BEAT-CF, NHMRC #1152376, CIA Snelling) and S. aureus bacteremia (SNAP, NHMRC #1184238, CIA Tong). Conventional RCTs, at the time of design, make assumptions about plausible effect size, incidence of the primary outcome, and sample size, holding these assumptions constant until trial completion.	Adaptive Platform Trials are an innovative trials methodology7-9 now established for oncology trials10 and recently funded for infectious diseases syndromes of community-acquired pneumonia (REMAP-CAP, NHMRC #1101719, CIA Webb), cystic fibrosis (BEAT-CF, NHMRC #1152376, CIA Snelling) and S. aureus bacteremia (SNAP, NHMRC #1184238, CIA Tong). Conventional RCTs, at the time of design, make assumptions about plausible effect size, incidence of the primary outcome, and sample size, holding these assumptions constant until trial completion.	Minor changes to align with the updated statistical appendix

ASCOT ADAPT CORE PROTOCOL VERSION 5.0 TO VERSION 6.0				
Section number and title in version 5.0	Section number and title in version 6.0	Original text	Changed to	Rationale
		Adaptive Platform Trials incorporate multiple statistical and design features that are not reliant on these types of pre-trial assumptions. Platform trials allow multiple questions to be evaluated simultaneously and sequentially within the platform, and evaluate interaction between different treatment options, to achieve the goal of determining the optimal combination of treatments for the disease as rapidly as possible. The move from ASCOT (conventional RCT) to ASCOT-ADAPT enables the benefit of the critical design features described below. Critical design features of ASCOT-ADAPT that will contribute substantially to enhanced trial efficiency and rapid implementation of trial findings include: First, the trial is highly pragmatic and embedded within routine care. The inclusion criteria are easily identified and exclusion criteria minimal. Wherever possible, routine clinical and administrative data will be used for data collection.	Adaptive Platform Trials incorporate multiple statistical and design features that are not reliant on these types of pre-trial assumptions. Platform trials allow multiple questions to be evaluated simultaneously and sequentially as data accrues and can evaluate interactions between different treatment options. They typically have the joint goals of optimising treatment for participants in the trial and also identifying the effects of treatment combinations for a disease as rapidly as possible. The move from ASCOT (conventional RCT) to ASCOT-ADAPT enables the benefit of the critical design features described below. Critical design features of ASCOT-ADAPT that will contribute substantially to enhanced trial efficiency and rapid implementation of trial findings include: First, the trial is highly pragmatic and embedded within routine care. The inclusion criteria are easily identified and exclusion criteria minimal. Wherever possible, routine clinical and	

ASCOT ADAPT CORE PROTOCOL VERSION 5.0 TO VERSION 6.0				
Section number and title in version 5.0	Section number and title in version 6.0	Original text	Changed to	Rationale
		Second, we will implement a universal trial master protocol (known for this trial as the Core Protocol) with several domains. By addressing multiple questions in parallel and evaluating interactions between interventions, the platform will reduce the time, cost and sample size required to reach definitive conclusions on optimal therapy. Third, frequent interim analyses will be used so that questions are concluded as soon as there is robust statistical confidence, not when a pre-specified sample size has been recruited. This allows the platform to match the size of the observed treatment effect, including no effect, to conclude superiority and / or non-inferiority (within a pre-specified delta) as soon as warranted by accrued data. Regular interim analyses will be undertaken using a Bayesian Hierarchical Model11 that estimates the probability of superiority and / or non-inferiority of every intervention that is being evaluated. The results of each interim analysis will be reviewed by an	administrative data will be used for data collection. Second, we will implement a universal trial master protocol (known for this trial as the Core Protocol) with several domains. By addressing multiple questions in parallel and evaluating interactions between interventions, the platform will reduce the time, cost and sample size required to reach definitive conclusions on optimal therapy. Third, frequent interim analyses will be used so that questions are concluded as soon as there is robust statistical confidence, not when a pre-specified sample size has been recruited. This allows the platform to match the size of any observed treatment effect, including no effect, to conclude superiority and / or non-inferiority (within a pre-specified delta) as soon as warranted by accrued data. Regular interim analyses will be undertaken using a Bayesian Hierarchical Model11 that estimates the probability of effectiveness and futility relative to pre-defined reference levels and superiority and inferiority	

ASCOT ADAPT CORE PROTOCOL VERSION 5.0 TO VERSION 6.0				
Section number and title in version 5.0	Section number and title in version 6.0	Original text	Changed to	Rationale
		independent DSMB responsible for making declarations based on the analysis of accumulating data. Pre-specified stopping rules, informed by pre-trial simulations, will be provided to the DSMB. Details of simulations are provided in the Statistical Simulation document. Fourth, we will implement response adaptive randomisation (RAR). RAR makes use of the frequent analyses. The proportion of patients randomised to different treatments will reflect the relative benefit of these treatments up to that point in the trial. If at an early stage, one treatment is looking more beneficial, then more patients will be randomised to that treatment. Although treatments will be allocated randomly, patients will preferentially be allocated to treatments that statistical models derived from trial data indicate are more likely to be the most effective treatments.	relative to all other treatments for all interventions being evaluated. The results from each interim analysis will be reviewed by an independent DSMB responsible for recommending actions based on the analysis of accumulating data. Pre-specified stopping rules, informed by pre-trial simulations, will be provided to the DSMB. Details of simulations are provided in the Statistical Simulation document. Fourth, we will implement response adaptive randomisation (RAR), which involves updating allocation probabilities based on the results from each interim analysis. Under RAR, the proportion of patients randomised to different treatments will progressively reflect the relative benefit of these treatments up to that point in the trial. Therefore, while treatments are randomised, the participants will be preferentially allocated to those that the data indicate are more likely to be the most effective treatments.	
Figure 1: Protocol structure	*Figure 1: Protocol structure*	-		Addition of Nepal

ASCOT ADAPT CORE PROTOCOL VERSION 5.0 TO VERSION 6.0				
Section number and title in version 5.0	Section number and title in version 6.0	Original text	Changed to	Rationale
1.3.2 Statistical Analysis and Simulations Supporting Document	1.3.2 Statistical Documentation	The Statistical Analysis appendix contains a detailed description of the statistical methods used for assessing the effect of interventions, for assessing interactions between treatment groups, and for the response-adaptive randomisation procedures. The Statistical Analysis appendix will be amended when new interventions or domains are added. This is read in conjunction with the Simulations Supporting Document which contains a record of the Monte Carlo simulations used to describe the operating characteristics of the trial across a range of plausible assumptions regarding outcomes, treatment effects, and interactions between interventions in different domains. The statistical power of the study (likelihood of type II error) and the likelihood of type I error are evaluated using these simulations. The Simulations Supporting Document will be maintained as an operational document, but conclusions from simulations will be included in	The primary statistical documents for the trial are the Statistical Analysis Appendix (SAA), a Trial Simulations Report (TSR) and the Statistical Implementation Guide (SIG). Both the SAA and the TSR are designed to be generic documents largely unaffected by the introduction of new interventions and domains. Both the TSR and the SIG are operational documents that are intended to be revised as the trial progresses. An overview of the purpose and indicative contents of these documents are presented below.	Minor changes to align with the updated statistical appendix
	1.3.2.1 Statistical Analysis		The SAA specifies the general statistical framework used in the trial. This includes, but is not limited to model specifications, definition of statistical quantities of interest, trial adaptations, decision criteria and approaches to reporting. As the SAA is a generic document it will be amended infrequently and will typically not need revision when new interventions or domains are added.	Minor changes to align with the updated statistical appendix
	1.3.2.2 Trial Simulations Report		The TSR specifies the methods and results from the Monte Carlo	Minor changes to align with the updated statistical appendix

ASCOT ADAPT CORE PROTOCOL VERSION 5.0 TO VERSION 6.0				
Section number and title in version 5.0	Section number and title in version 6.0	Original text	Changed to	Rationale
		protocol documents, which will be amended as required.	simulations used to characterise the trial operating characteristics. These were run across a range of plausible assumptions regarding outcomes, treatment effects, and interactions between interventions in different domains. The cumulative probability of declaring effectiveness, superiority, inferiority and futility are evaluated using these simulations, which can be interpreted in terms of statistical power and the probability of false positives occurring. The expected sample size by treatment arm is evaluated to provide an indication of the number of participants allocated per treatment arm. The TSR will be maintained as an **operational document** that will be updated over the course of the trial, but conclusions from simulations will be included in protocol documents, which will be amended as required.	
	1.3.2. Statistical Implementation Guide		The SIG is an operational document that provides information on the trial status and low-level explanation and implementation details for statistical models and analyses based on the evolving	Minor changes to align with the updated statistical appendix

ASCOT ADAPT CORE PROTOCOL VERSION 5.0 TO VERSION 6.0				
Section number and title in version 5.0	Section number and title in version 6.0	Original text	Changed to	Rationale
			state of the trial. Where necessary, that is where changes have occurred, a release of the SIG is made for each interim analysis. Unlike the SAA and the TSR, the SIG is not intervention agnostic and as such it contains details on treatment domains and interventions.	
Figure 2. Study administration and governance structure	*Figure 2. Study administration and governance structure*	-		Addition of Nepal
1.4.8 Statistical Committee	1.4.8 Statistical Committee	The Statistical Committee is responsible for the development of the statistical analysis plan and provide recommendations for the analysis and handling of outcome data. They will remain blinded to aggregated data until completion of final analysis for a domain.	The Statistical Committee is responsible for the development of the statistical analysis plan and provide recommendations for the analysis and handling of outcome data. They will remain blinded to aggregated data and results until completion of final analysis for a domain.	Minor changes to align with the updated statistical appendix
1.4.9 Analytic Team	1.4.9 Analytic Team	The analytical team is responsible for the conduct of the planned interim analyses in the trial by running predetermined statistical models at each adaptive analysis and providing this output to the DSMB. The analytic team will be unblinded to aggregate data.	The analytical team is responsible for the conduct of the planned interim analyses in the trial by running predetermined statistical models at each adaptive analysis and providing this output to the DSMB. The analytic will be unblinded to aggregate data and are therefore not permitted to contribute to variations in the design of the trial.	Minor changes to align with the updated statistical appendix

ASCOT
AustralaSian COVID-19 Trial

ASCOT ADAPT CORE PROTOCOL VERSION 5.0 TO VERSION 6.0				
Section number and title in version 5.0	Section number and title in version 6.0	Original text	Changed to	Rationale
2.2.1 Participant inclusion criteria	2.2.1 Participant inclusion criteria	1. Age ≥ 18 years 2. Admitted to an acute-care hospital 3. Confirmed SARS-CoV-2 by nucleic acid testing in the past 14 days 4. Able to be randomised within 14 days of symptom onset 5. At least one symptom or sign attributable to SARS-CoV-2 infection	1. Age ≥ 18 years 2. Admitted to an acute-care hospital 3. Confirmed SARS-CoV-2 by nucleic acid testing or rapid antigen testing in the past 14 days 4. Able to be randomised within 14 days of symptom onset 5. At least one symptom or sign attributable to SARS-CoV-2 infection	To allow for the use of Rapid Antigen Testing for inclusion criteria
2.3.1 Primary outcome	2.3.1 Primary outcome	There may be cases where a patient has been assessed as requiring intensive respiratory support (invasive or non-invasive ventilation) or vasopressor/inotropic support, but the patient or family has declined and the patient has been discharged home. If attempts to obtain 28-day data are unsuccessful or not possible, and the investigator had deemed at the time of discharge that the patient would be highly likely to die within 28 days from randomisation, these participants will be deemed to have met the primary outcome.	There may be cases where a patient has been assessed as requiring intensive respiratory support (invasive or non-invasive ventilation) or vasopressor/inotropic support, but the patient or family declined treatment and the patient was discharged home. If attempts to obtain 28-day data are unsuccessful or not possible, and the investigator had deemed at the time of discharge that the patient would be highly likely to die within 28 days from randomisation, these participants will be deemed to have met the primary outcome.	Minor changes to align with the updated statistical appendix

ASCOT ADAPT CORE PROTOCOL VERSION 5.0 TO VERSION 6.0				
Section number and title in version 5.0	Section number and title in version 6.0	Original text	Changed to	Rationale
2.4.2 Screening	2.4.2 Screening	Patients will be screened against the eligibility criteria outlined in this core protocol, as well as eligibility criteria outlined in each domain-specific appendix for the domains the site is participating in. All patients with a positive nucleic acid detection for SARS-CoV-2 and admitted to hospital will be referred by the pathology laboratory or the treating doctor to the site investigator or their delegate (sub-investigator or properly qualified research nurse), as soon as identified.	Patients will be screened against the eligibility criteria outlined in this core protocol, as well as eligibility criteria outlined in each domain-specific appendix for the domains the site is participating in. All patients with a positive nucleic acid or rapid antigen detection for SARS-CoV-2 and admitted to hospital will be referred by the pathology laboratory or the treating doctor to the site investigator or their delegate (sub-investigator or properly qualified research nurse), as soon as identified.	To allow for the use of Rapid Antigen Testing for inclusion criteria
2.4.4 Randomisation and blinding	2.4.4 Randomisation and blinding	Participants will be randomised using response adaptive randomisation, that is the ratio of randomisation to each intervention will be proportional to the posterior probability that it is the best intervention within that domain at the most recent data examination. The initial randomisation ratios will be equal across (interventions/regimens), e.g. 1:1:1 randomisation; in other words no assumptions will be made about the relative efficacy of each intervention prior to the	Participants will be randomised using response adaptive randomisation, that is the ratio of randomisation to each intervention will be proportional to the posterior probability that it is the best intervention within that domain at the most recent data examination. The initial randomisation ratios will be equal across all regimens; in other words no assumptions will be made about the relative efficacy of each intervention prior to the first examination of the accumulating data.	Minor changes to align with the updated statistical appendix

ASCOT ADAPT CORE PROTOCOL VERSION 5.0 TO VERSION 6.0				
Section number and title in version 5.0	Section number and title in version 6.0	Original text	Changed to	Rationale
		first examination of the accumulating data. As this is an open-label study, no unblinding procedures will be necessary in the event of a medical emergency.	As this is an open-label study, no unblinding procedures will be necessary in the event of a medical emergency.	
2.6 Study timeline	2.6 Study timeline	A simple frequentist design of ASCOT opened for recruitment at the first Australian site in April 2020. ASCOT ADAPT supersedes ASCOT and will include all data, participants and specimens already collected as part of ASCOT. ASCOT ADAPT will aim to take over from ASCOT in the last third of 2020.	A simple frequentist design of ASCOT opened for recruitment at the first Australian site in April 2020. ASCOT ADAPT supersedes ASCOT and will include all data, participants and specimens already collected as part of ASCOT. Recruitment in ASCOT ADAPT is perpetual until a conclusion can be made for all study interventions and there are no new interventions to be investigated, or the condition itself is no longer prevalent.	Removal of sentence stating the plan to open ASCOT ADAPT. This is no longer relevant as ASCOT ADAPT is now open and recruiting. Addition of text to explain that recruitment continues until a conclusion is reached.
Figure 4. Study Timelines	*Figure 4. Study Timelines*	-		Figure removed. Timeline for ASCOT ADAPT no longer relevant. As an adaptive trial, domains are added and dropped and recruitment perpetual until conclusions are reached. Due to the flexible and everchanging nature of the trial, a specific timeline cannot be predicted.
2.8.2 Allocation concealment	2.8.2 Allocation concealment	The randomised sequence allocation will be stored in the database and will not be available	The algorithm that produces the randomised allocation will be stored in the database and will not	Minor changes to align with the updated statistical appendix

ASCOT ADAPT CORE PROTOCOL VERSION 5.0 TO VERSION 6.0				
Section number and title in version 5.0	Section number and title in version 6.0	Original text	Changed to	Rationale
		to any investigators or member of study staff.	be available to any investigators or member of study staff.	
2.8.3 Implementation	2.8.3 Implementation	The allocation sequence will be generated by a statistician not involved in the day to day trial procedures. Participants will be enrolled by PIs or their delegates (research nurse or co-investigator). The person enrolling the participant will, following obtaining informed consent, obtain the treatment allocation by logging onto the electronic data capture system and completing the required fields before the system will allow randomisation and subsequent treatment allocation.	The allocation sequence will be generated by an algorithm that will be updated by a statistician not involved in the day to day trial procedures. Participants will be enrolled by PIs or their delegates (research nurse or co-investigator). The person enrolling the participant will, following obtaining informed consent, obtain the treatment allocation by logging onto the electronic data capture system and completing the required fields before the system will allow randomisation and subsequent treatment allocation.	Minor changes to align with the updated statistical appendix
2.9.2 Protocol Deviations and Serious Breaches	2.9.2 Protocol Deviations and Serious Breaches	The following protocol deviations will be documented and reported in the eCRF for this study: ○ Randomisation or any study procedures (apart from screening) have occurred prior to informed consent having been obtained ○ Incorrect dosing of study drug/wrongly prescribed study drug or treatment administration.	The following protocol deviations will be documented and reported in the eCRF for this study: ○ Randomisation or any study procedures (apart from screening) have occurred prior to informed consent having been obtained ○ Incorrect dosing of study drug/wrongly prescribed study drug or treatment administration.	As ASCOT is a pragmatic trial and follow up is sometimes not possible, Day 28 outcomes missing was removed as a protocol deviation. In light of recent breaches reported involving patients accidentally randomised when they should not have been (two occurrences), randomising a patient who is ineligible has been included as a protocol deviation.

ASCOT ADAPT CORE PROTOCOL VERSION 5.0 TO VERSION 6.0				
Section number and title in version 5.0	Section number and title in version 6.0	Original text	Changed to	Rationale
		○ Day 28 outcomes missing	○ Randomising a patient who does not meet eligibility criteria	
2.10.1 Statistical Analysis Plan	2.10.1 Statistical Analysis Plan	These models will be used to calculate the posterior probabilities of hypotheses of interest, including: effectiveness, futility, superiority, and inferiority of the interventions. These probabilities, in addition to informing the RAR, will be assessed against decision specific thresholds which will inform platform conclusions and trial adaptations such as dropping of less effective interventions. These thresholds will be selected by examining trial simulations under various scenarios. Full details of the statistical models, hypotheses, and decision thresholds are presented in the Statistical Analysis Appendix and the Simulation Supporting Document.	These models will be used to calculate the posterior probabilities of hypotheses of interest, including, but not-necessarily limited to effectiveness, futility, superiority, and inferiority of the interventions. These probabilities, in addition to informing the RAR, will be assessed against decision specific thresholds which will inform platform conclusions and trial adaptations such as dropping of less effective interventions. These thresholds will be selected by examining trial simulations under various scenarios. Full details of the statistical models, hypotheses, and decision thresholds are presented in the Statistical Analysis Appendix and the Trial Simulation Report.	Minor changes to align with the updated statistical appendix

Domain-Specific Appendix:

ANTICOAGULATION DOMAIN

ASCOT ADAPT: Australasian COVID-19 ADAptive Platform Trial

Anticoagulation Domain-Specific Appendix Version 1.0 dated 13 August 2020

Summary
In this domain of ASCOT ADAPT, participants with COVID-19 admitted to participating hospitals will be randomised to receive one of three interventions depending on availability and acceptability:

- Standard dose thromboprophylaxis
- Intermediate dose thromboprophylaxis
- Standard dose thromboprophylaxis plus aspirin

At this participating site the following interventions are available within this domain:

☐Standard dose thromboprophylaxis

☐Intermediate dose thromboprophylaxis

☐Standard dose thromboprophylaxis plus aspirin

ASCOT ADAPT: Anticoagulation Domain Summary	
Interventions	• Standard dose thromboprophylaxis • Intermediate dose thromboprophylaxis • Standard dose thromboprophylaxis plus aspirin
Unit-of-analysis and Strata	The unit-of-analysis for this domain is all patients who receive an allocation status in this domain. No strata are applied in the model that is used for analysis and specification of Response Adaptive Randomisation (RAR).
Evaluable treatment-by-treatment Interactions	No interactions will be evaluated with any other domain.
Nesting	None
Timing of Reveal	Randomisation with immediate reveal and initiation
Inclusions	Inclusion criteria are the same as the Platform see Core Protocol Section 2.2.1
Domain-Specific Exclusions	Patients will be excluded from this domain if they have any of the following: • Receiving therapeutic anticoagulation • Pre-existing indication for therapeutic anticoagulation and treating clinician intends to commence therapeutic anticoagulation • Receiving dual antiplatelet therapy • Contraindication to receive low molecular weight heparin or unfractionated heparin, including known or suspected history of heparin-induced thrombocytopenia or other adverse reaction to prior heparin exposure • Severe thrombocytopenia (platelet count less than 30 x 10^9/L) • Fibrinogen level less than 1g/L • History of intracranial haemorrhage in previous 3 months • Severe renal impairment, defined as creatinine clearance less than 15ml/min • A current or recurrent condition with a high risk of major bleeding (e.g. bleeding disorder) that would be considered a contraindication to receive thromboprophylaxis
Intervention-Specific Exclusions	Criteria that exclude a patient from one or more interventions are: • Receiving an antiplatelet agent will exclude a patient from receiving standard thromboprophylaxis plus aspirin • Known hypersensitivity to an agent specified in this domain will exclude a patient from receiving that agent
Outcome measures	Primary ASCOT ADAPT outcome: Death from any cause or requirement of new intensive respiratory support (invasive or non-invasive ventilation) or vasopressor/inotropic support in the 28 days after randomisation Secondary ASCOT ADAPT outcomes refer to Core Protocol Section 2.3.2 Secondary Domain-specific outcomes: 1. Confirmed deep venous thrombosis up to 28 days 2. Confirmed pulmonary embolus up to 28 days 3. Confirmed acute myocardial infarction up to 28 days 4. Confirmed ischemic cerebrovascular event up to 28 days 5. Major bleeding (as defined by ISTH) during index hospitalisation, censored at 28 days

	6. Clinically relevant non-major bleeding (as defined by the ISTH) during index hospitalisation, censored at 28 days 7. Heparin-induced thrombocytopenia during index hospitalisation, censored at 28 days

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1. ABBREVIATIONS

ACS	Acute coronary syndrome
AMI	Acute myocardial infarction
APTT	Activated partial thromboplastin time
ARDS	Acute Respiratory Distress Syndrome
COVID-19	Coronavirus Disease-19
DSA	Domain-Specific Appendix
DSWG	Domain-Specific Working Group
DSMB	Data Safety and Monitoring Board
DVT	Deep venous thrombosis
FBE	Full Blood Examination
HIT	Heparin induced thrombocytopenia
ICU	Intensive Care Unit
ISTH	International Society of Thrombosis and Haemostasis
ITSC	International Trial Steering Committee
LMWH	Low molecular weight heparin
LOS	Length of Stay
MACE	Major adverse cardiovascular events
MI	Myocardial Infarction
PE	Pulmonary embolus
PT	Prothrombin time
RAR	Response Adaptive Randomisation
RBC	Red blood cell
RCT	Randomised Controlled Trial
RR	Relative risk
RSA	Region-Specific Appendix
SAE	Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
UFH	Unfractionated heparin
VFD	Ventilator Free Days
VTE	Venous thromboembolism

2. PROTOCOL APPENDIX STRUCTURE

The structure of this protocol is different to that used for conventional trials because this trial is highly adaptive and the description of these adaptations is better understood and specified using a 'modular' protocol design. While all adaptations are pre-specified, the structure of the protocol is designed to allow the trial to evolve over time, for example by the introduction of new domains or interventions or both (see glossary, Section 1.2 Core Protocol for definitions of these terms) and commencement of the trial in new geographical regions.

The protocol has multiple modules, in brief, comprising a Core Protocol (overview and design features of the study), a Statistical Analysis Appendix (details of the current statistical analysis plan and models) and Simulations Appendix (details of the current simulations of ASCOT ADAPT), multiple Domain-Specific Appendices (DSA) (detailing all interventions currently being studied in each domain), and multiple Regions-Specific Appendices (RSA) (detailing regional management and governance).

The Core Protocol contains all information that is generic to the trial, irrespective of the regional location in which the trial is conducted and the domains or interventions that are being tested. The Core Protocol may be amended but it is anticipated that such amendments will be infrequent.

The Core Protocol does not contain information about the intervention(s) within each domain, because one of the trial adaptations is that domains and interventions will change over time. Information about interventions, within each domain, is covered in a DSA. These Appendices are anticipated to change over time, with removal and addition of options within an existing domain, at one level, and removal and addition of entire domains, at another level. Each modification to a DSA will be subject of a separate ethics application for approval.

The Core Protocol does not contain detailed information about the statistical analysis or simulations, because the analysis model will change overtime in accordance with the domain and intervention trial adaptations but this information is contained in the Statistical Analysis and Simulations Appendices. These Appendices are anticipated to change over time, as trial adaptations occur. Each modification will be subject to approval from the International Trial Steering Committee (ITSC) in conjunction with advice from the Statistics Working Group and the Data Safety and Monitoring Board (DSMB).

The Core Protocol also does not contain information that is specific to a particular region in which the trial is conducted, as the locations that participate in the trial are also anticipated to increase over time. Information that is specific to each region that conducts the trial is contained within a RSA. This includes information related to local management, governance, and ethical and regulatory aspects. It is planned that, within each region, only that region's RSA, and any subsequent modifications, will be submitted for ethical review in that region.

The current version of the Core Protocol, DSAs, RSAs, and the Statistical Analysis Appendix is listed in the Protocol Summary and on the study website (https://www.ascot-trial.edu.au/).

3. ANTICOAGULATION DOMAIN-SPECIFIC APPENDIX VERSION

The version of the Anticoagulation Domain-Specific Appendix is in this document's header and on the cover page.

3.1. Version history

Version 1: Approved by the Anticoagulation Domain-Specific Working Group (DSWG) on 13th August 2020

4. ANTICOAGULATION DOMAIN GOVERNANCE

4.1. Domain members

Chairs: Zoe McQuilten, Jason Roberts

Members: Sanjeev Chunilal
Jennifer Curnow
M Joseph John
James McFadyen
Eileen Merriman
Huyen Tran

4.2. Contact Details

Chair:

Associate Professor Zoe McQuilten
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5. ANTICOAGULATION DOMAIN-SPECIFIC WORKING GROUP AUTHORISATION

The Anticoagulation Domain-Specific Working Group (DSWG) have read the appendix and authorise it as the official Anticoagulation Domain-Specific Appendix for the study entitled ASCOT ADAPT. Signed on behalf of the committee,

Chair  Date 13 August 2020

Zoe McQuilten

6. BACKGROUND AND RATIONALE

6.1. Domain definition

This is a domain within ASCOT ADAPT to test the effectiveness of anticoagulation and antiplatelet agents in patients hospitalised, but not currently receiving intensive care level organ support, with COVID-19.

6.2. Domain-specific background

The rapidly evolving COVID-19 global pandemic is one of the greatest public health challenges since the Spanish flu pandemic over 100 years ago. Since the discovery of the SARS-CoV-2, which causes COVID-19, millions of cases have been diagnosed worldwide resulting in hundreds of thousands of deaths. The adverse effects of COVID-19 were initially considered to primarily affect the respiratory tract by causing pneumonia and acute respiratory distress syndrome (ARDS). However, it is now apparent that COVID-19 is associated with a prothrombotic state, which can manifest as microvascular thrombosis, venous or arterial thrombosis, the presence of which usually portends an adverse prognosis. Therefore, identifying interventions that reduce thrombotic complications is a priority for the management of patients with COVID-19.

6.2.1. Summary of current evidence on effects of SARS-CoV-2 on haemostasis and thrombosis risk

An emerging problem in the management of COVID-19 is the propensity of SARS-CoV-2 to cause microvascular, venous and arterial thrombosis, and thereby exacerbating organ injury (McFadyen et al., 2020). Patients with severe COVID-19 appear to have a hyperinflammatory response, which is linked to the development of acute respiratory distress syndrome (ARDS) and multiorgan failure (Jose

and Manuel, 2020). In addition, abnormal coagulation parameters, including prolongation of the prothrombin time (PT) and activated partial thromboplastin time (aPTT), are associated with a higher mortality from COVID-19, demonstrating the significance of coagulation abnormalities in COVID-19 (Tang et al., 2020). Furthermore, plasma D-dimer appears an important prognostic marker in COVID-19 with elevated D-dimer levels being observed more commonly in patients with severe COVID-19 when compared with non-severe disease (Lippi and Favaloro, 2020, Zhang et al., 2020).

Current data highlights that rates of venous thromboembolism (VTE) in patients with COVID-19 appear markedly increased. Indeed, the cumulative incidence of VTE is reported to be between 25 – 49% of patients with severe COVID-19, with pulmonary embolism (PE) being the most common thrombotic complication (Klok et al., 2020, Middeldorp et al., 2020, Helms et al., 2020). When compared with non-COVID ARDS, patients with COVID-19 ARDS have a substantially increased rate of PE diagnosis (2.1% versus 11.7%, respectively) and patients diagnosed with a thrombotic complication have more than a five-fold increase in all-cause mortality (Helms et al., 2020). Autopsy series have demonstrated that VTE (Deep venous thrombosis [DVT] reported in 7/12 [58%] and PE reported in 11/11 [100%]) are common findings in COVID-19 patients at autopsy even in those patients not suspected of a VTE diagnosis ante mortem (Lax et al., 2020, Wichmann et al., 2020). Massive PE has been attributed as the direct cause of death in over 30% of patients with COVID-19, highlighting the important interplay between COVID-19 and venous thrombosis (Wichmann et al., 2020).

In addition to macrovascular complications, there is a strong association of COVID-19 with microvascular thrombosis. Pulmonary microvascular thrombosis has been previously described in autopsies as a complication of severe ARDS and ARDS due to other coronaviruses including SARS-CoV and MERS-CoV (Franks et al., 2003, Li et al., 2016, Tomashefski et al., 1983). However, pulmonary microvascular thrombosis appears more pronounced in severe SARS-CoV-2 infection, with histology from patients with COVID-19-associated respiratory failure demonstrating a 9-fold increase in prevalence of alveolar capillary microthrombi when compared to patients with influenza (Ackermann et al., 2020). In this regard, autopsy findings have shown that platelet-fibrin thrombi are a common microscopic finding in the pulmonary microvasculature, occurring in 80-100% of lungs examined at autopsy (Fox et al., 2020, Carsana et al., 2020, Dolhnikoff et al., 2020). It is currently posited that the development of pulmonary microvascular thrombosis in COVID-19 may precipitate the onset of respiratory decompensation.

6.2.2. Rationale for use of higher intensity anticoagulation for COVID-19

The high rates of thrombosis observed in patients with severe COVID-19 admitted to ICU appears to persist despite the implementation of routine VTE chemoprophylaxis. Retrospective cohort series analysing the rates of VTE in patients with severe COVID-19 have demonstrated the cumulative incidence of VTE to range between 31-59% despite the use of routine VTE prophylaxis (Middeldorp et al., 2020, Helms et al., 2020). These data have led to the recommendation, endorsed by the International Society of Thrombosis and Haemostasis (ISTH), that all hospitalised patients receive VTE chemoprophylaxis (Bikdeli et al., 2020). However, given the high rates of VTE there remains much debate regarding the optimal dose of anticoagulant in patients with COVID-19. Moreover, it is currently postulated that hypoxaemic respiratory failure associated with severe COVID-19 may be precipitated by the onset of pulmonary microvascular thrombosis (Lang et al., 2020). This has led to many centres globally adopting a strategy of 'intermediate' dose anticoagulation or therapeutic anticoagulation in patients admitted with COVID-19. The data supporting intensified antithrombotic strategies remain limited to retrospective series which have suggested that empiric therapeutic anticoagulation in the setting of COVID-19 may be associated with improved outcomes (Paranjpe et al., 2020).

6.2.3.Rationale for use of aspirin in COVID-19

Recent data suggests that platelets may play an important role in modulating the prothrombotic phenotype associated with COVID-19. A small autopsy series demonstrated that all patients exhibited platelet-rich microthrombi in the lungs and other vascular beds (Rapkiewicz et al., 2020). In accordance with the notion that platelets may play a role in driving COVID-19 associated thrombosis, platelet function is altered in the setting of COVID-19 such that platelets display a hyperreactive phenotype and an increased propensity to form platelet-leucocyte aggregates. The platelet hyperreactivity associated with COVID-19 is due in part to enhanced thromboxane A2 generation (Manne et al., 2020). Accordingly, treatment of platelets from COVID-19 patients with aspirin in vitro abolishes the hyperactive phenotype (Manne et al., 2020).

Aspirin is a non-selective cyclooxygenase (COX) inhibitor which is currently used in secondary prevention in cardiovascular disease, in addition to the primary and secondary prevention of VTE. The use of aspirin is associated with an approximately 25% reduction of cardiovascular events (non-fatal myocardial infarction, non-fatal ischaemic stroke or vascular death) in high risk patients with a history of cardiovascular disease (Antithrombotic Trialists et al., 2009, Antithrombotic Trialists, 2002). Aspirin also demonstrates efficacy in reducing VTE in the setting of orthopaedic surgery, where aspirin treatment has been shown to reduce VTE by approximately 34% compared to control (2000). Likewise,

aspirin reduces VTE recurrence in patients with a history of unprovoked VTE where aspirin therapy was associated with a reduction of recurrent VTE compared to placebo (5.9% vs. 11.0% per year; hazard ratio, 0.55; 95% CI, 0.33 to 0.92; P=0.02)(Becattini et al., 2012).

There is preclinical evidence for the effect of aspirin in sepsis and ARDS, including murine models demonstrating improved gas exchange and survival in ARDS models. There is also observational data reporting an association between pre-hospital anti-platelet therapy and ARDS, including lower rates of admission to ICU and shorter hospital stay, improved mortality and lower risk of ARDS (Toner et al., 2015). There has only been one randomised controlled trial in patients at risk of ARDS, which did not find any beneficial effect of aspirin on risk of developing ARDS (Kor et al., 2016). However, a correlative study showed a reduction of ARDS in aspirin-treated patients if patients with evidence of pre-existing ARDS were excluded, as well as aspirin effects on biochemical markers on intravascular responses, supporting the rationale for use of aspirin to prevent ARDS (Abdulnour et al., 2018).

To date, no studies have evaluated the effect of aspirin on preventing microvascular or macrovascular thrombosis in patients with COVID-19.

6.2.4. Potential risks of higher intensity anticoagulation and anti-platelet agents

Prophylactic anticoagulation with LMWH is routinely used in hospitalised medical patients, and the safety profile is well known, with the risk of major bleeding low (<0.5%) (Mismetti et al., 2000, Abdel-Razeq, 2010). Rates of major bleeding with therapeutic anticoagulation with LMWH is approximately 1-5% depending on underlying risk and duration of therapy. In a large cohort study of patients commencing therapeutic anticoagulation with LMWH for VTE, the risk of major bleeding was low (between 2.0 to 3.5 per 1000 patients) (van Rein et al., 2017). There is lack of data concerning the bleeding risk of 'intermediate' (i.e. intensity between prophylactic and therapeutic) dose anticoagulation, which is not commonly used routinely in practice.

There is also little data on bleeding risk with aspirin when used in conjunction with intermediate dose anticoagulation. Data from a meta-analysis examining the benefit of therapeutic anticoagulation with unfractionated heparin (UFH), in addition to aspirin therapy, for the management of acute coronary syndromes (ACS) supports the concept that anticoagulation in addition to aspirin provides benefit in terms of reducing the risk of recurrent myocardial infarction and death (RR, 0.67; 95% CI, 0.44–1.02) when compared to aspirin monotherapy (Oler et al., 1996). Therapeutic anticoagulation with LMWH when added to aspirin also displays similar efficacy to therapeutic UFH in this patient group (Petersen

et al., 2004). However, the risk of major bleeding is increased nearly two-fold with the addition of therapeutic anticoagulation with UFH to aspirin (RR, 1.89; 95% CI, 0.66–5.38) in patients with ACS (Petersen et al., 2004). A similar increase in major bleeding is also observed when therapeutic anticoagulation with LMWH is added to aspirin (Petersen et al., 2004, Eikelboom et al., 2000). However, the OASIS-6 trial demonstrated the addition of a prophylactic dose of LMWH (fondaparinux, 2.5mg daily) when added to aspirin for the treatment of AMI reduced the risk of death or MI at 9 days by approximately a quarter (8.5% vs. 11.1%; relative risk (RR), 0.76; 95% CI, 0.64–0.89) with a non-significant reduction in major bleeding (1.8% vs. 2.1%; RR, 0.83; 95% CI, 0.84 to 1.06) (Yusuf et al., 2006).

More recently, the application of 'low dose' anticoagulants combined with aspirin has been examined for the prevention of major adverse cardiovascular events (MACE) in patients with stable coronary artery disease or peripheral artery disease. The COMPASS trial has demonstrated that low dose Rivaroxaban (2.5mg daily) in addition to aspirin, reduced the rate of MACE (HR, 0.76; 95% CI, 0.66–0.86) when compared to aspirin alone (Eikelboom et al., 2017). Whilst the bleeding risk was higher in the rivaroxaban plus aspirin group, as compared to aspirin alone (HR, 1.70; 95% CI, 1.40–2.05 and HR, 1.51), the use of low dose rivaroxaban plus aspirin was associated with an overall reduction in mortality (HR, 0.82; 95% CI, 0.71–0.96). The risk of major bleeding in the rivaroxaban plus aspirin group was 2.3% compared with 1.8% in the rivaroxaban alone group over a median follow-up of 23 months.

6.2.5.Need for a clinical trial

Given high rates of thrombotic events (both venous and arterial) in COVID-19 patients, there is a need to optimise thromboprophylaxis. However, higher doses of LMWH and anti-platelet agents may cause adverse effects, including bleeding. Therefore, a clinical trial is needed to determine if higher doses of LMWH and/or additional anti-platelet agent is effective and safe.

7. DOMAIN OBJECTIVES

The objective of this domain is to determine the effectiveness of anticoagulation and antiplatelet therapy for patients with COVID-19.

We hypothesise that the probability of all-cause mortality at 28 days after enrolment will differ based on the intensity of anticoagulation and use of antiplatelet agents. The following interventions will be available:

- Standard dose thromboprophylaxis
- Intermediate dose thromboprophylaxis
- Standard dose thromboprophylaxis plus aspirin

8. TRIAL DESIGN

This domain will be conducted as part of ASCOT ADAPT (see Core Protocol Section 1). Treatment allocation will be adaptive, as described in the Core Protocol Section 2.8.1.

8.1. Population

ASCOT ADAPT enrols patients with COVID-19 admitted to hospital who are not requiring intensive organ support (see Core Protocol Section 2.2).

8.2. Eligibility criteria

Patients are eligible for this domain if they meet all of the platform-level inclusion and none of the platform-level exclusion criteria (see Core Protocol Section 2.2.2). Patients eligible for ASCOT ADAPT may have conditions that exclude them from the Anticoagulation Domain.

8.2.1. Domain inclusion criteria

Nil.

8.2.2. Domain exclusion criteria

Patients will be excluded from this domain if they have any of the following:

- Receiving therapeutic anticoagulation
- Pre-existing indication for therapeutic anticoagulation and treating clinician intends to commence therapeutic anticoagulation
- Receiving dual antiplatelet therapy
- Contraindication to receiving low molecular weight heparin or unfractionated heparin, including the known or suspected history of heparin-induced thrombocytopenia or other adverse reaction to prior heparin exposure
- Severe thrombocytopenia (platelet count less than 30 x 10^9/L)
- Fibrinogen level less than 1g/L
- History of intracranial haemorrhage in the previous 3 months
- Severe renal impairment, defined as creatinine clearance less than 15ml/min

- A current or recurrent condition with a high risk of major bleeding (e.g. bleeding disorder) that would be considered a contraindication to receive thromboprophylaxis

8.2.3.Intervention exclusion criteria

Criteria that exclude a patient from one or more interventions are:

- Receiving an antiplatelet agent will exclude a patient from receiving standard thromboprophylaxis plus aspirin
- Known hypersensitivity to an agent specified in this domain will exclude a patient from receiving that agent.

8.3. Interventions

8.3.1.Anticoagulation and antiplatelet interventions

Patients will be randomly assigned to receive one of the following open-label study interventions:

- Standard dose thromboprophylaxis
- Intermediate dose thromboprophylaxis
- Standard dose thromboprophylaxis plus aspirin

8.3.1.1.1. Standard dose thromboprophylaxis

Patients will be administered low molecular weight heparin, choice of agent according to availability and local practice at the participating site. The dose of LMWH will be as outlined in Table 1.

8.3.1.1.2. Intermediate dose thromboprophylaxis

Patients will be administered low molecular weight heparin, choice of agent according to availability and local practice at the participating site. The dose of LMWH will be as outlined in Table 1.

8.3.1.1.3. Standard dose thromboprophylaxis plus aspirin

Patients will be administered prophylactic dose low molecular weight heparin, choice of agent according to availability and local practice at the participating site, with dose as outlined in Table 1. In addition, patients will receive 100mg aspirin daily.

Table 1 dosing of LMWH

	Weight	Prophylactic	Intermediate	Intermediate daily alternative dosing*
Enoxaparin	<50kg	20mg q24h	40mg q24h	
	50-120kg	40mg q24h	40mg q12h	80mg q24h
	>120kg	60mg q24h	60mg q12h	120mg q24h
Tinzaparin	<40kg	75IU/kg q24h	125IU/kg/day	
	40-120kg			
	>120kg			
Dalteparin	<40kg	2500IU q24h	5000IU q24h	
	40-120kg	5000IU q24h	5000IU q12h	10,000IU q24h
	>120kg	7500IU q24h	7500IU q12h	15,000IU q24h

*If there is a need to minimise dosing frequency, 24-hourly dosing can be considered, as provided in the alternative dosing.
Note: q24h = Every 24 hours

8.3.2. Timing of initiation and duration of administration of anticoagulation and antiplatelet therapy

Initiation of anticoagulation +/- antiplatelet agents will be from randomisation. The intervention will continue until hospital discharge, admission to intensive care unit (ICU) or for a maximum of 28 days from randomisation. If the patient remains an inpatient after 28 days, ongoing thromboprophylaxis will be according to usual local practice.

8.3.3. Discontinuation of study intervention

Study intervention (prophylactic anticoagulation or antiplatelet agent) should be discontinued in the event of clinically significant bleeding or other complication sufficient to warrant cessation in the opinion of the treating clinician. The study intervention may be recommenced if deemed appropriate by the treating clinician.

The occurrence of suspected or confirmed HIT must result in cessation of LMWH and management, including with alternative anticoagulation, according to local protocol.

Patients allocated to standard or intermediate-dose anticoagulation who develop an indication for therapeutic anticoagulation (e.g. pulmonary embolus) can commence therapeutic anticoagulation as clinically indicated.

8.4. Concomitant care

All treatment that is not specified by assignment within the platform will be determined by treating clinician.

8.5. Endpoints

8.5.1. Primary outcome

The primary endpoint for this domain is the ASCOT primary outcome as specified in Core Protocol Section 2.3.1.

8.5.2. Secondary outcomes

All secondary outcomes as specified in the Core Protocol Section 2.3.2.

The domain-specific secondary outcome measures will be:

1. Confirmed deep venous thrombosis up to 28 days
2. Confirmed pulmonary embolus up to 28 days
3. Confirmed acute myocardial infarction up to 28 days
4. Confirmed ischemic cerebrovascular event up to 28 days
5. Major bleeding (as defined by ISTH) during index hospitalisation, censored at 28 days
6. Clinically relevant non-major bleeding (as defined by the ISTH) during index hospitalisation, censored at 28 days
7. Heparin-induced thrombocytopenia during index hospitalisation, censored at 28 days

Definitions of secondary outcomes are provided in Appendix 1.

If patients have been discharged from hospital before day 28, a history of arterial or venous thrombosis will be sought from the patient, person responsible, or supervising medical practitioner during the day 28 follow-up telephone call. Confirmation of diagnosis will be required from hospital medical records, radiological reports, or a supervising medical practitioner.

9. TRIAL CONDUCT

9.1. Domain-specific data collection

9.1.1. Microbiology

No additional microbiology testing is required.

9.1.2. Clinical data collection

Additional domain-specific data will be collected.

- D-dimer at baseline if available
- Number of RBC units transfused
- Routine clinical tests results including coagulation studies, D-dimer, anti-Xa level

9.1.3. Domain-specific study timeline

Table 2: Domain-specific schedule of visits, data collection and follow-up.

Visit Day	**Day 0 (-14 to 0)**	**Day 1**	**Day 2 till d/c**	**Day 3**	**Day 7**	**Day 14**	**Day 28**	**Day 90**
Check eligibility	X							
Informed consent		X						
Randomise		X						
Commence anticoagulation +/- antiplatelet		X						
Monitoring for serious adverse events		X	X				X	
Routine blood tests – coagulation studies, D-dimer, anti-Xa levels[1]		X	X					
Monitoring for domain secondary outcomes		X	X				X	

[1] These tests are not mandatory. Collect if done as part of routine clinical care. Coagulation studies include fibrinogen, activated partial thromboplastin time (aPTT) and prothrombin time

9.1.4. Domain-specific study visit day details

All study visit details are specified in the Core Protocol in section 2.4.5. Additional domain-specific study procedures are outlined below.

9.1.4.1. Day 0/ Screening

Screening procedures are outlined in the Core Protocol section 2.4.5.1. Additional exclusion criteria apply to this domain, however no additional procedures are required. Criteria will be assessed using medical records and results of full blood examination (FBE), coagulation screen and renal function tests conducted as part of standard care.

9.1.4.2. Day 1

In addition to the activities outlined in the Core Protocol section 2.4.5.2, additional domain-specific activities will be conducted including:

- Commence anticoagulation +/- antiplatelet treatment.
- Monitoring for serious adverse events related to treatment (see Section 11.2). This includes participants enrolled in standard of care.
- Review of routine blood tests in participants randomised to all arms including standard of care. These tests are not mandatory, only collect if part of routine clinical care. Tests include coagulation studies (fibrinogen, activated partial thromboplastin time (aPTT) and prothrombin time), D-Dimer and anti-Xa levels.
- Monitoring for other domain secondary outcomes as outlined in section 8.5.2. and defined in Appendix 1, in participants randomised to all arms including standard of care.

9.1.4.3. Day 2 till hospital discharge

Activities on Day 2 till discharge are outlined in the Core Protocol section 2.4.5.3. Other domain-specific activities will be conducted on day 2 till discharge including:

- Monitoring for serious adverse events related to treatment (see Section 11.2). This includes participants enrolled in standard of care.
- Review of routine blood tests in participants randomised to all arms including standard of care. These tests are not mandatory, only collect if part of routine clinical care. Tests include coagulation studies (fibrinogen, activated partial thromboplastin time (aPTT) and prothrombin time), D-Dimer and anti-Xa levels.
- Monitoring for other domain secondary outcomes as outlined in section 8.5.2. and defined in Appendix 1, in participants randomised to all arms including standard of care.

9.1.4.4. Day 28

In addition to the activities outlined in the Core Protocol section 2.4.5.4 and section 2.4.5.5, domain-specific activities to be conducted include:

- Monitoring for serious adverse events related to treatment (see Section 11.2). This includes participants enrolled in standard of care.
- Monitoring for other domain secondary outcomes as outlined in section 8.5.2. and defined in Appendix 1, in participants randomised to all arms including standard of care.

9.2. Criteria for discontinuation

Refer to Core Protocol Section 2.4.7 for criteria for discontinuation of participation in the ASCOT trial.

9.3. Blinding

9.3.1. Blinding

All interventions will be open-label.

9.3.2. Unblinding

Not relevant.

10. STATISTICAL CONSIDERATIONS

10.1. Domain-specific stopping rules

If a Platform Conclusion of equivalence in the primary endpoint is demonstrated the DSMB and the ITSC may consider continuation of randomisation if clinically relevant differences in secondary endpoints have not been demonstrated and it is considered plausible that clinically relevant differences in one or more secondary endpoints may be capable of being demonstrated. In all other respects the stopping rules for this domain are those outlined in the Core Protocol Sections 2.10 and the Statistical Appendix.

10.2. Unit-of-analysis and strata

The unit-of-analysis for this domain is all patients who receive an allocation status in this domain. No strata are applied in the model that is used for analysis and specification of Response Adaptive Randomisation (RAR).

10.3. Timing of revealing of randomisation status

The timing of the revealing of allocation status and administration of interventions is specified to be Randomisation with immediate reveal and initiation (see Section 2.8.1 in Core Protocol).

10.4. Interactions with interventions in other domains

An *a priori* interaction with the Antiviral Domain is not considered likely and will not be incorporated into the statistical models used to analyse this domain.

An *a priori* interaction with the Antibody directed therapy Domain is not considered likely and will not be incorporated into the statistical models used to analyse this domain.

10.5. Nesting of interventions

Nesting is not applicable to this domain

10.6. Threshold odds ratio delta for equivalence

The threshold odds ratio for equivalence in this domain is that specified in the Core Protocol (Section 2.10 and the Statistical Appendix).

10.7. Post-trial Sub-groups

Pre-specified subgroups are outlined in the Core Protocol and Statistical Analysis Plan. Domain-specific post-hoc sub-groups will be used in analysis following the conclusion of one or more interventions in the domain. The *a priori* patient sub-groups of interest are:

- D-dimer above upper limit of normal at baseline
- Weight less than 120kg vs. weight ≥120kg

11. ETHICAL CONSIDERATIONS

11.1. Data Safety and Monitoring Board

The DSMB should be aware that the superiority, inferiority, or equivalence of different interventions with respect to the primary endpoint is possible, and if equivalence is demonstrated, determination of the optimal intervention may be based on secondary endpoints, such as venous and arterial thrombosis and major bleeding.

11.2. Potential domain-specific adverse events

Domain-specific adverse events, which should be reported as SAE, include:

- Major bleeding (as defined by ISTH definition)
- Heparin-induced thrombocytopenia (HIT)

Other SAEs should be reported only where, in the opinion of the site investigator, the event might reasonably have occurred as a consequence of a study intervention or study participation (see Core Protocol Section 2.12).

11.3. Domain-specific consent issues

No domain-specific consent issues.

12.GOVERNANCE ISSUES

12.1. Funding of domain

Funding sources for ASCOT are specified in the Core Protocol. This domain has not received any additional domain-specific funding.

12.2. Funding of domain interventions and outcome measures

No specific funding.

12.3. Domain-specific declarations of interest

All investigators involved in ASCOT maintain a registry of interests on the ASCOT website. These are updated periodically and publicly accessible on the study website.

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14. APPENDICES

14.1. Appendix 1: Definition of secondary outcomes

Outcome	Definition
Major Bleeding[1]	ISTH major bleeding in non-surgical patients is defined as having a symptomatic presentation and: • Fatal bleeding, and/or • Bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or • Bleeding causing a fall in haemoglobin level of 20 g L−1 (1.24 mmol L−1) or more, or leading to transfusion of two or more units of whole blood or red cells.
Clinically relevant non-major bleeding[1]	Any sign or symptom of haemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for the ISTH definition of major bleeding but does meet at least one of the following criteria: • requiring medical intervention by a healthcare professional • leading to hospitalisation or increased level of care • prompting a face to face (i.e., not just a telephone or electronic communication) evaluation
Deep vein thrombosis	Symptoms and/or signs of deep vein thrombosis AND evidence of new deep vein thrombosis on ultrasound (noncompressible venous segment thrombosis)
Pulmonary embolism	Diagnosed in clinically suspected patients (using widely accepted clinical criteria) AND either high-probability V-Q scan, positive CT pulmonary angiogram (CTPA) (i.e. demonstrated intraluminal filling defect) or pulmonary angiogram demonstrating emboli
Acute myocardial infarction[2]	[1]Detection of a typical rise and/or fall of troponin with at least one of the following: • Symptoms of acute myocardial ischemia; • New ischemic electrocardiographic (ECG) changes; • Development of pathological Q waves; • Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic aetiology; • Identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy
Acute ischemic stroke[3]	[2]Rapidly developing clinical signs of focal (or global) disturbance of cerebral function lasting more than 24 hours (unless interrupted by surgery or death) with no apparent cause other than of vascular origin. Distinction between an ischemic cause rather than haemorrhagic will be based on imaging results.

[1] International Society of Thrombosis and Haemostasis Definitions (Kaatz et al., 2015)
[2] Based on Fourth Universal Definition of Myocardial Infarction from American College of Cardiology
[3] Based on World Health Organization definition of stroke

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ASCOT
AustralaSian COVID-19 Trial

Domain-Specific Appendix:

ANTICOAGULATION DOMAIN

ASCOT ADAPT: Australasian COVID-19 Adaptive Platform Trial

Anticoagulation Domain-Specific Appendix Version 5.0 dated 05 August 2021

Summary

In this domain of ASCOT ADAPT, participants with COVID-19 admitted to participating hospitals will be randomised to receive one of three interventions depending on availability and acceptability:

- Standard dose thromboprophylaxis
- Intermediate dose thromboprophylaxis
- Therapeutic anticoagulation

At this participating site the following interventions are available within this domain:

☐ Standard dose thromboprophylaxis

☐ Intermediate dose thromboprophylaxis

☐ Therapeutic anticoagulation

ASCOT ADAPT: Anticoagulation Domain Summary	
Interventions	• Standard dose thromboprophylaxis • Intermediate dose thromboprophylaxis • Therapeutic anticoagulation
Unit-of-analysis and Strata	The unit-of-analysis for this domain is all patients who receive an allocation status in this domain. No strata are applied in the model that is used for analysis and specification of Response Adaptive Randomisation (RAR). RAR is outlined in the Statistical Analysis Appendix.
Evaluable treatment-by-treatment Interactions	An a priori interaction with nafamostat in the antiviral domain is considered possible and will be incorporated into the expanded statistical model used to analyse this domain. It is thought possible that the antifibrinolytic and weak anticoagulant properties of nafamostat may interact with the anticoagulant properties of agents in the anticoagulation domain. Effect modification, where nafamostat might be beneficial in one arm of the anticoagulation domain but detrimental in another, is thought to be unlikely, but will be looked for. Likewise, anticoagulation is expected to be beneficial to patients enrolled into any of the arms of the antiviral domain, including the nafamostat arm.
Nesting	None
Timing of Reveal	Randomisation with immediate reveal and initiation
Inclusions	Inclusion criteria are the same as the Platform see Core Protocol Section 2.2.1
Domain-Specific Exclusions	Patients will be excluded from this domain if they have any of the following: • Receiving dual antiplatelet therapy • The treating clinician intends to continue or commence therapeutic anticoagulation • Contraindication to receive low molecular weight heparin or unfractionated heparin, including known or suspected history of heparin-induced thrombocytopenia or other adverse reaction to prior heparin exposure such as hypersensitivity • Severe thrombocytopenia (platelet count less than 50 x 10^9/L) • History of intracranial haemorrhage in previous 3 months • Severe renal impairment, defined as estimated glomerular filtration rate less than 15ml/min/1.73m^2 • A current or recurrent condition with a high risk of major bleeding (e.g. bleeding disorder), or a baseline coagulation profile (within the previous 3 days) that indicates a high risk of bleeding, that would be considered a contraindication to receive therapeutic anticoagulation
Intervention-Specific Exclusions	None
Outcome measures	**Core ASCOT ADAPT primary outcome:** Death from any cause or requirement of new intensive respiratory support (invasive or non-invasive ventilation) or vasopressor/inotropic support in the 28 days after randomisation **Core ASCOT ADAPT secondary outcome measures:** refer to Core Protocol Section 2.3.2 **Domain-specific secondary outcome measures:** 1. Confirmed deep venous thrombosis up to 28 days after randomisation 2. Confirmed pulmonary embolus up to 28 days after randomisation 3. Confirmed acute myocardial infarction up to 28 days after randomisation 4. Confirmed ischemic cerebrovascular event up to 28 days after randomisation 5. Major bleeding (as defined by ISTH), censored at 28 days after randomisation 6. Clinically relevant non-major bleeding (as defined by the ISTH), censored at 28 days after randomisation

	7. Heparin-induced thrombocytopenia during index hospitalisation, censored at 28 days after randomisation 8. Other confirmed thrombotic event up to 28 days after randomisation

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1. ABBREVIATIONS

ACS	Acute coronary syndrome
AMI	Acute myocardial infarction
APTT	Activated partial thromboplastin time
ARDS	Acute Respiratory Distress Syndrome
COVID-19	Coronavirus Disease-19
DSA	Domain-Specific Appendix
DSWG	Domain-Specific Working Group
DSMB	Data and Safety Monitoring Board
DVT	Deep venous thrombosis
FBE	Full Blood Examination
HIT	Heparin induced thrombocytopenia
ICU	Intensive Care Unit
ISTH	International Society of Thrombosis and Haemostasis
ITSC	International Trial Steering Committee
LMWH	Low molecular weight heparin
LOS	Length of Stay
MACE	Major adverse cardiovascular events
MI	Myocardial Infarction
PE	Pulmonary embolus
PT	Prothrombin time
RAR	Response Adaptive Randomisation
RBC	Red blood cell
RCT	Randomised Controlled Trial
RR	Relative risk
RSA	Region-Specific Appendix
SAE	Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
UFH	Unfractionated heparin
VFD	Ventilator Free Days
VTE	Venous thromboembolism

2. PROTOCOL APPENDIX STRUCTURE

The structure of this protocol is different to that used for conventional trials because this trial is highly adaptive and the description of these adaptations is better understood and specified using a 'modular' protocol design. While all adaptations are pre-specified, the structure of the protocol is designed to allow the trial to evolve over time, for example by the introduction of new domains or interventions or both (see Section 1 of the Core Protocol for definitions of these terms) and commencement of the trial in new geographical regions.

The protocol has multiple modules, in brief, comprising a Core Protocol (overview and design features of the study), a Statistical Analysis Appendix (details of the current statistical analysis plan and models) and Simulations document (details of the current simulations of ASCOT ADAPT), multiple Domain-Specific Appendices (DSA) (detailing all interventions currently being studied in each domain), and multiple Region-Specific Appendices (RSA) (detailing regional management and governance).

The Core Protocol contains all information that is generic to the trial, irrespective of the regional location in which the trial is conducted and the domains or interventions that are being tested. The Core Protocol may be amended but it is anticipated that such amendments will be infrequent.

The Core Protocol does not contain information about the intervention(s) within each domain, because one of the trial adaptations is that domains and interventions will change over time. Information about interventions, within each domain, is covered in a DSA. These Appendices are anticipated to change over time, with removal and addition of options within an existing domain, at one level, and removal and addition of entire domains, at another level. Each modification to a DSA will be the subject of a separate ethics application for approval.

The Core Protocol does not contain detailed information about the statistical analysis or simulations, because the analysis model will change overtime in accordance with the domain and intervention trial adaptations but this information is contained in the Statistical Analysis Appendix and Simulations document. These documents are anticipated to change over time, as trial adaptations occur. Each modification will be subject to approval from the International Trial Steering Committee (ITSC) in conjunction with advice from the Statistics Working Group and the Data and Safety Monitoring Board (DSMB).

The Core Protocol also does not contain information that is specific to a particular region in which the trial is conducted, as the locations that participate in the trial are also anticipated to increase over

time. Information that is specific to each region that conducts the trial is contained within a RSA. This includes information related to local management, governance, and ethical and regulatory aspects. It is planned that, within each region, only that region's RSA, and any subsequent modifications, will be submitted for ethical review in that region.

The current version of the Core Protocol, DSAs, RSAs, and the Statistical Analysis Appendix is listed on the study website (https://www.ascot-trial.edu.au/).

3. ANTICOAGULATION DOMAIN-SPECIFIC APPENDIX VERSION

The version of the Anticoagulation Domain-Specific Appendix is in this document's header and on the cover page.

3.1. Version history

Version 1: Approved by the Anticoagulation Domain-Specific Working Group (DSWG) on 12th August 2020

Version 2: Approved by the Anticoagulation Domain-Specific Working Group (DSWG) on 2nd October 2020

Version 3: Approved by the Anticoagulation Domain-Specific Working Group (DSWG) on 6th November 2020

Version 4: Approved by the Anticoagulation Domain-Specific Working Group (DSWG) on 28th April 2021

Version 5: Approved by the Anticoagulation Domain-Specific Working Group (DSWG) on 5th August 2021

4. ANTICOAGULATION DOMAIN GOVERNANCE

4.1. Domain members

Chairs: Associate Professor Zoe McQuilten, Professor Jason Roberts

Members: A/Prof Sanjeev Chunilal

Dr Jennifer Curnow

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5. ANTICOAGULATION DOMAIN-SPECIFIC WORKING GROUP AUTHORISATION

The Anticoagulation Domain-Specific Working Group (DSWG) have read the appendix and authorise it as the official Anticoagulation Domain-Specific Appendix for the study entitled ASCOT ADAPT. Signed on behalf of the committee,

Chair _____ Date 5th August 2021

Zoe McQuilten

6. BACKGROUND AND RATIONALE

6.1. Domain definition

This is a domain within ASCOT ADAPT to test the effectiveness of anticoagulation agents in patients hospitalised, but not currently receiving intensive care level organ support, with COVID-19.

6.2. Domain-specific background

The rapidly evolving COVID-19 global pandemic is one of the greatest public health challenges since the Spanish flu pandemic over 100 years ago. Since the discovery of the SARS-CoV-2, which causes COVID-19, millions of cases have been diagnosed worldwide resulting in hundreds of thousands of deaths. The adverse effects of COVID-19 were initially considered to primarily affect the respiratory tract by causing pneumonia and acute respiratory distress syndrome (ARDS). However, it is now apparent that COVID-19 is associated with a prothrombotic state, which can manifest as microvascular thrombosis, venous or arterial thrombosis, the presence of which usually portends an adverse prognosis. Therefore, identifying interventions that reduce thrombotic complications is a priority for the management of patients with COVID-19.

6.2.1. Summary of current evidence on effects of SARS-CoV-2 on haemostasis and thrombosis risk

An emerging problem in the management of COVID-19 is the propensity of SARS-CoV-2 to cause microvascular, venous and arterial thrombosis, and thereby exacerbating organ injury (McFadyen et al., 2020). Patients with severe COVID-19 appear to have a hyperinflammatory response, which is linked to the development of acute respiratory distress syndrome (ARDS) and multiorgan failure (Jose and Manuel, 2020). In addition, abnormal coagulation parameters, including prolongation of the prothrombin time (PT) and activated partial thromboplastin time (aPTT), are associated with a higher mortality from COVID-19, demonstrating the significance of coagulation abnormalities in COVID-19 (Tang et al., 2020). Furthermore, plasma D-dimer appears an important prognostic marker in COVID-19 with elevated D-dimer levels being observed more commonly in patients with severe COVID-19 when compared with non-severe disease (Lippi and Favaloro, 2020, Zhang et al., 2020).

Current data highlights that rates of venous thromboembolism (VTE) in patients with COVID-19 appear markedly increased. Indeed, the cumulative incidence of VTE is reported to be between 25 – 49% of patients with severe COVID-19, with pulmonary embolism (PE) being the most common thrombotic complication (Klok et al., 2020, Middeldorp et al., 2020, Helms et al., 2020). When compared with non-COVID ARDS, patients with COVID-19 ARDS have a substantially increased rate of PE diagnosis (2.1% versus 11.7%, respectively) and patients diagnosed with a thrombotic complication have more than a five-fold increase in all-cause mortality (Helms et al., 2020). Autopsy series have demonstrated that VTE (Deep venous thrombosis [DVT] reported in 7/12 [58%] and PE reported in 11/11 [100%]) are common findings in COVID-19 patients at autopsy even in those patients not suspected of a VTE diagnosis ante mortem (Lax et al., 2020, Wichmann et al., 2020). Massive PE has been attributed as

the direct cause of death in over 30% of patients with COVID-19, highlighting the important interplay between COVID-19 and venous thrombosis (Wichmann et al., 2020).

In addition to macrovascular complications, there is a strong association of COVID-19 with microvascular thrombosis. Pulmonary microvascular thrombosis has been previously described in autopsies as a complication of severe ARDS and ARDS due to other coronaviruses including SARS-CoV and MERS-CoV (Franks et al., 2003, Li et al., 2016, Tomashefski et al., 1983). However, pulmonary microvascular thrombosis appears more pronounced in severe SARS-CoV-2 infection, with histology from patients with COVID-19-associated respiratory failure demonstrating a 9-fold increase in prevalence of alveolar capillary microthrombi when compared to patients with influenza (Ackermann et al., 2020). In this regard, autopsy findings have shown that platelet-fibrin thrombi are a common microscopic finding in the pulmonary microvasculature, occurring in 80-100% of lungs examined at autopsy (Fox et al., 2020, Carsana et al., 2020, Dolhnikoff et al., 2020). It is currently posited that the development of pulmonary microvascular thrombosis in COVID-19 may precipitate the onset of respiratory decompensation.

6.2.2. Rationale for use of higher intensity anticoagulation for COVID-19

The high rates of thrombosis observed in patients with severe COVID-19 admitted to ICU appears to persist despite the implementation of routine VTE chemoprophylaxis. Retrospective cohort series analysing the rates of VTE in patients with severe COVID-19 have demonstrated the cumulative incidence of VTE to range between 31-59% despite the use of routine VTE prophylaxis (Middeldorp et al., 2020, Helms et al., 2020). These data have led to the recommendation, endorsed by the International Society of Thrombosis and Haemostasis (ISTH), that all hospitalised patients receive VTE chemoprophylaxis (Bikdeli et al., 2020). However, given the high rates of VTE there remains much debate regarding the optimal dose of anticoagulant in patients with COVID-19. Moreover, it is currently postulated that hypoxaemic respiratory failure associated with severe COVID-19 may be precipitated by the onset of pulmonary microvascular thrombosis (Lang et al., 2020). This has led to many centres globally adopting a strategy of ‘intermediate’ dose anticoagulation or therapeutic anticoagulation in patients admitted with COVID-19.

The data supporting intensified antithrombotic strategies remain limited to retrospective series which have suggested that empiric therapeutic anticoagulation in the setting of COVID-19 may be associated with improved outcomes (Paranjpe et al., 2020). Recently, a multiplatform randomised clinical trial has evaluated therapeutic anticoagulation compared to standard thromboprophylaxis in moderate and severe COVID-19 patients. This trial used a harmonised protocol across three platform trials

(REMAP-CAP, ATTACC and ACTIV-IV) with combined analysis and stopping rules. The trial closed recruitment to moderate COVID-19 patients (hospitalised and not yet requiring intensive care support) in January 2021 after an interim analysis finding of superiority for the primary outcome of mortality and organ-support free days for therapeutic anticoagulation compared to low dose thromboprophylaxis (see https://www.attacc.org/presentations). The full data have not been analysed, presented or peer-reviewed, however based on the promising findings from the interim analysis, therapeutic anticoagulation was introduced into Version 4.0 of this domain-specific appendix. No trials to date have evaluated the efficacy or safety of intermediate dose anticoagulation with low dose aspirin or therapeutic anticoagulation in hospitalised COVID-19 patients.

6.2.3.Aspirin in COVID-19

The previous version of this appendix (version 4.0) included regimens with aspirin. Since the previous protocol was written data from RECOVERY and REMAP-CAP indicate that there is no clinical benefit to the inclusion of aspirin in therapeutic regimens.

The RECOVERY trial reported results for 14,892 patients randomly allocated to usual care plus aspirin or to usual care alone (RECOVERY Collaborative Group, 2021). There was no difference in the proportion of patients who met the primary outcome of 28 day mortality (1,222 [17%] in the aspirin group vs 1,299 (17%) in the usual care group). The rate ratio was similar across all pre-specified sub-groups. Allocation to aspirin was associated with a reduction of 1 day in median time until discharge alive from hospital compared to usual care (median 8 days vs. 9 days [IQR for each 5 to >28 days]) and an increased rate of discharge alive within 28 days (75% vs. 74%, rate ratio 1·06, 95% CI 1·02 to 1·10, p=0·0062) (table 2). With the use of aspirin, the incidence of thrombotic events was lower (4.6% vs. 5.3%; absolute difference 0.6%, SE 0.4%) and the incidence of major bleeding events was higher (1.6% vs. 1.0%; absolute difference 0.6%, SE 0.2%) in the aspirin group.

REMAP-CAP has reported results via Twitter for 1,467 critically ill patients. https://twitter.com/remap_cap/status/1409884643915149319. “At a planned adaptive analysis, the probability of futility of #antiplatelet therapy (defined as an odds ratio of < 1.2) was 98%, well above the platform threshold of 95%. Previously, aspirin and P2Y12 inhibition had been proven to be equivalent in the trial. The odds ratio for improving the primary outcome of death and organ support free days was 0.99 (95% Credible Interval 0.82 – 1.19) for these drugs, compared to control.”

Based on this external evidence, and supported by the data and safety monitoring board, the trial steering committee and anticoagulation working groups decided to cease aspirin containing intervention arms on the 28th of July 2021.

Patients prescribed aspirin as part of usual care can continue to receive aspirin and data on the use of aspirin will be collected as part of this version of the appendix (version 5.0).

6.2.4. Potential risks of higher intensity anticoagulation and anti-platelet agents

Prophylactic anticoagulation with LMWH is routinely used in hospitalised medical patients, and the safety profile is well known, with the risk of major bleeding low (<0.5%) (Mismetti et al., 2000, Abdel-Razeq, 2010). Rates of major bleeding with therapeutic anticoagulation with LMWH is approximately 1-5% depending on underlying risk and duration of therapy. In a large cohort study of patients commencing therapeutic anticoagulation with LMWH for VTE, the risk of major bleeding was low (between 2.0 to 3.5 per 1000 patients) (van Rein et al., 2017). There is lack of data concerning the bleeding risk of 'intermediate' (i.e. intensity between prophylactic and therapeutic) dose anticoagulation, which is not commonly used routinely in practice. In the preliminary findings from the multiplatform randomised trial referred to earlier, major bleeding was reported in 1.6% (14/853) of patients receiving therapeutic anticoagulation compared to 0.9% (7/742) in the usual care arm (see https://www.attacc.org/presentations).

There is also little data on bleeding risk with aspirin when used in conjunction with intermediate dose anticoagulation. Data from a meta-analysis examining the benefit of therapeutic anticoagulation with unfractionated heparin (UFH), in addition to aspirin therapy, for the management of acute coronary syndromes (ACS) supports the concept that anticoagulation in addition to aspirin provides benefit in terms of reducing the risk of recurrent myocardial infarction and death (RR, 0.67; 95% CI, 0.44–1.02) when compared to aspirin monotherapy (Oler et al., 1996). Therapeutic anticoagulation with LMWH when added to aspirin also displays similar efficacy to therapeutic UFH in this patient group (Petersen et al., 2004). However, the risk of major bleeding is increased nearly two-fold with the addition of therapeutic anticoagulation with UFH to aspirin (RR, 1.89; 95% CI, 0.66–5.38) in patients with ACS (Petersen et al., 2004). A similar increase in major bleeding is also observed when therapeutic anticoagulation with LMWH is added to aspirin (Petersen et al., 2004, Eikelboom et al., 2000). However, the OASIS-6 trial demonstrated the addition of a prophylactic dose of LMWH (fondaparinux, 2.5mg daily) when added to aspirin for the treatment of AMI reduced the risk of death or MI at 9 days by approximately a quarter (8.5% vs. 11.1%; relative risk (RR), 0.76; 95% CI, 0.64–0.89) with a non-

significant reduction in major bleeding (1.8% vs. 2.1%; RR, 0.83; 95% CI, 0.84 to 1.06) (Yusuf et al., 2006).

More recently, the application of 'low dose' anticoagulants combined with aspirin has been examined for the prevention of major adverse cardiovascular events (MACE) in patients with stable coronary artery disease or peripheral artery disease. The COMPASS trial has demonstrated that low dose Rivaroxaban (2.5mg daily) in addition to aspirin, reduced the rate of MACE (HR, 0.76; 95% CI, 0.66–0.86) when compared to aspirin alone (Eikelboom et al., 2017). Whilst the bleeding risk was higher in the rivaroxaban plus aspirin group, as compared to aspirin alone (HR, 1.70; 95% CI, 1.40–2.05 and HR, 1.51), the use of low dose rivaroxaban plus aspirin was associated with an overall reduction in mortality (HR, 0.82; 95% CI, 0.71–0.96). The risk of major bleeding in the rivaroxaban plus aspirin group was 2.3% compared with 1.8% in the rivaroxaban alone group over a median follow-up of 23 months.

6.2.5. Need for a clinical trial

Given high rates of thrombotic events (both venous and arterial) in COVID-19 patients, there is a need to optimise thromboprophylaxis. However, higher doses of LMWH may cause adverse effects, including bleeding. Therefore, a clinical trial is needed to determine if higher doses of LMWH is effective and safe.

7. DOMAIN OBJECTIVES

The objective of this domain is to determine the effectiveness of anticoagulation therapy for patients with COVID-19.

We hypothesise that the proportion of patients alive and not having required intensive respiratory or vasopressor support at 28 days after enrolment (primary endpoint for ASCOT ADAPT) will differ based on the intensity of anticoagulation. The following interventions will be available:

- Standard dose thromboprophylaxis
- Intermediate dose thromboprophylaxis
- Therapeutic anticoagulation

8. TRIAL DESIGN

This domain will be conducted as part of ASCOT ADAPT (see Core Protocol Section 1). Treatment allocation will be adaptive, as described in the Core Protocol Section 2.8.1.

8.1. Population

ASCOT ADAPT enrols patients with COVID-19 admitted to hospital who are not requiring intensive organ support (see Core Protocol Section 2.2).

8.2. Eligibility criteria

Patients are eligible for this domain if they meet all of the platform-level inclusion and none of the platform-level exclusion criteria (see Core Protocol Section 2.2.2). Patients eligible for ASCOT ADAPT may have conditions that exclude them from the Anticoagulation Domain.

8.2.1. Domain inclusion criteria

Nil.

8.2.2. Domain exclusion criteria

Patients will be excluded from this domain if they have any of the following:

- Receiving dual antiplatelet therapy
- The treating clinician intends to continue or commence therapeutic anticoagulation
- Contraindication to receiving low molecular weight heparin or unfractionated heparin, including the known or suspected history of heparin-induced thrombocytopenia or other adverse reaction to prior heparin exposure such as hypersensitivity
- Severe thrombocytopenia (platelet count less than 50 x 10^9/L)
- History of intracranial haemorrhage in the previous 3 months
- Severe renal impairment, defined as estimated glomerular filtration rate less than 15ml/min/1.73m^2
- A current or recurrent condition with a high risk of major bleeding (e.g. bleeding disorder), or a baseline coagulation profile (within the previous 3 days) that indicates a high risk of bleeding, that would be considered a contraindication to receive therapeutic anticoagulation.

8.2.3. Intervention exclusion criteria

Nil.

8.3. Interventions

8.3.1. Anticoagulation interventions

Patients will be randomly assigned to receive one of the following open-label study interventions:

- Standard dose thromboprophylaxis
- Intermediate dose thromboprophylaxis
- Therapeutic anticoagulation

8.3.1.1. Standard dose thromboprophylaxis

Patients will be administered low molecular weight heparin, choice of agent according to availability and local practice at the participating site. The dose of LMWH will be as outlined in Tables 1a and 1b.

8.3.1.2. Intermediate dose thromboprophylaxis

Patients will be administered low molecular weight heparin, choice of agent according to availability and local practice at the participating site. The dose of LMWH will be as outlined in Tables 1a and 1b.

8.3.1.3. Therapeutic anticoagulation

Patients will be administered therapeutic anticoagulation with low molecular weight heparin, choice of agent according to availability and local practice at the participating site, with dose as outlined in Tables 1a and 1b. Local protocols for therapeutic dose anticoagulation for acute venous thromboembolism (i.e. not venous prophylaxis) can also be followed including dose rounding. Unfractionated heparin can be used as an alternative to LMWH if clinically indicated (e.g. if a shorter acting or reversible anticoagulant is clinically indicated or if severe renal impairment). If unfractionated heparin is used, the dose/infusion rate and monitoring should be according to local hospital policy and guidelines that are used for the treatment of venous thromboembolism (i.e. not for acute coronary syndrome).

Table 1a dosing of LMWH if estimated creatinine clearance >30ml/min

	Weight	Standard Prophylactic	Intermediate	Intermediate daily alternative dosing*	Therapeutic anticoagulation^
Enoxaparin	<50kg	20mg q24h	40mg q24h		1mg/kg q12 OR 1.5mg/kg q24
	50-120kg	40mg q24h	40mg q12h	80mg q24h	
	>120kg	60mg q24h	60mg q12h	120mg q24h	
Tinzaparin	<40kg	75IU/kg q24h	125IU/kg/day		175IU/kg q24
	40-120kg				
	>120kg				
Dalteparin	<40kg	2500IU q24h	5000IU q24h		100IU/kg q12 OR 200IU/kg q24
	40-120kg	5000IU q24h	5000IU q12h	10,000IU q24h	
	>120kg	7500IU q24h	7500IU q12h	15,000IU q24h	

*If there is a need to minimise dosing frequency, 24-hourly dosing can be considered, as provided in the alternative dosing.
^Local protocols for acute VTE dosing can be followed including dose rounding and dosing for extreme body weights. If anti-Xa level monitoring is available, anti-Xa levels can be used to guide dosing in extremes of body weight. If no access to anti-Xa level monitoring, then suggest for high body weight cap enoxaparin dose at 150mg/kg for q12 dosing.

Note: q24h = Every 24 hours; q12 = Every 12 hours

Table 1b: dosing of LMWH if estimated creatinine clearance ≤30ml/min*

	Weight	Standard Prophylactic	Intermediate	Therapeutic anticoagulation
Enoxaparin	<50kg	20mg q24h	0.5mg/kg q24	1mg/kg q24
	50-120kg	20mg q24h		
	>120kg	40mg q24h		
Tinzaparin	<40kg	75IU/kg q24h	125IU/kg/day	175IU/kg q24
	40-120kg			
	>120kg			
Dalteparin	<40kg	1250U q24h	2500IU q24h	100IU/kg q24
	40-120kg	2500IU q24h	5000IU q24h	
	>120kg	5000IU q24h	5000IU q12h	

Unfractionated heparin	All categories	N/A	N/A	Administer continuous infusion, with dose/infusion rate and monitoring according to local protocol for anticoagulation for treatment of VTE

*Anti-Xa levels can be used to monitor if available, and if results suggest heparin accumulation dose reduction is permitted

8.3.2. Timing of initiation and duration of administration of anticoagulation therapy

Initiation of anticoagulation will be from randomisation. The intervention will continue until hospital discharge, requirement of intensive respiratory support (invasive or non-invasive ventilation) or vasopressor/inotropic support, or for a maximum of 28 days from randomisation. If the participant requires intensive respiratory support or vasopressor/inotropic support, the intervention may continue as part of usual clinical care as decided by the treating clinical team (or as part of an intensive care unit trial such as REMAP-CAP). If the patient remains an inpatient after 28 days, ongoing thromboprophylaxis will be according to usual local practice. If the patient is transferred to Hospital in the Home, the intervention may continue as part of usual clinical care as decided by the treating clinical team.

8.3.3. Discontinuation of study intervention

Study intervention (anticoagulation) should be discontinued in the event of clinically significant bleeding or other complication sufficient to warrant cessation in the opinion of the treating clinician. The study intervention may be recommenced if deemed appropriate by the treating clinician.

The occurrence of suspected or confirmed heparin induced thrombocytopenia (HIT) must result in cessation of heparin (LMWH or unfractionated heparin) and management, including with alternative anticoagulation, according to local protocol.

Patients allocated to standard or intermediate-dose anticoagulation who develop an indication for therapeutic anticoagulation (e.g. pulmonary embolus) can commence therapeutic anticoagulation as clinically indicated.

8.3.4. Co-administration with nafamostat

Patients who are allocated to nafamostat in the antiviral domain should have anticoagulation interventions administered as outlined above. It is not expected that nafamostat will significantly alter coagulation studies, so no additional monitoring above usual local practice is required. However, if

the aPTT is more than 1.5 times the upper limit of normal in the absence of a therapeutic heparin infusion or known lupus anticoagulant/lupus inhibitor, therapeutic dose anticoagulation (not standard or intermediate dose thromboprophylaxis) should be withheld and restarted once the aPTT is less than 1.5 times the upper limit of normal.

8.4. Concomitant care

All treatment that is not specified by assignment within the platform will be determined by treating clinician.

8.5. Endpoints

8.5.1. Primary outcome

The primary endpoint for this domain is the ASCOT ADAPT primary outcome as specified in Core Protocol Section 2.3.1: Death from any cause or requirement of new intensive respiratory support (invasive or non-invasive ventilation) or vasopressor/inotropic support in the 28 days after randomisation.

8.5.2. Secondary outcomes

All secondary outcomes as specified in the Core Protocol Section 2.3.2.

The domain-specific secondary outcome measures will be:

1. Confirmed deep venous thrombosis up to 28 days after randomisation
2. Confirmed pulmonary embolus up to 28 days after randomisation
3. Confirmed acute myocardial infarction up to 28 days after randomisation
4. Confirmed ischemic cerebrovascular event up to 28 days after randomisation
5. Major bleeding (as defined by ISTH), censored at 28 days after randomisation
6. Clinically relevant non-major bleeding (as defined by the ISTH), censored at 28 days after randomisation
7. Heparin-induced thrombocytopenia during index hospitalisation, censored at 28 days after randomisation
8. Other confirmed thrombotic event up to 28 days after randomisation

Definitions of secondary outcomes are provided in Appendix 1.

If patients have been discharged from hospital before day 28, a history of domain specific secondary outcomes will be sought from the patient, person responsible, or supervising medical practitioner during the day 28 follow-up telephone call. Confirmation of diagnosis will be required from hospital medical records, radiological reports, or a supervising medical practitioner.

9. TRIAL CONDUCT

9.1. Domain-specific data collection

9.1.1. Microbiology

No additional microbiology testing is required.

9.1.2. Clinical data collection

Additional domain-specific data will be collected.

- Whether on aspirin already at time of enrolment
- D-dimer at baseline if available
- Number of RBC units transfused if major bleeding has occurred
- Whether aspirin is administered during the acute hospitalisation

9.1.3. -Domain-specific study timeline

Table 2 Domain-specific schedule of visits, data collection and follow-up.

Visit Day	Day 0 (-3 to 0)	Day 1	Day 2 till d/c	Day 3	Day 28
Check eligibility	X				
Platelet count and creatinine	X				
Coagulation studies[1]	X			X	
Informed consent		X			
Randomise		X			
D-dimer if available[2]		X			
Commence anticoagulation, and monitor administration		X	X		
Monitoring for serious adverse events		X	X		X
Monitoring for domain secondary outcomes at discharge and follow-up			X		X

[1] Results from coagulation studies performed as standard of care. This can include whatever coagulation profile is standard of care at the site, e.g. PT/APTT and/or fibrinogen. Coagulation studies at day 0 can be collected at day -3 to 0. Day 3 can be +/1 day.
[2] Not mandatory. Collect if done as part of routine clinical care

9.1.4. Domain-specific study visit day details

All study visit details are specified in the Core Protocol in section 2.4.5. Additional domain-specific study procedures are outlined below.

9.1.4.1. Day 0/ Screening

Screening procedures are outlined in the Core Protocol section 2.4.5.1. Additional exclusion criteria apply to this domain, however no additional procedures are required. Criteria will be assessed using medical records and results of full blood examination (FBE), coagulation screen and renal function tests conducted as part of standard care.

9.1.4.2. Day 1

In addition to the activities outlined in the Core Protocol section 2.4.5.2, additional domain-specific activities will be conducted including:

- Commence anticoagulation.
- D-Dimer level if available.

9.1.4.3. Day 2 till hospital discharge

Activities on Day 2 till discharge are outlined in the Core Protocol section 2.4.5.3. Other domain-specific activities will be conducted on day 2 till discharge including:

- Monitoring for serious adverse events related to treatment (see Section 11.2).
- Monitoring for other domain secondary outcomes as outlined in section 8.5.2. and defined in Appendix 1.

9.1.4.4. Day 3

Domain-specific activities will be conducted on day 3:

- Recording results of coagulation studies performed as standard of care. This can include whatever coagulation profile is standard of care at the site, e.g. PT/APTT and/or fibrinogen

9.1.4.5. Day 28

In addition to the activities outlined in the Core Protocol section 2.4.5.4, domain-specific activities to be conducted include:

- Monitoring for serious adverse events related to treatment (see Section 11.2).
- Monitoring for other domain secondary outcomes as outlined in section 8.5.2. and defined in Appendix 1.

9.2. Criteria for discontinuation

Refer to Core Protocol Section 2.4.7 for criteria for discontinuation of participation in the ASCOT trial.

9.3. Blinding

9.3.1. Blinding

All interventions will be open-label.

9.3.2. Unblinding

Not relevant.

10. STATISTICAL CONSIDERATIONS

10.1. Domain-specific stopping rules

If a Platform Conclusion of equivalence in the primary endpoint is demonstrated the DSMB and the ITSC may consider continuation of randomisation if clinically relevant differences in secondary endpoints have not been demonstrated and it is considered plausible that clinically relevant differences in one or more secondary endpoints may be capable of being demonstrated. In all other respects the stopping rules for this domain are those outlined in the Core Protocol Sections 2.10 and the Statistical Appendix.

10.2. Unit-of-analysis and strata

The unit-of-analysis for this domain is all patients who receive an allocation status in this domain. No strata are applied in the model that is used for analysis and specification of Response Adaptive Randomisation (RAR). RAR is outlined in the Statistical Analysis Appendix.

10.3. Timing of revealing of randomisation status

The timing of the revealing of allocation status and administration of interventions is specified to be Randomisation with immediate reveal and initiation (see Section 2.8.1 in Core Protocol).

10.4. Interactions with interventions in other domains

An a priori interaction with nafamostat in the antiviral domain is considered likely and will be incorporated into the expanded statistical model used to analyse this domain. It is thought possible

that the anticoagulant and antifibrinolytic properties of nafamostat may interact with the anticoagulant properties of agents in the anticoagulation domain. Effect modification, where nafamostat might be beneficial in one arm of the anticoagulation domain but detrimental in another, is thought to be unlikely. Likewise, anticoagulation is expected to be beneficial to patients enrolled into any of the arms of the antiviral domain, including the nafamostat arm.
An *a priori* interaction with the Antibody directed therapy Domain is not considered likely and will not be incorporated into the statistical models used to analyse this domain.

10.5. Nesting of interventions

Nesting is not applicable to this domain

10.6. Threshold odds ratio delta for equivalence

The threshold odds ratio for equivalence in this domain is that specified in the Statistical Analysis Appendix.

10.7. Post-trial Sub-groups

Pre-specified subgroups are outlined in the Core Protocol and Statistical Analysis Appendix. Domain-specific post-hoc sub-groups will be used in analysis following the conclusion of one or more interventions in the domain. The *a priori* patient sub-groups of interest are:

- D-dimer above upper limit of normal at baseline
- Weight less than 120kg vs. weight ≥120kg
- Patients already on aspirin or not on aspirin at enrolment

11. ETHICAL CONSIDERATIONS

11.1. Data Safety and Monitoring Board

The DSMB should be aware that the superiority, inferiority, or equivalence of different interventions with respect to the primary endpoint is possible, and if equivalence is demonstrated, determination of the optimal intervention may be based on secondary endpoints, such as venous and arterial thrombosis and major bleeding.

11.2. Potential domain-specific adverse events

Domain-specific adverse events, which should be reported as SAR, include:

- Major bleeding (as defined by ISTH definition)
- Heparin-induced thrombocytopenia (HIT)

Other SAEs should be reported only where, in the opinion of the site investigator, the event might reasonably have occurred as a consequence of a study intervention or study participation (see Core Protocol Section 2.12). Serious adverse reactions occurring within 28 days of randomisation must be recorded and reported to the sponsor in accordance with the Safety Reporting SOP.

11.3. Domain-specific consent issues

No domain-specific consent issues.

12.GOVERNANCE ISSUES

12.1. Funding of domain

Funding sources for ASCOT are specified in the Core Protocol. This domain has not received any additional domain-specific funding.

12.2. Funding of domain interventions and outcome measures

No specific funding.

12.3. Domain-specific declarations of interest

All investigators involved in ASCOT maintain a registry of interests on the ASCOT website. These are updated periodically and publicly accessible on the study website.

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14. APPENDICES

14.1. Appendix 1: Definition of secondary outcomes

Outcome	Definition
Major Bleeding[1]	ISTH major bleeding in non-surgical patients is defined as having a symptomatic presentation and: • Fatal bleeding, and/or • Bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or • Bleeding causing a fall in haemoglobin level of 20 g L−1 (1.24 mmol L−1) or more, or leading to transfusion of two or more units of whole blood or red cells.
Clinically relevant non-major bleeding[1]	Any sign or symptom of haemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for the ISTH definition of major bleeding but does meet at least one of the following criteria: • requiring medical intervention by a healthcare professional • leading to hospitalisation or increased level of care • prompting a face to face (i.e., not just a telephone or electronic communication) evaluation
Deep vein thrombosis	Symptoms and/or signs of deep vein thrombosis AND evidence of new deep vein thrombosis on ultrasound (noncompressible venous segment thrombosis)
Pulmonary embolism	Diagnosed in clinically suspected patients (using widely accepted clinical criteria) AND either high-probability V-Q scan, positive CT pulmonary angiogram (CTPA) (i.e. demonstrated intraluminal filling defect) or pulmonary angiogram demonstrating emboli
Acute myocardial infarction[2]	[1]Detection of a typical rise and/or fall of troponin with at least one of the following: • Symptoms of acute myocardial ischemia; • New ischemic electrocardiographic (ECG) changes; • Development of pathological Q waves; • Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic aetiology; • Identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy
Acute ischemic stroke[3]	[2]Rapidly developing clinical signs of focal (or global) disturbance of cerebral function lasting more than 24 hours (unless interrupted by surgery or death) with no apparent cause other than of vascular origin. Distinction between an ischemic cause rather than haemorrhagic will be based on imaging results.
Other confirmed thrombotic event	Report venous or arterial thrombosis other than deep venous thrombosis, pulmonary embolism, acute myocardial infarction or acute ischemic stroke that is confirmed on imaging or other investigation (e.g. mesenteric ischemia, other systemic arterial thrombotic event).
Heparin-induced thrombocytopenia	HIT is defined as a decrease in platelets to less than 50% or to less than 100 x 10(9)/L and positive laboratory HIT assay.

[1] International Society of Thrombosis and Haemostasis Definitions (Kaatz et al., 2015)
[2] Based on Fourth Universal Definition of Myocardial Infarction from American College of Cardiology
[3] Based on World Health Organization definition of stroke

Trial Name:	Australasian COVID-19 Trial (ASCOT) ADAptive Platform Trial
Registration	ACTRN12620000445976 NCT04483960

The Anticoagulation Domain-Specific Appendix has undergone the following major amendments:

Version	Date	Major Change
Anticoagulation Appendix v1.0	13 August 2020	Initial submission to HREC. Interventions of standard dose thromboprophylaxis, intermediate dose thromboprophylaxis and standard dose thromboprophylaxis plus aspirin. No participants recruited.
Anticoagulation Appendix v2.0	02 October 2020	Changes to eligibility criteria and sample collection. No participants recruited.
Anticoagulation Appendix v3.0	06 November 2020	Minor changes to formatting. Minor change to reference the statistical appendix
Anticoagulation Appendix v4.0	28 April 2021	Addition of treatment arms: intermediate dose thromboprophylaxis plus aspirin and therapeutic anticoagulation. No participants recruited.
Anticoagulation Appendix v5.0	05 August 2021	Removal of treatment arms: standard dose thromboprophylaxis plus aspirin and intermediate dose thromboprophylaxis plus aspirin

Each detailed change is provided in full in the tables below.

ANTICOAGULATION DOMAIN-SPECIFIC APPENDIX VERSION 1.0 TO VERSION 2.0				
Section number and title in version 1	**Section number and title in amendment (version 2)**	**Original text**	**Changed to**	**Rationale**
Whole document	Whole document	Header: ASCOT ADAPT Anticoagulation Domain-Specific Appendix Version 1.0 dated 13 August 2020	Header: ASCOT ADAPT Anticoagulation Domain-Specific Appendix Version 2.0 dated 02 October 2020	Updated to reflect new version.
		N/A	N/A	Table of contents updated
Cover page	Cover page	Anticoagulation Domain-Specific Appendix Version 1.0 dated 13 August 2020	Anticoagulation Domain-Specific Appendix Version 2.0 dated 02 October 2020	Updated version and date of DSA to reflect the amendment.
ASCOT ADAPT: Anticoagulation Domain Summary	ASCOT ADAPT: Anticoagulation Domain Summary	• Various text	Various text	Fields amended/updated to reflect the amendments in the body of the appendix.
3.1 Version History	3.1 Version History	Version 1: Approved by the Anticoagulation Domain-Specific Working Group (DSWG) on 13th of August 2020	Version 1: Approved by the Anticoagulation Domain-Specific Working Group (DSWG) on 13th of August 2020 Version 2: Approved by the Anticoagulation Domain-Specific Working Group (DSWG) on 2nd October 2020	Updated to reflect approval of the latest version.
7. Domain objectives	7. Domain objectives	We hypothesise that the probability of all-cause mortality at 28 days after enrolment will differ based on the intensity of anticoagulation and use of	We hypothesise that the proportion of patients alive and not having required intensive respiratory or vasopressor support at 28 days after enrolment	Changed hypothesis to align with primary outcome in Core Protocol and other DSAs.

ANTICOAGULATION DOMAIN-SPECIFIC APPENDIX VERSION 1.0 TO VERSION 2.0				
Section number and title in version 1	**Section number and title in amendment (version 2)**	**Original text**	**Changed to**	**Rationale**
		antiplatelet agents. The following interventions will be available:	(primary endpoint for ASCOT ADAPT) will differ based on the intensity of anticoagulation and use of antiplatelet agents. The following interventions will be available:	
8.2.2. Domain exclusion criteria	8.2.2. Domain exclusion criteria	Patients will be excluded from this domain if they have any of the following: • Receiving therapeutic anticoagulation • Pre-existing indication for therapeutic anticoagulation and treating clinician intends to commence therapeutic anticoagulation • Receiving dual antiplatelet therapy • Contraindication to receiving low molecular weight heparin or unfractionated heparin, including the known or suspected history of heparin-induced thrombocytopenia or other adverse reaction to prior heparin exposure • Severe thrombocytopenia (platelet count less than 30 x 10^9/L)	Patients will be excluded from this domain if they have any of the following: • Receiving dual antiplatelet therapy • The treating clinician intends to continue or commence therapeutic anticoagulation • Contraindication to receiving low molecular weight heparin or unfractionated heparin, including the known or suspected history of heparin-induced thrombocytopenia or other adverse reaction to prior heparin exposure such as hypersensitivity • Severe thrombocytopenia (platelet count less than 30 x 10^9/L) • History of intracranial haemorrhage in the previous 3 months	The order of exclusion criteria has been amended to appear more logical to investigators. The requirement for fibrinogen level to be assessed has been removed as this may not be available to sites in India. Instead, the requirement for baseline coagulation profile to be assessed has been added to the final criterion.

ANTICOAGULATION DOMAIN-SPECIFIC APPENDIX VERSION 1.0 TO VERSION 2.0				
Section number and title in version 1	**Section number and title in amendment (version 2)**	**Original text**	**Changed to**	**Rationale**
		• Fibrinogen level less than 1g/L • History of intracranial haemorrhage in the previous 3 months • Severe renal impairment, defined as creatinine clearance less than 15ml/min • A current or recurrent condition with a high risk of major bleeding (e.g. bleeding disorder) that would be considered a contraindication to receive thromboprophylaxis	• Severe renal impairment, defined as estimated glomerular filtration rate less than 15ml/min/1.73m^2 • A current or recurrent condition with a high risk of major bleeding (e.g. bleeding disorder), or a baseline coagulation profile (within the previous 3 days) that indicates a high risk of bleeding, that would be considered a contraindication to receive thromboprophylaxis	
8.2.3. Intervention exclusion criteria	8.2.3. Intervention exclusion criteria	• Known hypersensitivity to an agent specified in this domain will exclude a patient from receiving that agent.	• Hypersensitivity to aspirin will exclude a patient from receiving standard thromboprophylaxis plus aspirin.	Hypersensitivity to heparin is covered in the domain exclusions. If the participant is hypersensitive to heparin then no options are available in the domain. The only other agent in the domain is aspirin, therefore this is now the only agent that this criterion applies to.
8.5.2. Secondary outcomes	8.5.2. Secondary outcomes	5. Major bleeding (as defined by ISTH) during index hospitalisation, censored at 28 days 6. Clinically relevant non-major bleeding (as defined by the ISTH) during index	5. Major bleeding (as defined by ISTH), censored at 28 days after randomisation 6. Clinically relevant non-major bleeding (as defined by the ISTH), censored at 28 days after randomisation	To allow collection of outpatient related events, these secondary outcomes are no longer specific to occurring during index hospitalisation. In addition, it has now been clarified that all secondary outcomes are assessed up to 28 days after randomisation.

ANTICOAGULATION DOMAIN-SPECIFIC APPENDIX VERSION 1.0 TO VERSION 2.0				
Section number and title in version 1	**Section number and title in amendment (version 2)**	**Original text**	**Changed to**	**Rationale**
		hospitalisation, censored at 28 days		
9.1.2. Clinical data collection	9.1.2. Clinical data collection	Additional domain-specific data will be collected. • D-dimer at baseline if available • Number of RBC units transfused • Routine clinical tests results including coagulation studies, D-dimer, anti-Xa level	Additional domain-specific data will be collected. • Whether on aspirin already at time of enrolment • D-dimer at baseline if available • Number of RBC units transfused if major bleeding has occurred	Aspirin use has been added as this will inform a pre-specified sub-group analysis. It has been clarified that number of RBC units transferred is only required if major bleeding has occurred. Routine test results are no longer required for this domain.
9.1.3 Domain-specific study timeline	9.1.3 Domain-specific study timeline	N/A	N/A	The study timeline (Table 2) for this domain has been updated to reflect changes in domain-specific procedures.
9.1.4.2. Day 1	9.1.4.2. Day 1	In addition to the activities outlined in the Core Protocol section 2.4.5.2, additional domain-specific activities will be conducted including: • Commence anticoagulation +/- antiplatelet treatment. • Monitoring for serious adverse events related to treatment (see Section 11.2).	In addition to the activities outlined in the Core Protocol section 2.4.5.2, additional domain-specific activities will be conducted including: • Commence anticoagulation +/- antiplatelet treatment. • D-Dimer level if available.	Results from routine blood tests are no longer required for this domain. D-dimer will be collected if available as this will be used in sub-group analyses. Secondary outcomes do not need to be collected on day 1.

ANTICOAGULATION DOMAIN-SPECIFIC APPENDIX VERSION 1.0 TO VERSION 2.0				
Section number and title in version 1	Section number and title in amendment (version 2)	Original text	Changed to	Rationale
		This includes participants enrolled in standard of care. • Review of routine blood tests in participants randomised to all arms including standard of care. These tests are not mandatory, only collect if part of routine clinical care. Tests include coagulation studies (fibrinogen, activated partial thromboplastin time (aPTT) and prothrombin time), D-Dimer and anti-Xa levels. • Monitoring for other domain secondary outcomes as outlined in section 8.5.2. and defined in Appendix 1, in participants randomised to all arms including standard of care.		
9.1.4.3. Day 2 till hospital discharge	9.1.4.3. Day 2 till hospital discharge	Activities on Day 2 till discharge are outlined in the Core Protocol section 2.4.5.3. Other domain-specific activities will be conducted on day 2 till discharge including: • Monitoring for serious adverse events related to	Activities on Day 2 till discharge are outlined in the Core Protocol section 2.4.5.3. Other domain-specific activities will be conducted on day 2 till discharge including:	Results from routine blood tests are no longer required and these have been removed.

ANTICOAGULATION DOMAIN-SPECIFIC APPENDIX VERSION 1.0 TO VERSION 2.0				
Section number and title in version 1	Section number and title in amendment (version 2)	Original text	Changed to	Rationale
		treatment (see Section 11.2). This includes participants enrolled in standard of care. • Review of routine blood tests in participants randomised to all arms including standard of care. These tests are not mandatory, only collect if part of routine clinical care. Tests include coagulation studies (fibrinogen, activated partial thromboplastin time (aPTT) and prothrombin time), D-Dimer and anti-Xa levels. • Monitoring for other domain secondary outcomes as outlined in section 8.5.2. and defined in Appendix 1, in participants randomised to all arms including standard of care.	• Monitoring for serious adverse events related to treatment (see Section 11.2). • Monitoring for other domain secondary outcomes as outlined in section 8.5.2. and defined in Appendix 1.	
9.1.4.4. Day 28	9.1.4.4. Day 28	In addition to the activities outlined in the Core Protocol section 2.4.5.4 and section 2.4.5.5, domain-specific activities to be conducted include: • Monitoring for serious adverse events related to treatment (see Section 11.2).	In addition to the activities outlined in the Core Protocol section 2.4.5.4 and section 2.4.5.5, domain-specific activities to be conducted include: • Monitoring for serious adverse events related to treatment (see Section 11.2).	These procedures apply to all treatment arms in this domain and therefore it does not need to be specified that this includes standard of care.

ANTICOAGULATION DOMAIN-SPECIFIC APPENDIX VERSION 1.0 TO VERSION 2.0				
Section number and title in version 1	**Section number and title in amendment (version 2)**	**Original text**	**Changed to**	**Rationale**
		This includes participants enrolled in standard of care. • Monitoring for other domain secondary outcomes as outlined in section 8.5.2. and defined in Appendix 1, in participants randomised to all arms including standard of care.	• Monitoring for other domain secondary outcomes as outlined in section 8.5.2. and defined in Appendix 1.	
10.4. Interactions with interventions in other domains	10.4. Interactions with interventions in other domains	An *a priori* interaction with the Antiviral Domain is not considered likely and will not be incorporated into the statistical models used to analyse this domain.	An a priori interaction with nafamostat in the antiviral domain is considered likely and will be incorporated into the expanded statistical model used to analyse this domain. It is thought possible that the anticoagulant and antifibrinolytic properties of nafamostat may interact with the anticoagulant and antiplatelet properties of agents in the anticoagulation domain. Effect modification, where nafamostat might be beneficial in one arm of the anticoagulation domain but detrimental in another, is thought to be unlikely. Likewise, anticoagulation is expected to be beneficial to patients enrolled into any of the arms of the	Due to the addition of nafamostat to the antiviral domain, an interaction is now expected. The safety and statistical implications of this have now been considered in this section.

ANTICOAGULATION DOMAIN-SPECIFIC APPENDIX VERSION 1.0 TO VERSION 2.0				
Section number and title in version 1	**Section number and title in amendment (version 2)**	**Original text**	**Changed to**	**Rationale**
			antiviral domain, including the nafamostat arm.	
10.7. Post-trial sub-groups	10.7. Post-trial sub-groups	The *a priori* patient *s*ub-groups of interest are: • D-dimer above upper limit of normal at baseline • Weight less than 120kg vs. weight ≥120kg	The *a priori* patient *s*ub-groups of interest are: • D-dimer above upper limit of normal at baseline • Weight less than 120kg vs. weight ≥120kg • Patients already on aspirin or not on aspirin at enrolment	Use of aspirin at time of enrolment has been added as a sub-group of interest.
11.2 Potential domain-specific adverse events	11.2 Potential domain-specific adverse events	Other SAEs should be reported only where, in the opinion of the site investigator, the event might reasonably have occurred as a consequence of a study intervention or study participation (see Core Protocol Section 2.12).	Other SAEs should be reported only where, in the opinion of the site investigator, the event might reasonably have occurred as a consequence of a study intervention or study participation (see Core Protocol Section 2.12). Serious adverse reactions occurring within 28 days of randomisation must be recorded and reported to the sponsor in accordance with the Safety Reporting SOP.	Clarified that SARs are collected until 28 days after randomisation and referred to Safety Reporting SOP.

ANTICOAGULATION DOMAIN-SPECIFIC APPENDIX VERSION 2.0 TO 3.0				
Section number and title in version 2	**Section number and title in amendment (version 3)**	**Original text**	**Changed to**	**Rationale**
Whole document	Whole document	Header: ASCOT ADAPT Anticoagulation Domain-Specific Appendix Version 2.0 dated 02 October 2020	Header: ASCOT ADAPT Antibody Domain-Specific Appendix Version 3.0 dated 06 November 2020	Updated to reflect new version.
		N/A	N/A	Table of contents updated
		N/A	N/A	Minor administrative changes including pagination, formatting changes.
Cover page	Cover page	Anticoagulation Domain-Specific Appendix Version 2.0 dated 02 October 2020	Anticoagulation Domain-Specific Appendix Version 3.0 dated 06 November 2020	Updated version and date of DSA to reflect the amendment.
		N/A	N/A	Minor formatting changes regarding the positioning of logos.
ASCOT ADAPT: Anticoagulation Domain Summary	ASCOT ADAPT: Anticoagulation Domain Summary	Various text	Various text	Fields amended/updated to reflect the amendments in the body of the appendix.
3.1 Version History	3.1 Version History	Version 1: Approved by the Anticoagulation Domain-Specific Working Group (DSWG) on 13th of August 2020 Version 2: Approved by the Anticoagulation Domain-Specific Working Group	Version 1: Approved by the Anticoagulation Domain-Specific Working Group (DSWG) on 13th of August 2020 Version 2: Approved by the Anticoagulation Domain-Specific Working Group	Updated to reflect approval of the latest version.

ANTICOAGULATION DOMAIN-SPECIFIC APPENDIX VERSION 2.0 TO 3.0				
Section number and title in version 2	**Section number and title in amendment (version 3)**	**Original text**	**Changed to**	**Rationale**
		(DSWG) on 2nd October 2020	(DSWG) on 2nd October 2020 Version 3: Approved by the Antibody Domain-Specific Working Group (DSWG) on 6th November 2020	
10.2. Unit-of-analysis and strata	10.2. Unit-of-analysis and strata	The unit-of-analysis for this domain is all patients who receive an allocation status in this domain. No strata are applied in the model that is used for analysis and specification of Response Adaptive Randomization (RAR).	The unit-of-analysis for this domain is all patients who receive an allocation status in this domain. No strata are applied in the model that is used for analysis and specification of Response Adaptive Randomiszation (RAR). RAR is outlined in the Statistical Analysis Appendix.	Addition of reference to the Statistical Analysis Appendix that specifies RAR relevant to this domain.

ASCOT
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ANTICOAGULATION DOMAIN-SPECIFIC APPENDIX VERSION 3.0 TO 4.0				
Section number and title in version 3	**Section number and title in amendment (version 4)**	**Original text**	**Changed to**	**Rationale**
Whole document	Whole document	Header: ASCOT ADAPT Antibody Domain-Specific Appendix Version 3.0 dated 06 November 2020	Header: ASCOT ADAPT Anticoagulation Domain-Specific Appendix Version 4.0 dated 28th April 2021	Updated to reflect new version.
		N/A	N/A	Table of contents updated
		N/A	N/A	Minor formatting, spelling/grammar and wording changes throughout document.
Cover page	Cover page	Anticoagulation Domain-Specific Appendix Version 3.0 dated 06 November 2020	Anticoagulation Domain-Specific Appendix Version 4.0 dated 28th April 2021	Updated version and date of DSA to reflect the amendment.
		N/A	Addition of CREDID logo in cover page header.	The trial will be expanding into Denmark and CREDID will act as local sponsor within that country.
Summary	Summary	In this domain of ASCOT ADAPT, participants with COVID-19 admitted to participating hospitals will be randomised to receive one of three interventions depending on availability and acceptability: - Standard dose thromboprophylaxis - Intermediate dose thromboprophylaxis - Standard dose thromboprophylaxis plus aspirin	In this domain of ASCOT ADAPT, participants with COVID-19 admitted to participating hospitals will be randomised to receive one of three interventions depending on availability and acceptability: - Standard dose thromboprophylaxis - Intermediate dose thromboprophylaxis - Standard dose thromboprophylaxis plus aspirin	Two additional anticoagulation treatments have been added as emerging evidence from other platform trials suggests that a therapeutic dose of anticoagulation may be beneficial to moderately and severely ill patients hospitalised with COVID-19. The combination of intermediate dose anticoagulation with low dose aspirin has not been studied in any complete trials to date, therefore this arm has also been added.

ANTICOAGULATION DOMAIN-SPECIFIC APPENDIX VERSION 3.0 TO 4.0				
Section number and title in version 3	**Section number and title in amendment (version 4)**	**Original text**	**Changed to**	**Rationale**
		At this participating site the following interventions are available within this domain: ☐ Standard dose thromboprophylaxis ☐ Intermediate dose thromboprophylaxis ☐ Standard dose thromboprophylaxis plus aspirin	- Intermediate dose thromboprophylaxis plus aspirin - Therapeutic anticoagulation At this participating site the following interventions are available within this domain: ☐ Standard dose thromboprophylaxis ☐ Intermediate dose thromboprophylaxis ☐ Standard dose thromboprophylaxis plus aspirin ☐ Intermediate dose thromboprophylaxis plus aspirin ☐ Therapeutic anticoagulation	
ASCOT ADAPT: Anticoagulation Domain Summary	ASCOT ADAPT: Anticoagulation Domain Summary	Various text	Various text	Fields amended/updated to reflect the amendments in the body of the appendix.
3.1 Version History	3.1 Version History	Version 1: Approved by the Anticoagulation Domain-Specific Working Group (DSWG) on 13th of August 2020	Version 1: Approved by the Anticoagulation Domain-Specific Working Group (DSWG) on 13th of August 2020	Updated to reflect approval of the latest version.

ANTICOAGULATION DOMAIN-SPECIFIC APPENDIX VERSION 3.0 TO 4.0				
Section number and title in version 3	**Section number and title in amendment (version 4)**	**Original text**	**Changed to**	**Rationale**
		Version 2: Approved by the Anticoagulation Domain-Specific Working Group (DSWG) on 2nd October 2020 Version 3: Approved by the Antibody Domain-Specific Working Group (DSWG) on 6th November 2020	Version 2: Approved by the Anticoagulation Domain-Specific Working Group (DSWG) on 2nd October 2020 Version 3: Approved by the Antibody Domain-Specific Working Group (DSWG) on 6th November 2020 Version 4: Approved by the Antibody Domain-Specific Working Group (DSWG) on 28th April 2020	
4. ANTICOAGULATION DOMAIN GOVERNANCE	4. ANTICOAGULATION DOMAIN GOVERNANCE	Various text	Various text	Updating member's titles. Adding contact details of co-chair, Jason Roberts.
6.2. Domain-specific background	6.2. Domain-specific background anticoagulation for COVID-19	Various text	Various text	Addition of text outlining results from the recent interim analysis of multiple platform trials (see https://www.attacc.org/presentations) demonstrating a benefit of therapeutic anticoagulation and their reporting of relatively low bleeding risk.

ANTICOAGULATION DOMAIN-SPECIFIC APPENDIX VERSION 3.0 TO 4.0				
Section number and title in version 3	**Section number and title in amendment (version 4)**	**Original text**	**Changed to**	**Rationale**
7.DOMAIN OBJECTIVES	7.DOMAIN OBJECTIVES	We hypothesise that the proportion of patients alive and not having required intensive respiratory or vasopressor support at 28 days after enrolment (primary endpoint for ASCOT ADAPT) will differ based on the intensity of anticoagulation and use of antiplatelet agents. The following interventions will be available: - Standard dose thromboprophylaxis - Intermediate dose thromboprophylaxis - Standard dose thromboprophylaxis plus aspirin	We hypothesise that the proportion of patients alive and not having required intensive respiratory or vasopressor support at 28 days after enrolment (primary endpoint for ASCOT ADAPT) will differ based on the intensity of anticoagulation and use of antiplatelet agents. The following interventions will be available: - Standard dose thromboprophylaxis - Intermediate dose thromboprophylaxis - Standard dose thromboprophylaxis plus aspirin - Intermediate dose thromboprophylaxis plus aspirin - Therapeutic anticoagulation	Addition of two new anticoagulation treatment arms.
8.2.2.Domain exclusion criteria	8.2.2.Domain exclusion criteria	Patients will be excluded from this domain if they have any of the following: - … - A current or recurrent condition with a high risk of major bleeding (e.g.	Patients will be excluded from this domain if they have any of the following: - … - A current or recurrent condition with a high risk of major bleeding (e.g.	Replacement of thromboprophylaxis with therapeutic anticoagulation, as therapeutic anticoagulation is more relevant.

ANTICOAGULATION DOMAIN-SPECIFIC APPENDIX VERSION 3.0 TO 4.0				
Section number and title in version 3	Section number and title in amendment (version 4)	Original text	Changed to	Rationale
		bleeding disorder), or a baseline coagulation profile (within the previous 3 days) that indicates a high risk of bleeding, that would be considered a contraindication to receive thromboprophylaxis	bleeding disorder), or a baseline coagulation profile (within the previous 3 days) that indicates a high risk of bleeding, that would be considered a contraindication to receive therapeutic anticoagulation.	
8.2.3. Intervention exclusion criteria	8.2.3. Intervention exclusion criteria	Criteria that exclude a patient from one or more interventions are: - Receiving an antiplatelet agent will exclude a patient from receiving standard thromboprophylaxis plus aspirin - Hypersensitivity to aspirin will exclude a patient from receiving standard thromboprophylaxis plus aspirin	Criteria that exclude a patient from one or more interventions are: - Receiving an antiplatelet agent will exclude a patient from receiving standard thromboprophylaxis plus aspirin - Receiving an antiplatelet agent will exclude a patient from receiving intermediate dose thromboprophylaxis plus aspirin - Known hypersensitivity to aspirin will exclude a	Extension of the current exclusion criteria to also include the two new anticoagulation treatment arms.

ANTICOAGULATION DOMAIN-SPECIFIC APPENDIX VERSION 3.0 TO 4.0				
Section number and title in version 3	**Section number and title in amendment (version 4)**	**Original text**	**Changed to**	**Rationale**
			patient from receiving standard thromboprophylaxis plus aspirin and intermediate dose thromboprophylaxis plus aspirin	
8.3. Interventions	8.3. Interventions	Various text	Various text	Addition of text with information regarding the administration of the two new treatment arms. Also includes: - Specification that the aspirin dose can be between 75 to 150 mg daily (originally 100mg). This was changed to reflect the variation in local practice. - Splitting of table 1 to create two separate dosing tables: one for normal creatinine clearance (>30ml/min), and one for low creatinine clearance (<30ml/min) - Considerations for co-administering anticoagulation treatments with nafamostat.
8.5.2. Secondary outcomes	8.5.2. Secondary outcomes	The domain-specific secondary outcome measures will be:	The domain-specific secondary outcome measures will be:	Addition of a secondary outcome to ensure any thrombotic events are captured

ANTICOAGULATION DOMAIN-SPECIFIC APPENDIX VERSION 3.0 TO 4.0				
Section number and title in version 3	Section number and title in amendment (version 4)	Original text	Changed to	Rationale
		1. Confirmed deep venous thrombosis up to 28 days after randomisation 2. Confirmed pulmonary embolus up to 28 days after randomisation 3. Confirmed acute myocardial infarction up to 28 days after randomisation 4. Confirmed ischemic cerebrovascular event up to 28 days after randomisation 5. Major bleeding (as defined by ISTH), censored at 28 days after randomisation 6. Clinically relevant non-major bleeding (as defined by the ISTH), censored at 28 days after randomisation 7. Heparin-induced thrombocytopenia during index hospitalisation, censored at 28 days after randomisation	1. Confirmed deep venous thrombosis up to 28 days after randomisation 2. Confirmed pulmonary embolus up to 28 days after randomisation 3. Confirmed acute myocardial infarction up to 28 days after randomisation 4. Confirmed ischemic cerebrovascular event up to 28 days after randomisation 5. Major bleeding (as defined by ISTH), censored at 28 days after randomisation 6. Clinically relevant non-major bleeding (as defined by the ISTH), censored at 28 days after randomisation 7. Heparin-induced thrombocytopenia during index hospitalisation, censored at 28 days after randomisation 8. Other confirmed thrombotic event up to	

ANTICOAGULATION DOMAIN-SPECIFIC APPENDIX VERSION 3.0 TO 4.0				
Section number and title in version 3	**Section number and title in amendment (version 4)**	**Original text**	**Changed to**	**Rationale**
			28 days after randomisation	
9.1.3. Domain-specific study timeline	9.1.3. Domain-specific study timeline	Schedule of visits (Table 2) showed coagulation studies being collected at day 0	Schedule of visits (Table 2) shows coagulation studies being collected at day 0 and day 3	Addition that coagulation studies will also be collected on Day 3 (+/- 1 day).
N/A	9.1.4.4. Day 3	N/A	9.1.4.4. Day 3 Domain-specific activities will be conducted on day 3: - Recording results of coagulation studies performed as standard of care. This can include whatever coagulation profile is standard of care at the site, e.g. PT/APTT and/or fibrinogen	Addition that coagulation studies will also be collected on Day 3 (+/- 1 day).
13. References	13. References	N/A	N/A	Reference list updated to include additional references added to the DSA.
14.1. Appendix 1: Definition of secondary outcomes	14.1. Appendix 1: Definition of secondary outcomes	-	Other confirmed thrombotic event: Report venous or arterial thrombosis other than deep venous thrombosis, pulmonary embolism, acute myocardial infarction or acute ischemic stroke that is confirmed on imaging or other investigation (e.g. mesenteric ischemia, other	Other thrombotic events will be collected as a safety-specific secondary outcome. Addition of the definition of other thrombotic events.

ANTICOAGULATION DOMAIN-SPECIFIC APPENDIX VERSION 3.0 TO 4.0				
Section number and title in version 3	Section number and title in amendment (version 4)	Original text	Changed to	Rationale
			systemic arterial thrombotic event).	

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ANTICOAGULATION DOMAIN-SPECIFIC APPENDIX VERSION 4.0 TO 5.0				
Section number and title in version 4.0	Section number and title in amendment (version 5.0)	Original text	Changed to	Rationale
Whole document	Whole document	Header: ASCOT ADAPT Anticoagulation Domain-Specific Appendix Version 4.0 dated 28th April 2021	Header: ASCOT ADAPT Anticoagulation Domain-Specific Appendix Version 5.0 dated 05 August 2021	Updated to reflect new version.
		N/A	N/A	Table of contents updated
		N/A	N/A	Minor formatting, spelling/grammar and wording changes throughout document.
Cover page	Cover page	Anticoagulation Domain-Specific Appendix Version 4.0 dated 28th April 2021	Anticoagulation Domain-Specific Appendix Version 5.0 dated 05 August 2021	Updated version and date of DSA to reflect the amendment.
Anticoagulation Domain Summary Table	Anticoagulation Domain Summary Table	Various fields	Various fields	Fields amended/updated to reflect the amendments in the body of the appendix.
ASCOT ADAPT: Anticoagulation Domain Summary	ASCOT ADAPT: Anticoagulation Domain Summary	In this domain of ASCOT ADAPT, participants with COVID-19 admitted to participating hospitals will be randomised to receive one of three interventions depending on availability and acceptability: •Standard dose thromboprophylaxis •Intermediate dose thromboprophylaxis •Standard dose thromboprophylaxis plus aspirin	In this domain of ASCOT ADAPT, participants with COVID-19 admitted to participating hospitals will be randomised to receive one of three interventions depending on availability and acceptability: •Standard dose thromboprophylaxis •Intermediate dose thromboprophylaxis •Therapeutic anticoagulation	To accommodate for the removal of aspirin treatment arm

ANTICOAGULATION DOMAIN-SPECIFIC APPENDIX VERSION 4.0 TO 5.0				
Section number and title in version 4.0	Section number and title in amendment (version 5.0)	Original text	Changed to	Rationale
		•Intermediate dose thromboprophylaxis plus aspirin •Therapeutic anticoagulation At this participating site the following interventions are available within this domain: ☐ Standard dose thromboprophylaxis ☐ Intermediate dose thromboprophylaxis ☐ Standard dose thromboprophylaxis plus aspirin ☐ Intermediate dose thromboprophylaxis plus aspirin ☐ Therapeutic anticoagulation"	At this participating site the following interventions are available within this domain: ☐ Standard dose thromboprophylaxis ☐ Intermediate dose thromboprophylaxis ☐ Therapeutic anticoagulation"	
3.1 Version History	3.1 Version History	Version 1: Approved by the Anticoagulation Domain-Specific Working Group (DSWG) on 13th of August 2020 Version 2: Approved by the Anticoagulation Domain-Specific Working Group (DSWG) on 2nd October 2020 Version 3: Approved by the Anticoagulation Domain-Specific	Version 1: Approved by the Anticoagulation Domain-Specific Working Group (DSWG) on 13th of August 2020 Version 2: Approved by the Anticoagulation Domain-Specific Working Group (DSWG) on 2nd October 2020 Version 3: Approved by the Anticoagulation Domain-Specific	Updated to reflect approval of the latest version.

ANTICOAGULATION DOMAIN-SPECIFIC APPENDIX VERSION 4.0 TO 5.0				
Section number and title in version 4.0	Section number and title in amendment (version 5.0)	Original text	Changed to	Rationale
		Working Group (DSWG) on 6th November 2020 Version 4: Approved by the Anticoagulation Domain-Specific Working Group (DSWG) on 28th April 2021	Working Group (DSWG) on 6th November 2020 Version 4: Approved by the Anticoagulation Domain-Specific Working Group (DSWG) on 28th April 2021 Version 5: Approved by the Anticoagulation Domain-Specific Working Group (DSWG) on 5th August 2021	
6.2.3 Rationale for use of aspirin in COVID-19	6.2.3 Aspirin in COVID-19	[Paragraphs removed relating to the use of aspirin in the study]	[Paragraphs added relating to the previous use of aspirin in the trial and results from other trials, that have led to the dropping of aspirin in this domain]	To accommodate for the removal of aspirin treatment arm
6.2.5 Need for a clinical trial	6.2.5 Need for a clinical trial	Given high rates of thrombotic events (both venous and arterial) in COVID-19 patients, there is a need to optimise thromboprophylaxis. However, higher doses of LMWH and anti-platelet agents may cause adverse effects, including bleeding. Therefore, a clinical trial is needed to determine if higher doses of LMWH and/or additional	Given high rates of thrombotic events (both venous and arterial) in COVID-19 patients, there is a need to optimise thromboprophylaxis. However, higher doses of LMWH may cause adverse effects, including bleeding. Therefore, a clinical trial is needed to determine if higher doses of LMWH is effective and safe.	

ANTICOAGULATION DOMAIN-SPECIFIC APPENDIX VERSION 4.0 TO 5.0				
Section number and title in version 4.0	Section number and title in amendment (version 5.0)	Original text	Changed to	Rationale
		anti-platelet agent is effective and safe.		
7. Domain Objectives	7. Domain Objectives	The objective of this domain is to determine the effectiveness of anticoagulation and antiplatelet therapy for patients with COVID-19. We hypothesise that the proportion of patients alive and not having required intensive respiratory or vasopressor support at 28 days after enrolment (primary endpoint for ASCOT ADAPT) will differ based on the intensity of anticoagulation and use of antiplatelet agents. The following interventions will be available: •Standard dose thromboprophylaxis •Intermediate dose thromboprophylaxis •Standard dose thromboprophylaxis plus aspirin •Intermediate dose thromboprophylaxis plus aspirin •Therapeutic anticoagulation	The objective of this domain is to determine the effectiveness of anticoagulation therapy for patients with COVID-19. We hypothesise that the proportion of patients alive and not having required intensive respiratory or vasopressor support at 28 days after enrolment (primary endpoint for ASCOT ADAPT) will differ based on the intensity of anticoagulation. The following interventions will be available: •Standard dose thromboprophylaxis •Intermediate dose thromboprophylaxis •Therapeutic anticoagulation	
8.2.3. Intervention exclusion criteria	8.2.3. Intervention exclusion criteria	Criteria that exclude a patient from one or more interventions are:	None	

ANTICOAGULATION DOMAIN-SPECIFIC APPENDIX VERSION 4.0 TO 5.0				
Section number and title in version 4.0	Section number and title in amendment (version 5.0)	Original text	Changed to	Rationale
		•Receiving an antiplatelet agent will exclude a patient from receiving standard thromboprophylaxis plus aspirin •Receiving an antiplatelet agent will exclude a patient from receiving intermediate dose thromboprophylaxis plus aspirin •Known hypersensitivity to aspirin will exclude a patient from receiving standard thromboprophylaxis plus aspirin and intermediate dose thromboprophylaxis plus aspirin		
8.3.1 Anticoagulation and antiplatelet interventions	8.3.1 Anticoagulation interventions	Patients will be randomly assigned to receive one of the following open-label study interventions: •Standard dose thromboprophylaxis •Intermediate dose thromboprophylaxis •Standard dose thromboprophylaxis plus aspirin •Intermediate dose thromboprophylaxis plus aspirin •Therapeutic anticoagulation	Patients will be randomly assigned to receive one of the following open-label study interventions: •Standard dose thromboprophylaxis •Intermediate dose thromboprophylaxis •Therapeutic anticoagulation	
8.3.1.3 Standard dose thromboprophylaxis plus aspirin	[removed]	Patients will be administered standard prophylactic dose low molecular weight heparin, choice of agent according to availability	[removed]	

ANTICOAGULATION DOMAIN-SPECIFIC APPENDIX VERSION 4.0 TO 5.0				
Section number and title in version 4.0	Section number and title in amendment (version 5.0)	Original text	Changed to	Rationale
		and local practice at the participating site, with dose as outlined in Tables 1a and 1b. In addition, patients will receive (can be 75 to 150mg) aspirin daily.		
8.3.1.4 Intermediate dose thromboprophylaxis plus aspirin	[removed]	Patients will be administered intermediate dose low molecular weight heparin, choice of agent according to availability and local practice at the participating site, with dose as outlined in Tables 1a and 1b. In addition, patients will receive low dose aspirin (can be 75 to 150mg) daily.	[removed]	
8.3.2 Timing of initiation and duration of administration of anticoagulation and antiplatelet therapy	8.3.2 Timing of initiation and duration of administration of anticoagulation	Initiation of anticoagulation +/- antiplatelet agents will be from randomisation. The intervention will continue until hospital discharge, admission to intensive care unit (ICU) or for a maximum of 28 days from randomisation. If the patient remains an inpatient after 28 days, ongoing thromboprophylaxis will be according to usual local practice.	Initiation of anticoagulation will be from randomisation. The intervention will continue until hospital discharge, requirement of intensive respiratory support (invasive or non-invasive ventilation) or vasopressor/inotropic support, or for a maximum of 28 days from randomisation. If the participant requires intensive respiratory support or vasopressor/inotropic support, the intervention may continue as part of usual clinical care as decided by the treating clinical team (or as part of an intensive care unit trial such as	Clarification added for when treatment discontinues. Unless clinically indicated, there are no concerns with continuation of treatment in HITH nor upon requirement of intensive respiratory support (invasive or non-invasive ventilation) or vasopressor/inotropic support.

ANTICOAGULATION DOMAIN-SPECIFIC APPENDIX VERSION 4.0 TO 5.0				
Section number and title in version 4.0	Section number and title in amendment (version 5.0)	Original text	Changed to	Rationale
			REMAP-CAP). If the patient remains an inpatient after 28 days, ongoing thromboprophylaxis will be according to usual local practice. If the patient is transferred to Hospital in the Home, the intervention may continue as part of usual clinical care as decided by the treating clinical team.	
8.3.3 Discontinuation of study intervention	8.3.3 Discontinuation of study intervention	Study intervention (anticoagulation and/or antiplatelet agent) should be discontinued in the event of clinically significant bleeding or other complication sufficient to warrant cessation in the opinion of the treating clinician.	Study intervention (anticoagulation) should be discontinued in the event of clinically significant bleeding or other complication sufficient to warrant cessation in the opinion of the treating clinician.	To accommodate for the removal of aspirin treatment arm
8.3.4 Co-administration with nafamostat	8.3.4 Co-administration with nafamostat	Patients who are allocated to nafamostat in the antiviral domain should have anticoagulation and antiplatelet interventions administered as outlined above.	Patients who are allocated to nafamostat in the antiviral domain should have anticoagulation interventions administered as outlined above.	
9.1.2 Clinical data collection	9.1.2 Clinical data collection	Additional domain-specific data will be collected. •Whether on aspirin already at time of enrolment •D-dimer at baseline if available •Number of RBC units transfused if major bleeding has occurred	Additional domain-specific data will be collected. •Whether on aspirin already at time of enrolment •D-dimer at baseline if available •Number of RBC units transfused if major bleeding has occurred	

ANTICOAGULATION DOMAIN-SPECIFIC APPENDIX VERSION 4.0 TO 5.0				
Section number and title in version 4.0	Section number and title in amendment (version 5.0)	Original text	Changed to	Rationale
			•Whether aspirin is administered during the acute hospitalisation	
9.1.3 Domain-Specific Study Timeline Table 2 Domain-specific schedule of visits, data collection and follow-up	9.1.3 Domain-Specific Study Timeline Table 2 Domain-specific schedule of visits, data collection and follow-up	N/A	[Table updated to remove references to aspirin/antiplatelets]	
9.1.4.2 Day 1	9.1.4.2 Day 1	In addition to the activities outlined in the Core Protocol section 2.4.5.2, additional domain-specific activities will be conducted including: • Commence anticoagulation +/- antiplatelet treatment. • D-Dimer level if available.	In addition to the activities outlined in the Core Protocol section 2.4.5.2, additional domain-specific activities will be conducted including: • Commence anticoagulation • D-Dimer level if available.	
10.4 Interactions with interventions in other domains	10.4 Interactions with interventions in other domains	It is thought possible that the anticoagulant and antifibrinolytic properties of nafamostat may interact with the anticoagulant and antiplatelet properties of agents in the anticoagulation domain.	It is thought possible that the anticoagulant and antifibrinolytic properties of nafamostat may interact with the anticoagulant properties of agents in the anticoagulation domain.	

ASCOT ADAPT Statistical Analysis Appendix

Australasian-India COVID-19 Trial Adaptive Platform Trial
August 2020 - Version 1.0

Contents

Version History

Version	Date	Summary
1.0	August 2020	Statistical analysis plan ASCOT ADPAT

Abbreviations

Abbreviation	Definition
ICU	Intensive care unit
ITT	Intention-to-treat
MC	Monte Carlo
MCMC	Markov chain Monte Carlo
PP	Per-protocol
RAR	Response adaptive randomisation
WHO	World Health Organisation

1 Introduction

Australasian COVID-19 Trial: An Adaptive Platform Trial (ASCOT-ADAPT) is a multi-centre randomised adaptive platform clinical trial to assess clinical, virological and immunological outcomes in patients with SARS-CoV-2 infection (COVID-19) The design allows for multiple interventions nested within intervention domains, a combination of which comprise a participants treatment regimen. The trial is designed to be perpetual and continue studying interventions with no designated target sample size. The goals are to learn about treatment effects of the interventions under study, and to effectively treat participants enrolled into the trial by shifting towards effective interventions as evidence is accrued.

This statistical analysis appendix is intended as a technical description of the statistical design and analysis plan for the trial. Given the potential for available treatments to change as the trial progresses the aim is to present the general framework without reference to specific treatment interventions.

Section 2 outlines the basics of the trial design as they relate to the statistical modelling, Section 3 defines the trial outcome measures of interest, Section 4 introduces the statistical models and priors, Section 5 presents the model quantities which will be used at analyses to inform trial decisions and adaptations, and Section 6 outlines these adaptations.

2 Structure of Trial

2.1 Target Population

Inclusion criteria

- Age $\geq$ 18 years.
- Admitted to an acute-care hospital.
- Confirmed SARS-CoV-2 by nucleic acid testing in the past 14 days.
- Able to be randomised within 14 days of symptom onset.
- At least one acute symptom attributable to SARS-CoV-2 infection.

Exclusion criteria

- Currently receiving acute intensive respiratory support (invasive or non-invasive mechanical ventilation) or vasopressor/inotropic support. Note, participants already on community based non-invasive ventilation (either CPAP or BiPAP) can still be recruited. Humidified high flow nasal oxygen will not be considered an exclusion criterion.
- Previous participation in the trial.
- Treating team deems enrolment in the study is not in the best interest of the patient.
- Death is deemed to be imminent and inevitable within the next 24 hours.
- Either patient or their primary treating clinician are not committed to active treatment.

2.2 Treatment Domains

A treatment domain consists of a collection of competing interventions within a common clinical mode. The expectation is that each trial participant is randomly allocated to only one intervention (which may be a combination of individual intervention available as a stand-alone option in the domain) within each domain. In this sense, the domain interventions are mutually exclusive treatment options. The actual treatment

domains in use will be specified in the core protocol, however, for generalisability, this documents discusses the analysis in terms of generic domains.

In this document, domains are labelled by capital letters, A, B, C, and when necessary a generic domain will be represented by d. Within each domain there will be a number of distinct intervention options denoted by subscripts, $d_1, d_2, ...d_{K_d}$ where 1 generally indicates no treatment or standard of care within that domain. Additionally, if participants are ineligible for a domain or the domain was unavailable to them at the time of randomisation an additional distinct treatment option d_0 may be defined and assigned to these participants. Additionally, as the trial progresses interventions may be dropped and introduced within a domain. While K_d denotes the total number of interventions available in the domain over the course of the trial, K'_d will indicate the number of actively randomised treatments within a domain.

The number of domains and/or treatments within a domain may change as the trial progresses, but for concreteness, this document will refer to 3 treatment domains A, B, and C.

2.3 Regimen

A treatment regimen consists of a collection of one selected intervention from each treatment domain. Assuming that every intervention from each domain may be given in combination with all interventions from every other domain, the number of distinct regimens is equal to $K_A \times K_B \times K_C$. A treatment regimen may be denoted by an index $j = 1, 2, ..., K_A K_B K_C$ or by a string indicating the comprising interventions. For example, the regimen composed of treatment 1 from domain A, treatment 2 from domain B and treatment 0 from domain C may be represented by $A_1 B_2 C_0$. For any particular regimen j, the notation $d(j)$ will refer to the intervention from domain d which forms part of the regimen j, such as $\{A(j) = A_1, B(j) = B_2, C(j) = C_0\}$ for the previous example regimen.

2.4 Standard of Care

Standard of care will vary between regions and sites, and over the course of the trial. At the time of writing, it is likely to include low-dose dexamethasone (6mg daily IV or PO for 10 days) in all patients requiring supplemental oxygen, and remdesivir in those regions/sites where it is available, again for patients requiring supplemental oxygen. Standard of care is not dictated by the core protocol, but data will be collected on any agents used as standard and adjusted for in the statistical model where deemed relevant. Currently, adjustment will be made for corticosteroids and remdesivir.

2.5 Subgroups

Treatment effect heterogeneity will be explored for the following variables as measured at baseline across all domains:

- country/region
- days since symptom onset ≤ 7 days or > 7 days
- required supplemental oxygen at time of randomisation or oxygen saturation less than 94% at room air
- < 60 years of age or ≥ 60 years of age
- receipt of remdesivir at time of randomisation
- receipt corticosteroid at time of randomisation

- receipt of any other agent intended to be an antiviral agent against SARS-CoV-2
- participants receiving ACE inhibitor/ATII blocker therapy at the time of presentation

Other domain-specific subgroup analyses may be specified in the domain appendices. Any other subgroup analyses will be post-hoc and reported as such.

2.6 Randomisation

Patients are randomised to regimens which consist of one intervention from each domain. Initially, all interventions within a domain and therefore all regimens will be allocated with equal probability. Participants will only be randomised to regimens comprising interventions for which they are eligible and interventions which are available at the time of enrolment.

Following an analysis, some interventions in a domain may have been dropped, or new interventions added. Interventions in a domain with non-zero randomisation probability (including standard of care) will be referred to as the actively allocated interventions.

Response adaptive randomisation will be used to update the allocation ratios to the actively allocated interventions following each sequential analysis. The standard of care option within each domain will have a fixed allocation of $1/K'_d$ where K'_d is the number of actively allocated interventions in the domain.

3 Endpoints and Estimands

3.1 Primary Outcome

Death from any cause or requirement of new intensive respiratory support (invasive or non-invasive ventilation) or vasopressor/inotropic support in the 28 days after randomisation. This includes any participant who receives non-invasive mechanical ventilation (either CPAP or BIPAP, apart from the below considerations) any time after enrolment even if not transferred to ICU. It does NOT include the use of humidified high-flow nasal prong oxygen.

Participants on pre-existing home BiPAP or CPAP will not be considered to have met the primary outcome unless they have either:

- required invasive mechanical ventilation (i.e. intubation), or
- graduated from CPAP only whilst asleep to BiPAP at any time, or
- raduated from BiPAP only whilst asleep to BiPAP for $>$12 hours/day, or
- died by day 28.

This endpoint applies across all domains.

There may be cases where a patient has been assessed as requiring intensive respiratory support (invasive or non-invasive ventilation) or vasopressor/inotropic support, but the patient or family has declined and the patient has been taken home. If attempts to obtain 28-day data are unsuccessful or not possible, and the investigator deems that the patient will be highly likely to die within 28 days from randomisation, these participants will be deemed to have met the primary outcome.

3.2 Secondary Outcomes

1. Time to clinical recovery during the first 28 days after enrolment. Time to clinical recovery is defined as the first day, during the 28 days after enrolment, on which a patient satisfies categories 1, 2, or 3 on the WHO eight-point ordinal outcome scale
2. WHO 8-point ordinal outcome scale at days 7 and 28. Admission to a Hospital in the Home unit is not counted as hospitalisation for the purposes of this ordinal scale. Patients who have been admitted to hospital and transferred to a Hospital in the Home unit will be assessed as either ordinal score 1 or 2. The ordinal score is:
    i. Not hospitalised, no limitations on activities
    ii. Not hospitalised, limitation on activities
    iii. Hospitalised, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalization was extended for infection control purposes)
    iv. Hospitalised, not requiring supplemental oxygen but requiring ongoing medical care (COVID-19 related or other medical conditions)
    v. Hospitalised, requiring supplemental oxygen
    vi. Hospitalised, on non-invasive ventilation or high flow oxygen devices
    vii. Hospitalised, on invasive mechanical ventilation or ECMO
    viii. Death.
3. All-cause mortality at 28 and 90 days after randomisation.
4. Days alive and free of hospital by 28 days after randomisation. Days spent in a Hospital in the Home unit will not be counted as days in hospital as hospital means 'acute-care hospital' for the purposes of this endpoint.
5. Days alive and free of invasive or non-invasive ventilation by 28 days after randomisation
6. Presence of patient reported outcome of shortness of breath at days 14, 28, and 90 after randomisation.
    - Dichotomous comparison of a subjective measure of shortness of breath such as: "Are you currently experiencing shortness of breath that you didn't have before you got COVID, or which is worse now than before you got COVID?"
    - Ordinal comparison of the modified Medical Research Council (mMRC) breathlessness scale:
        - Grade 0 - I only get breathless with strenuous exercise
        - Grade 1 - I get short of breath when hurrying on level ground or walking up a slight hill
        - Grade 2 - On level ground, I walk slower than people of the same age because of breathlessness, or I have to stop for breath when walking at my own pace on the level
        - Grade 3 - I stop for breath after walking about 100 metres or after a few minutes on level ground
        - Grade 4 - I am too breathless to leave the house or I am breathless when dressing or undressing
7. Quality of life as measured by EQ-5D-5L questionnaire at days 28 and 90.

3.3 Covariates

Baseline covariates which will be part of the primary analyses include:

- country/region
- site
- time of enrolment

- age < 60 or ≥ 60 years
- required supplemental oxygen at time of randomisation or oxygen saturation less than 94% at room air.

3.4 Estimands

The primary estimand will be the relative log-odds of the primary outcome for each treatment at the planned endpoint of 28 days after randomisation for all randomised participants irrespective of post-randomisation events. This is a *de facto* (effectiveness) estimand. Data collected after post-randomisation events such as treatment withdrawal or protocol deviations will be included in the primary analysis.

A secondary estimand will be the log-odds of the primary outcome for each treatment at the planned endpoint of 28 days after randomisation for participants without protocol deviations. This is a *de jure* (efficacy) estimand. Primary endpoint data collected after protocol deviations have occurred will not be included in this secondary analysis.

4 Statistical Modelling

Inferences in the trial will be based on Bayesian models. The models will take into account the trial implementation by accounting for variation in outcomes by region (country), site, and time since trial commencement. The primary model will estimate treatment effects assuming no interaction between treatments across different domains. Secondary models will investigate interaction effects across treatment domains and treatment effect heterogeneity by subgroup. All model parameter posteriors and posterior quantities will be estimated using Markov chain Monte Carlo draws from the joint posterior density.

4.1 Analysis Population

The primary analysis population will include all participants who were randomised to at least one of the interventions and have passed the primary endpoint of 28 days after randomisation with their primary outcome status either known or known to be missing. At sequential analyses, participants who have been randomised but have not yet reached the primary endpoint will be excluded. This analysis set will follow the intention-to-treat (ITT) principle (treatment-policy estimand) in that all randomised patients will be included and analysed according to the regimen to which they were initially allocated irrespective of any deviations from this regimen or any other protocol deviations. This analysis population will inform the primary estimand.

A secondary analysis population will include all participants who are randomised to at least one of the interventions. However, this analysis set will follow the per-protocol (PP) definition with randomised patients included in the analysis only if no protocol deviations occurred prior to the endpoint.

4.2 Primary Model

The following symbols will be used throughout:

- $r = 1, ..., R$ will denote regions.
- $s = 1, ..., S_r$ will denote sites within a region.

- $t = 1, ..., T$ will denote participant cohort grouped according to time of enrolment and timing of sequential analysis relative to trial commencement.
- $d = A, B, C$ or $d = 1, 2, 3$ will denote domains, d_k will denote treatment k within domain d, and Q will denote the number of domains.

For a participant i enrolled in the study the notation $r(i) = 1, ..., R$ will be used to indicate the region to which that participant belongs, similarly for site, $s(i)$, cohort $t(i)$, and for each domain $A(i), B(i), C(i)$.

The primary outcome will be modelled by logistic regression (with crossed random-effects) with linear predictor and probability of outcome for a participant $i = 1, 2, 3, ...$

$$\eta_i = \beta_0 + \sum_d x_{d(i)}^{\mathsf{T}} \beta_d + \rho_{r(i)} + \zeta_{s(i)} + \tau_{t(i)} + z_i^{\mathsf{T}} \alpha$$
$$\pi_i = \text{logit}^{-1}(\eta_i).$$

The terms in the model are:

- β_0 - the model intercept which represents the baseline average log-odds of response on standard of care within the reference group.
- β_d - the parameters reflecting the effect of each treatment, the interpretation of which is dependent on the structure of the domain design matrix X_d with x_d the relevant row from this matrix.
- ρ_r - the change in baseline response associated with region r.
- ζ_s - the change in baseline response associated with site s.
- τ_t - adjusts for change in the baseline response over time since the trial commenced. Each t represents a cohort of patients recruited in a given period of time and the initial cohort is the reference group ($\tau_1 = 0$).
- α - other covariates specified for inclusion in the primary model.

The design matrices will be specified in terms of treatment coding and may include interactions for combinations of interventions within a domain. For example if intervention d_3 was the combination of d_1 and d_2 given together as opposed to each alone then β_{d3} would denote an interaction term coefficient.

At times it will be more useful to consider the model in terms of the the response under each regimen $j = 1, 2, ..., K_A K_B K_C$ within the referent group, i.e.

$$\eta_j = \beta_0 + \sum_d x_{d(j)}^{\mathsf{T}} \beta_d$$
$$\pi_j = \text{logit}^{-1}(\eta_j)$$

where $d(j)$ returns the treatment from domain d which is used in regimen j.

4.3 Primary Model Priors

4.3.1 Treatments

The baseline-response, β_0, and the treatment effects β_d are given the following priors

$$\beta_0 \sim \text{Normal}(0, 10^2)$$
$$\beta_{dk} \overset{\text{iid}}{\sim} \text{Normal}(0, 1), \quad k = 0, 1, ..., d_{K_d},\ d = 1, 2, 3, ...$$

The treatment effect parameter β_d consists of a reference treatment with $\beta_{d1} = 0$ and will also include a term for domain ineligibility or unavailability β_{d0}. For example, suppose at trial commencement two domains A and B are open and later in the trial a third domain C is opened. Participants who entered the trial prior to domain C opening were not randomised to that domain. Given that domain C was unavailable to these participants they would contribute to β_{C0}.

4.3.2 Regions

Region $r = 1$ will be the reference region and all other regions $r = 2, ..., R$ will have prior

$$\begin{aligned}\rho_1 &= 0 \\ \rho_r &\overset{\text{iid}}{\sim} N(0,1), \quad r = 2, ..., R.\end{aligned}$$

4.3.3 Sites

Sites are nested within region and will be treated as exchangeable within region with priors

$$\begin{aligned}\xi_{rs} &\overset{\text{iid}}{\sim} \text{Normal}\left(0, \sigma^2_{\xi_r}\right), \quad s = 1, ..., S_r, \ r = 1, ..., R. \\ \sigma_{\xi_r} &\overset{\text{iid}}{\sim} \text{Half-}t(3, 0.1^2),\end{aligned}$$

The mean of zero indicates that on average the sites have expected baseline-response ρ_r.

4.3.4 Cohorts

There is potential for standard of care to improve over time as the trial progresses, and the possibility that the selected population may gradually change. The use of response-adaptive randomisation means that allocation ratios to interventions will also change over-time and effects may be confounded by these other temporal changes. Therefore, time must be accounted for in the model.

Participant cohorts will be defined as sequential sets of participants where the grouping is according to the participants time of enrolment since the trial commenced. Participants recruited closer together in time will be expected to have a more similar experience than those recruited distantly in time.

The prior for the models time component will be a random-walk according to

$$\begin{aligned}\tau_1 &= 0 \\ \tau_t &= \tau_{t-1} + \sigma_\tau \epsilon_t \\ \epsilon_t &\overset{\text{iid}}{\sim} N(0,1), \quad t = 2, ..., T \\ \sigma_\tau &\sim \text{Half-}t(3, 0.1^2).\end{aligned}$$

This prior enforces some smoothing of the baseline response across cohorts expecting only small variations between cohorts in temporal proximity.

4.3.5 Other Covariates

Other covariates parameters will have prior

$$\alpha \overset{\text{iid}}{\sim} N(0, 10^2)$$

4.4 Between Domain Interactions

Interactions between treatments in different domains may be investigated as part of an extended model where deemed relevant. Only two-way interactions will be considered. The extended model has the general form

$$\begin{aligned}\eta_i &= \beta_0 + \sum_d x_{d(i)}^{\mathsf{T}}\beta_d + \sum_{d_1<d_2}\left(x_{d_1(i)}^{\mathsf{T}} \otimes x_{d_2(i)}^{\mathsf{T}}\right)\gamma_{d_1 d_2} + \rho_{r(i)} + \zeta_{s(i)} + \tau_{t(i)} \\ \gamma_{kl} &\sim \text{Normal}(0, 0.1^2)\end{aligned}$$

where a informative prior on no interaction effect is specified.

The interaction may only be of interest for a subset of domains or interventions (the rest having $\gamma_{d_1 d_2} = 0$).

4.5 Subgroup Analyses

Subgroup effects which borrow information across groups are of interest. The primary analysis model may be extended to allow for varying treatment effects by subgroup, for example for region the model would be extended via

$$\begin{aligned}\eta_i &= \beta_0 + \sum_d x_{d(i)}^{\mathsf{T}}\beta_d + \sum_d x_{d(i)}^{\mathsf{T}}\rho_{d,r(i)} + \rho_{0,r(i)} + \zeta_{s(i)} + \tau_{t(i)} + z_i^{\top}\alpha \\ \rho_r|\Omega_\rho &\overset{\text{iid}}{\sim} N(0, \Omega_\rho),\ r = 1, ..., R \\ \Omega_\rho &\sim p(\Omega_\rho)\end{aligned}$$

where $p(\Omega_r)$ is the prior on the covariance of the region treatment effects. One approach is to specify the prior marginal standard deviations and correlation separately (Joe, 2006; Lewandowski et al., 2009; Tokuda et al., 2011). The prior covariance is specified as

$$\begin{aligned}\Omega_\rho &= \text{diag}(\omega)\Lambda\text{diag}(\omega) \\ \omega_l &\sim \text{Half-}t(3, 1) \\ \Lambda &\sim \text{LKJ}(1).\end{aligned}$$

4.6 Ineligible or Unavailable

At the time of enrolment, a participant may be ineligible for a particular domain. If a participant is not eligible for a given domain then that participant will not be randomised to an intervention for that domain. The participant will be included in the primary analysis as long as they are eligible for at least one other domain. A covariate will indicate ineligibility for each domain to account for possible association between participant factors determining domain ineligibility and the primary outcome.

At the time of enrolment, a participant may be eligible for all domains, but ineligible for certain interventions within some domains. If a participant is ineligible for any actively allocated interventions (but eligible for an inactive intervention) in the domain then they will be treated as ineligible for the domain itself. If a participant is only eligible for one actively allocated intervention, then the participant may receive it, however they will be treated as ineligible for the domain itself. If a participant is eligible for at least two actively allocated interventions, the participant will be randomised amongst those eligible interventions and

treated as eligible for the domain. The participant will be included in the primary analysis and a covariate indicating their intervention specific ineligibility will be included to account for possible associations between participant factors determining ineligibility for a particular intervention and the outcome. Each intervention will have it's own ineligibility effect where necessary.

If a domain is unavailable at the time of randomisation, then the participant will be categorised as ineligible. If an intervention is unavailable at a site at the time of a participants randomisation, then that participant will be treated as ineligible for the intervention and randomised to the available interventions in the domain so long as there is more than one available.

The assumption being made in the above is that ineligibility for any domain or treatment, and unavailability of any domain or treatment, has no effect on treatment response to the interventions in the other domains.

The covariate vector, e_i, which indicate intervention ineligibility will be included in the primary model with coefficient, ξ, with prior

$$\xi \sim N(0, 10^2).$$

4.7 Missing Data

In the primary analysis, missing primary outcome data will not be imputed and participants without primary outcome data will be excluded from the sequential analyses. Missing covariate information may be imputed based on other available data (e.g. missing region, site or time of enrolment).

4.8 Sensitivity Analyses

Sensitivity analyses may include applying the same model to a different analysis population or varying the primary model. In particular, the following sensitivity analyses will be explored:

- the per-protocol analysis.
- separate models fit to domain eligible subsets: for example, for each domain sensitivity analyses will restrict to only those participants who were eligible for the domain and only participants who were eligible for all interventions in the domain.
- sensitivity of the results to the choice of priors: allowing priors to be less or more informative than those specified in this SAP.
- method of handling missing primary outcome data, e.g. complete-case analysis, worst-case, or best-case scenarios.
- varying the assumption made for the primary endpoint regarding participants who discharged against medical advice.

5 Statistical Quantities

Certain quantities derived from the model parameter posterior densities will be used to inform the response adaptive randomisation and trial decisions. Posterior quantities of particular interest are defined here.

5.1 Best Regimen

In Section 4.2 η_j was defined as the log-odds of response under a given regimen. Define $j^\star = \text{argmin}_j \eta_j$ to be the regimen which minimises the log-odds of response. The probability that regimen j is the best regimen (in terms of minimising the log-odds of response) is

$$\phi_j = \mathbb{P}[\text{regimen } j \text{ is best}] = \mathbb{P}[j^\star = j] = \mathbb{P}[\eta_j < \eta_l, \forall l \neq j], \quad j = 1, ..., K_A K_B K_C.$$

5.2 Best Treatment

Define the probability that a treatment combination within a domain d is in the best regimen $j^\star$ by

$$\varphi_{dk} = \mathbb{P}[\text{treatment } d_k \text{ is in best regimen}] = \mathbb{P}[d(j^\star) = k], \quad k = 1, ..., K_d \quad .$$

Since each regimen contains only one intervention from each domain (which may be no intervention) the probabilities satisfy $\Sigma_{k=1}^{K_d} \varphi_{dk} = 1$ for each domain.

In the absence of interactions across domains as specified in the primary model this is equivalent to

$$\varphi_{dk} = \mathbb{P}[\text{treatment } d_k \text{ is best in domain}] = \mathbb{P}\left[\underset{l=1,...,K_d}{\text{argmin}} \ (x_{d(l)}^\mathsf{T} \beta_d) = k\right], \quad k = 1, ..., K_d$$

If an intervention k in domain d has low probability of being the best then the intervention may be dropped. If one intervention has high probability of being the best then all other interventions in the domain may be dropped.

5.3 Treatment Contrasts

Define the probability that a treatment combination in a domain has a lower log-odds of the outcome than another treatment combination in the same domain by

$$\psi_{kl}^d(\Delta) = \mathbb{P}[\text{treatment } d_k \text{ better than treatment } d_l] = \mathbb{P}\left[x_{d(k)}^\mathsf{T} \beta_d < x_{d(l)}^\mathsf{T} \beta_d + \Delta\right], \quad k, l \in \{1, ..., K_d\}.$$

where Δ is a reference relative treatment effect.

For example:

- The probability that treatment $k > 1$ in domain d is effective (better than standard of care, $k = 1$) is $\psi_{k1}^d(0)$.
- The probability that treatment k is futile (reduces the log-odds of response by no more than $-\log(1.1)$) compared to no treatment is $\psi_{k1}^d(-\log(1.1))$.
- The probability that treatment k is non-inferior to a treatment l (reduces the log-odds of response by no less than $\log(1.1)$) is $\psi_{kl}^d(\log(1.1))$.

6 Trial Adaptations and Statistical Decisions

As the trial proceeds, some aspects of the trial status may change, for example new sites may begin recruiting or availability of treatments may change at sites. Similarly, treatments and/or domains may be added or removed based on the trial results themselves, or due to information external to the trial. The model previously specified has been outlined so as to be generic, where the basic model components remain consistent even if the particulars may change over time.

For adaptations internal to the trial, predefined rules are put in place to inform trial decisions conditional on the primary model. Pending review, these statistical decisions will inform platform conclusions such as declaring an intervention effective or superior in a domain and dropping interventions from active randomisation. The following sections outline these adaptations.

6.1 Sequential Analyses

Analyses will be conducted frequently throughout the trial. The first analysis will not be conducted before at least $100 \times \max_d(K_d)$, that is, at least 100 participants per active treatment option within the largest domain. Subsequent analyses will be planned to occur at perpetually at fixed intervals (every 1 month) as long as the trial proceeds. If recruitment is slow, there may be little change in sample size from one analysis to the next, in which case, the analysis may be skipped.

The analyses will use all the data on participants who have reached the primary endpoint and have outcome data available to inform the current model. The current model will be used to inform updates to allocation ratios and statistical decisions.

The pre-specified adaptations are outlined below.

6.2 Response-Adaptive Randomisation

Following each analysis, the allocation probabilities to treatments within domains will be updated to be proportional to the probability that each treatment results in the lowest log-odds of response amongst all in that domain. If still active, the control option within each domain will have fixed allocation of $\rho_{d1} = 1/K'_d$ where K'_d is the number of active interventions in the domain following the current analysis. Otherwise, $\rho_{d1} = 0$. For non-control treatments, the allocation probabilities to active arms are

$$\varrho_{dk} = (1 - \rho_{d1}) \left[\sqrt{\frac{\varphi_{dk}}{n_{dk}}} \Bigg/ \left(\sum_k \sqrt{\frac{\varphi_{dk}}{n_{dk}}} \right) \right], \quad k > 1,\ d = 1, 2, 3$$

where φ_{dk} is the probability treatment k is best in domain d and n_{dk} is the number having received treatment k in domain d.

The probability of receiving a given regimen, j, made up of treatments $A(j), B(j), C(j)$ from domains A, B, C respectively is then $\rho_j = \varrho_{A(j)}\varrho_{B(j)}\varrho_{C(j)}$ assuming the participant is eligible for all interventions and domains. If a new participant is ineligible for an intervention then $\varrho_{dk} = 0$ will be set for that intervention for the participant and the remaining values re-normalised.

6.3 Effectiveness

At each analysis, the posterior probability that an intervention is effective (better than standard of care, see Section 5.3) will be compared to a threshold of 0.99. If this threshold is exceeded then a statistical decision of effectiveness will be made for the intervention and the no treatment option may be dropped from the set of active interventions in the domain (allocation probability set to 0 for the domain standard of care).

Table 1: Intervention effectiveness.

Decision	Comparison	Quantity	Threshold	Action
d_k is effective	d_k vs d_1	$\psi^d_{k1}(0)$	> 0.99	Drop d_0

6.4 Futility

At each analysis, the posterior probability that an intervention is futile (insufficiently better than standard of care, see Section 5.3 or insufficiently better than another reference treatment) with respect to a reference effect size of $\log(1.1)$ will be compared to a threshold of 0.95. If this threshold is exceeded then a statistical decision of futility will be made for the intervention and the treatment option may be dropped from the set of active interventions in the domain (allocation probability set to 0 for the futile intervention).

The two contrasts of primary interest are the comparison of each treatment with the reference treatment $(\psi_{k1}(-\log(1.1))$, and where relevant, the comparison of combination of within domain treatments versus either given alone. For example, if treatment option l is the combination of treatment options k_1 and k_2 given together then the contrasts $\psi^d_{l,k_1}(-\log(1.1))$ and $\psi^d_{l,k_2}(-\log(1.1))$ may be of interest as additional futility checks for intervention l.

Table 2: Intervention futile.

Decision	Comparison	Quantity	Threshold	Action
d_k is futile	d_k vs d_1	$\psi^d_{k1}(-\ln(1.1))$	> 0.95	Drop d_k

6.5 Superiority

At each analysis, the posterior probability that an intervention is superior (in the best regimen, see Section 5.2) will be compared to a threshold of 0.99. If this threshold is exceeded then a statistical decision of superiority will be made for the intervention and all other treatment options may be dropped from the set of active interventions in the domain (allocation probability set to 1 for the superior intervention).

Table 3: Intervention superior.

Decision	Comparison	Quantity	Threshold	Action
d_k is superior	d_k vs all d	φ_{dk}	> 0.99	Drop all d but d_k

6.6 Inferiority

At each analysis, the posterior probability that an intervention is superior (in the best regimen, see Section 5.2) will be compared to a threshold of $0.01/(K'_d - 1)$. If this threshold is not exceeded then a statistical decision of inferiority will be made for the intervention and the treatment option may be dropped from the set of active interventions in the domain (allocation probability set to 0 for the inferior intervention).

Table 4: Intervention inferior.

Decision	Comparison	Quantity	Threshold	Action
d_k is inferior	d_k vs all d	φ_{dk}	$< 0.01/(K'_d - 1)$	Drop d_k

6.7 Introducing Interventions

When a new intervention is introduced into a domain, a run-in period will initiate fixed allocation probability of $1/K'_d$ where K'_d is the number of active interventions including the new one. This will last until an initial sample size of at least 50 participants has been allocated to this intervention across all regimens. Existing interventions in the domain will have their RAR allocation probability rescaled to sum to $1 - 1/K'_d$. Once the initial sample size has been exceeded the new intervention will be included in the RAR with all other active interventions.

6.8 Model Deviations

The primary analysis model will be assessed for adequacy. Additional models (either simpler or more complex) may be investigated as part of checks of sensitivity, stability, and model fit. If any issues or concerns arise (for example, strong evidence of interactions across treatment domains), all changes or updates to the specified primary model will be documented and reported.

6.9 Reporting

6.9.1 Blinding

When reporting the results of a statistical decision for a domain, the number allocated to each intervention and the number ineligible or for whom the domain was unavailable will be disclosed. There are other domains to which participants will have also been randomised. Due to the response adaptive randomisation, the allocation ratios to these other domains may be informative of the relative performance of these interventions. To maintain blinding to the results in the other domains, data on the proportion allocated to these other domain interventions will not be disclosed when reporting the baseline characteristics of participants in the reported domain.

6.9.2 Platform Conclusions

When a statistical decision has been made a platform conclusion may be declared following review of the data, analysis and results.

If a statistical decision of superiority of an intervention in a domain has occurred and upon review a platform conclusion is declared then at sites where the intervention is available the superior intervention will be allocated with probability 1 until a new intervention has been added to the domain. If the intervention is not available at a site then randomisation may continue to the non-superior interventions.

If a statistical decision of inferiority of an intervention in a domain has occurred and upon review a platform conclusion is declared then this intervention will have its allocation probability fixed to 0 and will be dropped from the set of currently active interventions within the domain.

If a statistical decision of effectiveness of an intervention in a domain has occurred and upon review a platform conclusion is declared then at sites where the intervention is available, the allocation probability to the domain standard of care option will be set to zero. If the effective intervention is not available at a site, then randomisation to the domain standard of care may still be allowed.

If a statistical decision of futility of an intervention in a domain has occurred and upon review a platform conclusion is declared of futility then this intervention would have its allocation probability fixed to 0 and will be dropped from the set of currently active interventions within the domain.

In some instances, despite a statistical decision being reached and a platform conclusion declared the above actions may be delayed. For example, if an intervention is found futile but further information is of interest for secondary outcomes, randomisation could continue.

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ASCOT ADAPT Statistical Analysis Appendix

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Contents

Version History

Version 2.2 - Nov 2021

- Authors: Mark Jones

1. Minor typo edits
2. Simplified modelled notation removing interaction
3. Removed placeholders for delayed reveal and evolution of soc.

Version 2.1 - Aug 2021

- Authors: Mark Jones

1. Clarified purpose and limitations
2. Revised structure, migrated content from SAP
3. Removed duplication taken from other documents

Version 2.0 - Oct 2020

- Authors: James Totterdell

1. Revise RAR rules to enforce minimum of 1/3 to each intervention in a domain of only two interventions

Version 1.0 - Aug 2020

- Authors: James Totterdell

1. Statistical analysis plan ASCOT ADPAT

1 Introduction and Purpose

This document presents the general framework for the statistical design and analysis plan for ASCOT-ADAPT. It is an entry point for analysts and others to gain familiarity with the technical aspects of the trial. Additionally, the document is intended to provide sufficient detail to satisfy governance, oversight and/or external bodies that the trial has a sound theoretical basis and has adequately pre-specified the analyses and related matters.

The following documents were reviewed when preparing this document:

- Core protocol for ASCOT-ADAPT
- Domain-specific appendices to the core protocol
- CRFs are reviewed at their current versions if applicable.

Statisticians working on analyses for the platform must read this document in conjunction with the other statistical documentation to get a complete understanding of the analytical approach. While the Statistical Appendix is intended to undergoe relatively little change over time, the Implementation Guide is specific to the current state and structure of the trial and is expected to change.

Our implementation of the analytical documentation hierarchy aims to minimise duplication at the cost of some cross-referencing between documents. Concepts and topics introduced in higher level documents can be expanded upon in lower level documents (such as the Implementation Guide), but as a rule, duplicating content from other documents is avoided.

Specifically, analysts must read this document in conjunction with the Implementation Guide document, the Simulation Appendix and the consolidated Statistical Glossary and Abbreviations. We also note that domain specific variations might be included into the statistical considerations sections of the domain specific appendices.

We have purposely kept the level of detail to a minimum in order to constrain the size and simplify documentation management processes. Additionally, in order to provide a stable and relevant characterisation of the analytical approach over the duration of the trial, the content of this document avoids referencing specific treatment interventions. In brief, the contents of this document are as follows. Section 2 outlines the general trial structure, Section 3 defines and provides some brief discussion on the trial outcome measures of interest, Section 4 introduces the statistical models and priors, Section 5 presents the model quantities which will be used at analyses to inform trial decisions and adaptations, Section 6 outlines the platform conclusion procedure, Section 7 describes the quantities used to make operating decisions for the trial, Section 8 outlines trial adaptations and Section 9 discusses trial reporting.

This document was written and reviewed by those authors detailed in the Version History section. All contributors were blinded to treatment allocations and treatment-related study results at the time of their contributions. The versions of the statistical documentation applicable at the time of each interim analysis are bundled under the github release directory.

2 Structure of Trial

2.1 Target Population

The inclusion and exclusion criteria of the target population are introduced and discussed in the Core Protocol.

2.2 Treatment Domains

A treatment domain comprises a collection of competing interventions within a common clinical modality.

An intervention might be a unique compound, such as Tocilizumab, or the combination of multiple compounds administered simultaneously, such as Tocilizumab plus Kaletra. Alternatively, there may be multiple interventions within a domain that are the same compound, but administered at different dosages.

For generalisability, this document discusses the analyses in terms of generic domains without reference to the specifics, which are primarily detailed in the core protocol and domain specific appendicies.

While the number of domains will change as the trial evolves, here we only consider three domains. These domains are denoted by capital letters, A, B, C, and a generic domain will be represented by d. Within each domain there will be a number of distinct interventions denoted by subscripts, $d_1, d_2, ...d_{K_d}$ where 1 generally indicates no treatment or standard of care within that domain. K_d denotes the total number of interventions available in the domain over the course of the trial and K'_d will be used to indicate the number of treatments that are currently open to enrolment. We also include a special arm d_0 as a way to denote 'not randomised.'

For a participant to be randomised, there must be two or more interventions in one or more domains available to them at the enrolling site. However, there are several scenarios under which the full set of regimens are not available to a participant. These scenarios relate to site-level and/or participant-level characterisitics, for example:

- one or more domains are not open for enrolment at the site where the participant is to be enrolled
- one or more treatments within one or more domains are not available for assignment at the site where the participant is enrolled
- the participant is not eligible for one or more domains
- the participant is not eligible for one or more treatments within one or more domains

Additionally, consideration must be given to the temporal evolution of the trial whereby new domains and/or interventions are added at some time after the start of the trial. As none of the existing participants were randomised to the new domains, they will not contribute to the evaluation of relative effects within those domains. More concretely, these participants will not contribute as members of the 'control' arm within the added domains as they will be given the 'not randomised' d_0 assignment.

If only a subset of domains are available to a participant, then they can be randomised to the available domains. As these participants are excluded from contributing to the relative comparisons within the other domains, their individual likelihood will include a 'not randomised' parameter for each excluded domain. Clearly, while a 'not randomised' arm d_0 is accommodated within one or more of the other domains, participants should not be thought of as having been randomised to these arms.

If only a subset of interventions are available within a domain, then the participant can still be randomised to this domain. However, the allocation probabilities must be re-weighted for this participant prior to randomisation. Typically this might be achieved by dividing the allocation probabilities for the available arms by the sum of these probabilities.

Further detail on accounting for these scenarios can be found in the Ineligible or Unavailable section and in the Implementation Guide document.

As the trial progresses, domains may be added, new interventions may be added to an existing domain and existing interventions may be permanently halted (e.g. a futile arm) or suspended (e.g. suspend standard of care when no investigational arms are open to enrolment). If there are no arms open to enrolment in a domain, then it is considered closed. The maximum number of arms that are available within a domain and across the whole trial are informed by simulation to ensure acceptable trial performance characteristics.

2.3 Regimens

Each trial participant is randomly allocated to a regimen, which comprises a collection of interventions, one selected from each treatment domain. Assuming that every intervention from each domain may be given in combination with all interventions from every other domain, the number of distinct regimens is equal to $K_A \times K_B \times K_C$. A treatment regimen may be denoted by an index $j = 1, 2, ..., K_A K_B K_C$ or by a string indicating the component interventions. For example, the regimen composed of treatment 1 from domain A, treatment 2 from domain B and treatment 0 from domain C (not randomised to domain C) may be represented by $A_1 B_2 C_0$. For any particular regimen j, the notation $d(j)$ will refer to the intervention from domain d which forms part of the regimen j, such as $\{A(j) = A_1, B(j) = B_2, C(j) = C_0\}$ for the previous example regimen.

2.4 Standard of Care

Standard of care is described in the Core Protocol although this description may be extended/varied in domain specific appendicies. Data will be collected on any agents used as standard and adjusted for in the statistical model where deemed relevant, see Covariates and the Implementation Guide.

Note that as participants are randomised to regimens, e.g. $A_1 B_2 C_0$, they may simultaneously contribute to the estimation of parameters associated with the standard of care in some domains and investigational arms in other domains.

2.5 Subgroups

Treatment effect heterogeneity will be explored for subgroups defined by the following variables as measured at baseline across all domains:

- country/region
- days since symptom onset ≤ 7 days or > 7 days
- < 60 years of age or ≥ 60 years of age
- receipt of corticosteroid
- receipt of remdesivir
- receipt of other agent intended to be an antiviral agent against SARS-CoV-2
- participants receiving ACE inhibitor/ATII blocker therapy at the time of presentation
- required supplemental oxygen at time of randomisation or oxygen saturation less than 94% at room air

Other domain-specific subgroup analyses may be specified in the domain specific appendices. Any other subgroup analyses will be post-hoc and reported as such.

2.6 Randomisation

Initially, all interventions within a domain (and therefore all regimens) will be allocated with equal probability. Participants will only be randomised to regimens comprising interventions for which they are eligible and interventions that are available at the time of enrolment.

Following an analysis, some interventions in a domain might be (permanently) dropped from the platform, or new interventions added. Interventions in a domain that have a non-zero randomisation probability (including standard of care) will be referred to as intervention arms that are open for enrolment or *live interventions*.

Response adaptive randomisation will be used to update the allocation ratios for the live intervention arms following each scheduled analysis. For domains with more than 2 actively allocated interventions, the standard of care option (if still active) will have a fixed allocation of $1/K'_d$ where K'_d is the number of actively allocated interventions in the domain. If a domain has only 2 interventions (one of which is standard of care), then the minimum allocation probability is $1/3$. If the SOC has been replaced then that arm receives fixed allocation as above from the time it replaces the SOC.

Further detail on the specific randomisation algorithm used is provided in the Response-Adaptive Randomisation section.

3 Endpoints and Estimands

3.1 Primary Outcome

The primary outcome is discussed in the Core Protocol. However, for the purposes of this document, the primary outcome is a dichotomous variable with death from any cause or requirement of new intensive respiratory support (invasive or non-invasive ventilation) or vasopressor/inotropic support in the 28 days after randomisation coded as one.

3.2 Secondary Outcomes

The secondary outcomes are introduced in the Core Protocol and include dichotomous, ordinal and positive discrete random variables.

3.3 Covariates

Baseline covariates which will be part of the primary analyses include:

- country/region
- site
- epoch of enrolment
- age < 60 or ≥ 60 years

The Implementation Guide discusses the way these terms are parameterised.

3.4 Estimands

The primary estimand will be the log-odds of the primary endpoint for each treatment relative to standard of care at the planned endpoint of 28 days after randomisation for all randomised participants irrespective of post-randomisation events, see Analysis Population and Missing Data. The primary estimand is applied in the Sequential Analyses.

A secondary estimand will be the log-odds of the primary outcome for each treatment relative to standard of care at the planned endpoint of 28 days after randomisation for participants without protocol deviations. Primary endpoint data collected after protocol deviations have occurred will not be included in this secondary analysis.

4 Statistical Modelling

Inferences in the trial will be based on Bayesian methods. The models used will account for the trial implementation by adjusting for variation in outcomes by region (country), site, time since trial commencement and age. In general, the primary model will estimate treatment effects assuming no interaction between treatments across different domains. However, specific combinations may consider interactions and these will be detailed in the Implementation Guide. Secondary models will also investigate interaction effects across treatment domains and treatment effect heterogeneity by subgroup. All model posterior distributions and derived quantities will be estimated using Markov chain Monte Carlo draws from the joint posterior density.

Throughout of this section, the following notation will be used:

- $r = 1, ..., R$ denotes regions.
- $s = 1, ..., S_r$ denotes sites within a region.
- $t = 1, ..., T$ denotes participant cohort grouped according to time of enrolment
- d_k denotes treatment k within domain $d \in \mathcal{D}$, where $\mathcal{D}$ denotes the set of domains.

4.1 Analysis Population

The primary analysis population will inform the primary estimand and includes all participants who were randomised to at least one of the interventions and have passed the primary endpoint of 28 days after randomisation with their primary endpoint status either known or known to be missing.

This primary analysis population will be used for all core outcomes and will follow the intention-to-treat (ITT) principle. All randomised patients will be included and analysed according to the regimen to which they were initially allocated irrespective of any deviations from this regimen or any other protocol deviations.

Participants that have reached follow up, but for whom information has not yet been gathered will be treated as missing until the data has been entered. This assumes that we believe that data entry nor retrieving participant outcome status is differential across treatment groups. Participants who have been randomised, but have not yet reached the primary endpoint, will be excluded.

A secondary analysis population will include all participants who are randomised to at least one of the interventions. However, this analysis set will follow the per-protocol (PP) definition with randomised patients included in the analysis only if no protocol deviations occurred prior to the endpoint.

Intervention availability may vary over time and both domain and eligibility criteria for interventions may also vary. Therefore, a number of analysis populations will be of interest to inform sensitivity and additional analyses complementing the results from the primary set of analyses.

The final analysis (for the platform conclusion) will only use data for those participants who were enrolled into the platform prior to the platform conclusion.

Further detail on analysis sets can be found in the Primary Model Document.

4.2 Primary Model

For a participant i enrolled in the study the notation $r(i) = 1, ..., R$ will be used to indicate the region to which that participant belongs, similarly for site, $s(i)$ and cohort $t(i)$.

The primary outcome will be modelled by logistic regression for a participant $i = 1, 2, 3, \ldots, n$ as follows

$$\pi_i = \text{logit}^{-1}(\eta_i)$$
$$\eta_i = \beta_0 + \sum_d x_{d(i)}^{\mathsf{T}} \beta_d + \rho_{r(i)} + \xi_{r(i),s(i)} + \tau_{t(i)} + z_i^{\mathsf{T}} \alpha$$

where

- π_i is the probability of response for participant i
- η_i is the log-odds of response for participant i
- β_0 represents the baseline log-odds of response in the reference population
- β_d is a vector of parameters for each domain reflecting the effect of each treatment which depends upon the domain design matrix X_d of which $x_{d(i)}^{\mathsf{T}}$ is a row
- ρ_r is the change in log-odds associated with region r
- $\xi_{r,s}$ is the change in log-odds associated with site s nested within region r
- τ_t is the change in baseline response specific to participants recruited during epoch t
- α represents other covariates specified for model inclusion (see Covariates, but also includes intervention specific ineligibilities)

Notes:

- Interactions between treatments in different domains may be investigated as part of an extended model where deemed relevant.
- Only two-way interactions will be considered.
- The design matrices may include interactions for combinations of interventions within a domain. For example if intervention d_3 was the combination of d_1 and d_2 given together as opposed to each alone then β_{d3} would denote an interaction term coefficient.
- Interactions may only be of interest for a subset of domains or interventions with the rest having any redundant parameters fixed to zero.

Finally, at times (see Best Regimen) it might be more useful to consider the model in terms of the the response under each regimen $j = 1, 2, ..., K_A K_B K_C$ i.e.

$$\eta_j = \beta_0 + \sum_d x_{d(j)}^{\mathsf{T}} \beta_d$$
$$\pi_j = \text{logit}^{-1}(\eta_j)$$

where $d(j)$ returns the treatment from domain d which is used in regimen j.

4.3 Models for Secondary Outcomes

The analysis model of each secondary outcome will use a similar model structure (linear predictor) as that used for the primary outcome. Binary variables will be analysed by logistic regression, ordinal outcomes by cumulative logistic regression, and discrete time-to-event outcomes by continuation ratio logistic regression

4.3.1 Binary Outcomes

An independent Bayesian logistic regression model will be used for each binary outcome. The outcome will be coded so that the odds-ratios have a logical direction for implying a treatment benefit. For example, if we are considering death as the response, then the coding will be such that an odds-ratio < 1 will imply a reduction in the odds of death and thus treatment benefit. The model form will be

$$\text{logit}\left[\Pr(y_i = 1)\right] = \eta_i, \quad i = 1, ..., n$$

for participant i with outcome y_i, and linear predictor η_i. The linear predictor, η_i, will take a similar form to the primary analysis model and the model will use the same priors. Sensitivity analyses may vary the form of the linear predictor.

Referencing the Core Protocol, the binary secondary outcomes are:

- all-cause mortality at 28 days after randomisation
- dichotomous comparison of a subjective measure of shortness of breath at 28 days after randomisation

4.3.2 Ordinal Outcomes

An independent Bayesian cumulative logistic regression model will be used for each ordinal outcome. Similar to Binary Outcomes, the outcome will be coded so that the odds-ratios have a logical direction to imply treatment benefit. The model form will be

$$\text{logit}\left[\Pr(y_i > j)\right] = \alpha_j + \eta_i, \quad j = 1, ..., J-1, \quad i = 1, ..., n.$$

for participant i, with outcome category y_i, category specific intercept α_j, and linear predictor η_i. The linear predictor, η_i, will take the same form as in the primary analysis model and the model will use the same priors on parameters in the linear predictor. The model will assume proportional odds effect of each treatment across outcomes, i.e. η is assumed to be constant across categories. Sensitivity analyses will vary the form of the linear predictor and assume a more informative prior on the category specific probabilities.

Referencing the Core Protocol, the ordinal secondary outcomes are:

- WHO 8-point ordinal outcome scale at day 28 after randomisation
- Days alive and free of hospital by 28 days after randomisation
- Days alive and free of invasive or non-invasive ventilation by 28 days after randomisation
- Ordinal comparison of the modified Medical Research Council (mMRC) breathlessness scale.

4.3.3 Time-to-event Outcomes

An independent discrete-time-to-event proportional continuation ratio logistic model (Allison, 1982; Cox, 1982) will be used for each time-to-event outcome *measured in days*. Similar to Binary Outcomes, the outcome will be coded so that the odds-ratios have a logical direction to imply treatment benefit. Outcomes are censored as specified in the outcome definition (e.g. at day 28). The model will assume proportional conditional odds ratios of each intervention across all times. The model form will be

$$\text{logit}\left[\Pr(y_i = u | y_i \geq u)\right] = \alpha_u + \eta_i, \quad u = 1, ..., U$$

where u denotes discrete time (e.g. days), α_u is the time-varying intercept and η_i the participant specific linear predictor. The linear predictor, η_i, will take the form as in the primary analysis model and the model will use the same priors on parameters in the linear predictor. Under this model, the hazard is defined as a conditional probability and the intercepts can be interpreted as the logit (yes, *logit*, not *log*) of the baseline hazard and the linear predictor represents the additive effect of the covariates on the logit of the hazard. Sensitivity analyses will vary the form of the linear predictor and assume a more informative prior on the baseline log continuation ratios (e.g. smoothness).

Referencing the Core Protocol, the time-to-event secondary outcomes are:

- Time to clinical recovery (in days) during the first 28 days after enrolment

4.4 Primary Model Priors

4.4.1 Treatments

The baseline-response (intercept term) β_0, and the treatment effects β_d are given the following priors

$$\begin{aligned}\beta_0 &\sim \text{Normal}(0, 2.5^2)\\ \beta_{dk} &\overset{\text{iid}}{\sim} \text{Normal}(0,1), \quad k = 0, 1, ..., d_{K_d},\ d = 1, 2, 3, ...\end{aligned}$$

The treatment effect parameter β_d consists of a reference treatment, β_{d1}, and will also include a term for not being randomised, β_{d0}, to account for ineligibility and unavailability. For example, suppose at trial commencement two domains A and B are open and later in the trial a third domain C is opened. Participants who entered the trial prior to domain C opening were not randomised in that domain. Given that domain C was unavailable to these participants they would only contribute to β_{C0} (the not randomised parameter) in domain C.

4.4.2 Treatment interactions

Treatment interactions may arise within a domain or across domains. The treatment effect parameters for interactions are specified on a case by case basis in the Implementation Guide. However, as a general rule an informative prior on no interaction effect is specified.

4.4.3 Regions

Region $r = 1$ will be the reference region and all other regions $r = 2, ..., R$ will have prior

$$\begin{aligned}\rho_1 &= 0\\ \rho_r &\overset{\text{iid}}{\sim} N(0,1), \quad r = 2, ..., R.\end{aligned}$$

4.4.4 Sites

Sites are nested within region and will be treated as exchangeable within region with priors

$$\begin{aligned}\xi_{rs} &\overset{\text{iid}}{\sim} \text{Normal}\left(0, \sigma^2_{\xi_r}\right), \quad s = 1, ..., S_r \quad r = 1, ..., R.\\ \sigma_{\xi_r} &\overset{\text{iid}}{\sim} \text{Half-}t(3,1),\end{aligned}$$

The mean of zero implies that on average the sites in region r have expected baseline-response $\beta_0 + \rho_r$.

4.4.5 Temporal Cohorts

There is potential for both background care and circulating virus strains to show structural variation (i.e. not just random variation due to noise) as the trial progresses. Participants recruited closer together in time are expected to have a more similar experience than those recruited further apart in time. The use of response-adaptive randomisation means that allocation ratios to interventions will be updated and therefore intervention effects may be confounded by these temporal changes.

To account for temporal trends, participant are grouped into sequential cohorts relative to the most recently randomised participant included in the analysis and thus relating to a particular epoch in the trial. Epochs span 4 week windows and participants are included in a single cohort, although cohorts may be pooled with the next most recent one if there is insufficient data ($<$ 5 randomised participants).

The prior for the models time component will be a random-walk

$$\begin{aligned}
\tau_1 &= 0 \\
\tau_t &= \tau_{t-1} + \sigma_\tau \epsilon_t \\
\epsilon_t &\overset{\text{iid}}{\sim} N(0,1), \quad t = 2, ..., T \\
\sigma_\tau &\sim \text{Half-}t(3,1).
\end{aligned}$$

where t $= 1$ implies that the participant was randomised within 4 weeks of the most recent participant, t $= 2$ that they were randomised more than 4 weeks past but within 8 weeks, etc. This prior enforces some smoothing of the baseline response across cohorts expecting only small variations between cohorts in temporal proximity.

4.4.6 Age Parameters

Age is dichotomised as less than 60 years of age (reference category), or greater than or equal to 60 years of age. The parameter priors will be

$$\begin{aligned}
\alpha_0 &= 0 \\
\alpha_1 &\sim \text{Normal}(0, 2.5^2).
\end{aligned}$$

4.4.7 Other Covariates

Nominally, other covariates parameters will assume a default prior of

$$\alpha \overset{\text{iid}}{\sim} N(0, 2.5^2)$$

with variations specified in the Implementation Guide.

4.4.8 Intercept terms for ordinal models

The prior for the intercept terms for ordinal models will be implied from a uniform Dirichlet prior on the category specific probabilities.

4.5 Subgroup Analyses

For subgroups, the primary analysis model (ignoring the potential interaction components for simplicity of presentation) will be extended to allow for varying treatment effects by subgroup. For example, for region the model would be extended via

$$\eta_i = \beta_0 + \sum_d x_{d(i)}^{\mathsf{T}} \beta_d + \sum_d x_{d(i)}^{\mathsf{T}} \rho_{d,r(i)} + \rho_{0,r(i)} + \zeta_{s(i)} + \tau_{t(i)} + z_i^{\top} \alpha$$

$$\rho_r | \Omega_\rho \overset{\text{iid}}{\sim} N(0, \Omega_\rho),\ r = 1, \ldots, R \quad \Omega_\rho \sim p(\Omega_\rho)$$

where $p(\Omega_r)$ is the prior on the covariance of the region treatment effects. We specify the priors on the marginal standard deviations and correlation separately (Joe, 2006; Lewandowski et al., 2009; Tokuda et al., 2011)

$$\begin{aligned} \Omega_\rho &= \text{diag}(\omega) \Lambda \text{diag}(\omega) \\ \omega_l &\sim \text{Half-}t(3, 1) \\ \Lambda &\sim \text{LKJ}(1). \end{aligned}$$

4.6 Ineligible or Unavailable

At the time of enrolment, a participant may be ineligible for one or more domains. If a participant is ineligible for a given domain then that participant will not be randomised to any intervention for that domain. However, the participant will be included in the primary analysis as long as they are eligible for at least one other domain. A covariate will indicate ineligibility for each applicable domain to account for possible association between participant factors determining domain ineligibility and the primary outcome.

Alternatively, a participant may be eligible for all domains, but ineligible for domains-specific interventions as follows:

- If a participant is ineligible for all the interventions that are open for enrolment in the domain then they will be treated as ineligible for the domain itself (even if they happen to be eligible for an inactive intervention within the domain).
- If a participant is only eligible for one of the interventions open for enrolment, then the participant may receive it, however, they will be treated as ineligible for the domain itself.
- If a participant is eligible for at least two actively allocated interventions, the participant will be randomised amongst those eligible interventions and treated as eligible for the domain but ineligible for the other interventions in the domain.

When applicable, the participant will be included in the primary analysis and a covariate indicating their intervention specific ineligibility will be included to account for possible associations between participant factors determining ineligibility for a particular intervention and the outcome. Each intervention will have it's own ineligibility effect as required. The covariate vector, e_i, which is used to indicate intervention ineligibility will be included in the primary model and the associated parameters will use the prior

$$\xi \sim N(0, 10^2).$$

The intervention specific eligibilities are coded as standalone co-variates introduced as needed separate from the domain specific ones. For example, if there was a specific ineligibility for treatment $A2$ only, then a new variable e_{A2}, say, would be introduced indicating that a participant was ineligible for $A2$, but could still be randomised to another intervention in domain A, allowing for a different baseline among such participants. That participant may still be eligible for $A1$, $A3$, $A4$ and is therefore still randomised to the domain. While the domain coding would stay the same, if $e_{A2} = 1$,

then the participant cannot have received $A2$, meaning they aren't directly comparable to those participants who could have received $A2$. Domain ineligibility takes priority over intervention ineligibility, e.g. if ineligible for the domain, then it doesn't matter that they were also ineligible for $A2$.

The assumption being made in the above is that ineligibility for any domain or treatment, and also unavailability of any domain or treatment, does not modify treatment response to the interventions in the other domains.

More detail on the parameterisation can be found in the Implementation Guide document.

4.7 Missing Data

In the primary analysis, missing primary outcome data will not be imputed and participants without primary outcome data will be excluded from the sequential analyses. For example, participants that have reached the 28 day endpoint, but for whom information has not yet been gathered, will be treated as missing.

If the randomisation assignment is missing the patient will be assumed to be ineligible for that domain. If a participants eligibility is unknown, they will be assumed to be ineligible for that domain or intervention.

Missing covariate information may be imputed based on other available data (e.g. missing region, site or time of enrolment). Alternatively, the category mean will be used as the imputed value.

4.8 Sensitivity Analyses

Sensitivity analyses may include applying the same model to a different analysis population or varying the primary model. In particular, the following sensitivity analyses will be explored:

- the per-protocol analysis.
- analysis based solely on contemporaneous controls, defined as enrolments in the last 3 months.
- separate models fit to domain eligible subsets:
  - for each domain analyses will restrict to only those participants who were eligible for the domain
  - for each domain analyses will restrict to only participants who were eligible for all interventions in the domain
- sensitivity of the results to the choice of priors: allowing priors to be less or more informative than those specified in this document.
- method of handling missing primary outcome data, e.g. complete-case analysis, worst-case, or best-case scenarios.
- varying the assumption made for the primary endpoint regarding participants who discharged against medical advice.

4.9 Model Deviations

The primary analysis model will be assessed for adequacy. Additional models (either simpler or more complex) may be investigated as part of checks of sensitivity, stability, and model fit. If any issues or concerns arise (for example, strong evidence of interactions across treatment domains), all changes or updates to the specified primary model will be documented and reported.

5 Statistical Quantities

Certain quantities derived from the model parameter posterior densities will be used to inform the response adaptive randomisation and trial decisions. Posterior quantities of particular interest are defined here.

5.1 Best Regimen

In the Primary Model section, η_j was defined as the log-odds of response under a given regimen. Defining $j^\star = \text{argmin}_j(\eta_j)$ to be the **regimen** which minimises the log-odds of response, the probability that regimen j is the best regimen (in terms of minimising the log-odds of response) is

$$\phi_j = \mathbb{P}[\text{regimen } j \text{ is best}] = \mathbb{P}[j^\star = j] = \mathbb{P}[\eta_j < \eta_l, \forall l \neq j], \quad j = 1, ..., K_A K_B K_C.$$

5.2 Best Treatment (treatment in best regimen)

Recalling that for any particular regimen j, the notation $d(j)$ refers to the intervention from domain d which forms part of the regimen j (see Regimens), we define the probability that a treatment within a domain d is in the best regimen $j^\star$ by

$$\varphi_{dk} = \mathbb{P}[\text{treatment } d_k \text{ is in best regimen}] = \mathbb{P}[d(j^\star) = k], \quad k = 1, ..., K_d \quad .$$

Since each regimen contains only one intervention from each domain (which may be no intervention) the probabilities satisfy $\Sigma_{k=1}^{K_d} \varphi_{dk} = 1$ for each domain.

In the absence of interactions across domains, this is equivalent to

$$\varphi_{dk} = \mathbb{P}[\text{treatment } d_k \text{ is best in domain}] = \mathbb{P}\left[\text{argmin}_{l=1,...,K_d}(x_{d(l)}^\mathsf{T}\beta_d) = k\right], \quad k = 1, ..., K_d$$

where $x_{d(l)}^\mathsf{T}$ is a row from the domain design matrix corresponding to a particular treatment arm (including SOC if present) and therefore $x_{d(l)}^\mathsf{T}\beta_d$ is the contribution to the linear predictor for treatment l in domain d. If the best option from domain d is the one that reduces the log-odds by the largest amount and β_d is known then the best treatment arm is clearly

$$k = \text{argmin}_{l=1,...,K_d}(x_{d(l)}^\mathsf{T}\beta_d)$$

However, β_d is random, therefore our interest rests in

$$\mathbb{P}\left[\text{argmin}_{l=1,...,K_d}(x_{d(l)}^\mathsf{T}\beta_d) = k\right], \quad k = 1, ..., K_d$$

i.e. the probability that the treatment arm is best, as above.

If an intervention k in domain d has low probability of being the best then the intervention may be dropped. If one intervention has high probability of being the best then all other interventions in the domain may be dropped.

5.3 Treatment Contrasts

We define the probability that an intervention has a lower log-odds of the outcome than another intervention in the same domain by

$$\psi^d_{kl}(\Delta) = \mathbb{P}[\text{intervention } d_k \text{ better than intervention } d_l] = \mathbb{P}\left[x^{\mathsf{T}}_{d(k)}\beta_d < x^{\mathsf{T}}_{d(l)}\beta_d + \Delta\right],$$
$$k, l \in \{1, ..., K_d\}.$$

where Δ is a reference relative treatment effect.

For example:

- The probability that treatment $k > 1$ in domain d is effective (better than standard of care, $k = 1$) is $\psi^d_{k1}(0)$.
- The probability that treatment k is futile (reduces the log-odds of response by no more than $-\log(1.1)$) compared to no treatment is $\psi^d_{k1}(-\log(1.1))$.
- The probability that treatment k is non-inferior to a treatment l (reduces the log-odds of response by no less than $\log(1.1)$) is $\psi^d_{kl}(\log(1.1))$.

The concepts of effectiveness, futility and non-inferiority are expanded upon in the Trial Decision Criteria section.

6 Decision processes

For adaptations internal to the trial, predefined rules are evaluated based on statistical decision quantities derived from the primary model and pre-specified thresholds, see Trial Decision Criteria.

When a decision threshold is exceeded and criterion is met, the applicable oversight bodies (see Core Protocol) will consider the result and may determine a platform conclusion for public reporting. For example, an intervention may be declared effective or superior in a domain.

6.1 Platform conclusion procedure

The following high-level steps are involved in arriving at a platform conclusion:

1. interim analysis indicate a criterion has been met, see Trial Decision Criteria
2. results reported to DSMC for review
3. DSMC meet (as deemed necessary) and determine whether to report that a criterion has been met and recommend the implied action to the TSC
4. all participants enrolled up until the time when the action was enacted are followed up
5. a final (platform conclusion) analysis is run on the completed follow-up for those enrolled participants
6. the final analysis is used as the basis for further reporting

7 Trial Decision Criteria

Trial decision criteria are based on probability statements and are evaluated and used to direct the progression of the trial, see Trial Adaptations. Mathematically, the criteria are defined as the outputs of indicator functions applied to inequalities that define effectiveness, futility etc.

7.1 Effectiveness

At each analysis, the posterior probability that an intervention is effective (better than standard of care, see Treatment Contrasts) will be compared to a threshold of 0.99. If this threshold is exceeded then a trial decision of effectiveness will be made for the intervention and the standard of care treatment option may be dropped from the set of active interventions in the domain (allocation probability set to 0 for all regimens which include that domain standard of care, $d(1)$).

Table 1: Intervention effectiveness.

Decision	Comparison	Quantity	Threshold	Action
d_k is effective	d_k vs d_1	$\psi^d_{k1}(0)$	> 0.99	Drop d_1

7.2 Futility

At each analysis, the posterior probability that an intervention is futile (insufficiently better than standard of care, see Treatment Contrasts or insufficiently better than another reference treatment) with respect to a reference effect size of $\log(1.1)$ will be compared to a threshold of 0.95. If this threshold is exceeded then a trial decision of futility will be made for the intervention and the treatment option may be dropped from the set of active interventions in the domain (allocation probability set to 0 for the futile intervention).

The two contrasts of primary interest are the comparison of each treatment with the reference treatment $(\psi_{k1}(-\log(1.1))$, and where relevant, the comparison of combination of within domain treatments versus either given alone. For example, if treatment option l is the combination of treatment options k_1 and k_2 given together then the contrasts $\psi^d_{l,k_1}(-\log(1.1))$ and $\psi^d_{l,k_2}(-\log(1.1))$ may be of interest as additional futility checks for intervention l.

Table 2: Intervention futile.

Decision	Comparison	Quantity	Threshold	Action
d_k is futile	d_k vs d_1	$\psi^d_{k1}(-\ln(1.1))$	> 0.95	Drop d_k

7.3 Superiority

At each analysis, the posterior probability that an intervention is superior (in the best regimen, see Best Treatment (treatment in best regimen)) will be compared to a threshold of 0.99. If this threshold is exceeded then a statistical

decision of superiority will be made for the intervention and all other treatment options may be dropped from the set of active interventions in the domain (allocation probability set to 1 for the superior intervention).

Table 3: Intervention superior.

Decision	Comparison	Quantity	Threshold	Action
d_k is superior	d_k vs all d	φ_{dk}	> 0.99	Drop all d but d_k

7.4 Inferiority

At each analysis, the posterior probability that an intervention is superior (in the best regimen, see Best Treatment (treatment in best regimen)) will be compared to a threshold of $0.01/(K'_d - 1)$. If this threshold is not exceeded then a statistical decision of inferiority will be made for the intervention and the treatment option may be dropped from the set of active interventions in the domain (allocation probability set to 0 for the inferior intervention).

Table 4: Intervention inferior.

Decision	Comparison	Quantity	Threshold	Action
d_k is inferior	d_k vs all d	φ_{dk}	$< 0.01/(K'_d - 1)$	Drop d_k

8 Trial Adaptations

As the trial proceeds, some aspects of the trial status may change, for example randomisation probabilities are updated, new sites may start recruiting or treatment availability may change. Additionally, treatments and/or domains can be added or removed based on the trial results themselves, or due to information external to the trial.

8.1 Sequential Analyses

Analyses will be conducted frequently throughout the trial. The analyses will use all the data on participants who have reached the primary endpoint and have outcome data available to inform the current model. The results from the analyses, using the current primary model, inform updates to allocation ratios and statistical decisions.

The first analysis will be conducted after a minimum of $100 \times \max_d(K_d)$, that is, at least 100 participants per active treatment option within the largest domain have been enrolled *and* reached the 28-day primary endpoint. Subsequent analyses will be scheduled at fixed intervals (every 2 months) as long as the trial proceeds. However, if insufficient number participants have enrolled (< 50), the interim analysis can be postponed in increments of 1 month by notification to the DSMC. If recruitment is slower or faster than expected, there may be small or large changes in sample size from one analysis to the next, in which case the timing of analyses may be reviewed. The present schedule is adopted on the basis of logistics and pragmatically managing workload for the analysts, DSMC and personnel involved in data extraction and cleaning.

8.2 Actions Arising from Platform Conclusions

When a trial decision criteria is met, a platform conclusion may be declared and the following updates made. In some instances, despite a statistical decision being reached and a platform conclusion declared the following actions may be delayed. For example, if an intervention is found futile but further information is of interest for secondary outcomes, randomisation could continue.

8.2.1 Superiority

If a statistical decision of intervention superiority in a domain has occurred then, after review, a platform conclusion is declared and the intervention will be allocated with probability 1 at sites where it is available until a new intervention has been added to the domain. If the intervention is not available at a site then randomisation may continue to the non-superior interventions.

8.2.2 Inferiority

If a statistical decision of intervention inferiority in a domain has occurred then, after review, a platform conclusion is declared and the intervention will have its allocation probability fixed to 0 and will be dropped from the set of currently active interventions within the domain.

8.2.3 Effectiveness

If a statistical decision of intervention effectiveness in a domain has occurred then, after review, a platform conclusion is declared and the allocation probability to the domain standard of care option will be set to zero. If the effective intervention is not available at a site, then randomisation to the domain standard of care may still be allowed.

8.2.4 Futility

If a statistical decision of intervention futility in a domain has occurred then, after review, a platform conclusion is declared and this intervention will have its allocation probability fixed to 0 and will be dropped from the set of currently active interventions within the domain.

8.3 Response-Adaptive Randomisation

Following each analysis, the randomisation allocation probabilities will be updated to be proportional to the probability that each regimen results in the lowest log-odds of response among all active regimens, see Best Regimen.

The marginal allocation probability for each intervention will be determined and, in order to maintain a degree of power on the intervention comparisons with standard of care, the allocation probabilities will be corrected to achieve a minimum marginal allocation.

If active, the standard of care option within each domain will have a targeted marginal allocation of $1/K'_d$ where K'_d is the number of active interventions in the domain following the current analysis. If the domain includes only standard of care and one other active intervention, then a minimum allocation probability of $1/3$ will be targeted to either intervention.

The allocation probabilities to regimens are updated as

$$\rho_j \propto \sqrt{\frac{\phi_j}{n_j + 1}}, \quad j = 1, 2, ..., K_A K_B K_C$$

where ϕ_j is the probability regimen j is best and n_j is the number having received regimen j.

The marginal allocation probabilities to each intervention, k in a domain d, are then calculated as

$$\varrho_{dk} = \sum_{\{j|d(j)=k\}} \rho_j$$

where $d(j)$ is the intervention from domain d that is a component of regimen j.

If the value of $\varrho_{d1} < 1/K'_d$, that is the allocation to standard of care in domain d less than target, or $\varrho_{dk} < 1/3$ (in the event where there is only one other active intervention) then the values of ρ_j will be iteratively adjusted until the target marginal allocation is achieved. The correction can be made according to the following rule, assuming that δ is the target marginal allocation

$$\rho_j = \begin{cases} \delta \frac{\rho_j}{\sum_{d(j)=k} \rho_j} & \text{if } d(j) = k \\ (1-\delta) \frac{\rho_j}{\sum_{d(j)\neq k} \rho_j} & \text{if } d(j) \neq k \end{cases}$$

If multiple domains need to be corrected then the above may be iterated over domains until convergence of the allocation probabilities. The corrected regimen allocation probabilities are then used to assign regimens to future

participants. The correction aims to maintain sufficient allocations to standard of care at the expense of potentially reducing the probability a participant receives the most probably best regimen at the time of their enrolment.

Once completed, these updates are communicated to the personal required to update the randomisation system, which will happen by default and not require formal recommendation by the DSMC. The updated allocation probabilities are communicated to the DSMC in the closed interim report.

Finally, we note that the randomisation system adopts the following policies:

- If a new participant is Ineligible or Unavailable for an intervention then any regimen involving that intervention will have $\rho_j = 0$ set for those regimens and the remaining values re-normalised to sum to one when randomising that participant.
- The randomisation process will use the same set of allocation probabilities for all sites, i.e. with no site level stratification. However, given the use of RAR, imbalance in number of persons per arm is expected.

8.4 Adding Interventions

When a new intervention is introduced into a domain, a run-in period will initiate fixed allocation probability of $1/K'_d$ where K'_d is the number of active interventions including the new one. This will last until at least 50 participants have been allocated to the new intervention across all regimens. Existing interventions in the domain will have their RAR allocation probability rescaled to sum to $1 - 1/K'_d$. Once the initial sample size has been exceeded the new intervention will be included in the RAR with all other active interventions.

New domains are introduced with balanced randomisation for each treatment within the new domain until at least 50 participants have been allocated to each new arm.

9 Reporting

Reporting covers considerations relating to internal (e.g. reporting results of sequential analyses to DSMC) and external reporting (e.g. reporting for publication in the academic press). The analyses identified in this document will be included in future trial reports and manuscripts. Exploratory analyses not necessarily identified here may be performed to augment the planned analyses. Any post-hoc or unplanned analyses not specified here will be clearly identified in any statistical reports and manuscripts for publication.

The DSMC has reviewed and accepted the interim reporting template.

9.1 Blinding

When publicly reporting the results of a statistical decision for a domain, the number allocated to each intervention and the number ineligible and/or for whom the domain was unavailable will be disclosed.

To maintain blinding to the performance of interventions in other domains, data on the proportions allocated to these other interventions will not be disclosed when reporting the baseline characteristics of participants in the reported domain.

9.2 Model Parameter Summaries

Where models have been used to inform inference, a summary of model parameters and the pre-specified posterior quantities of interest will be reported. At a minimum, for each model parameter we will report the mean, standard deviation, median, and 95% credible intervals (equal-tailed). Where a transformation is more appropriate, transformed parameters will be reported (e.g. odds-ratios, hazard-ratios etc.). Evidence of effects will be quantified by posterior probabilities over the relevant set of parameter values.

9.3 Participant Progression

When reporting on scheduled analyses (and other reporting when deemed necessary), a CONSORT-style flow diagram will illustrate patient progression through the platform and domains. Number (percentage) of participants randomised to each domain and intervention will be given for all randomised participants. Reasons for ineligibility will be presented by platform, domain, and intervention. Reasons for study withdrawal will be presented by intervention group.

Cumulative randomisation charts will be presented overall and by study site.

9.4 Participant Characteristics

When reporting interim analyses (and other repoting when deemed necessary), the following listings present data which will be collected at baseline. Descriptive summaries of these variables (counts and proportions for discrete, median and inter-quartile range for continuous) will be tabulated and presented in aggregate and by intervention.

Demographic:

- age (years)
- sex

- ethnicity
- weight (kg)
- vaccination status

Co-morbidities:

- chronic cardiac disease
- hypertension
- obesity
- chronic lung disease
- obstructive sleep apnoea
- asthma
- diabetes
- chronic kidney disease
- dialysis
- moderate or severe liver disease
- dementia
- malignant neoplasm in last two years
- iatrogenic immunosuppression
- smoking status

Prognostic factors:

- on room air for any of preceding 24 hours
- peripheral oxygen saturation (if on room air) (SpO2%)
- respiratory rate (breaths/minute)
- Glasgow coma scale (GCS) < 15
- highest recorded Urea last 24 hours (mmol/L)
- highest recorded c-reactive protein (CRP) last 24 hours (g/L)

9.5 Protocol Adherence

The protocol for intervention dosing are provided in the relevant domain-specific appendix to the core protocol. When reporting interim analyses (and other reporting when deemed necessary), adherence to the treatment protocol and protocol deviations will be summarised descriptively for each intervention.

9.6 Graphical and Descriptive Summaries

For each outcome, summaries will be presented in aggregate and by intervention group. Where longitudinal measures are available, cross-sectional summaries will be presented across time-points.

Dichotomous outcomes will be summarised by counts and proportions in each category. Ordinal outcomes will be presented using stacked bar plots, cumulative probability plots, and will be summarised by the frequency of each outcome category. Time-to-event outcomes will be presented using Kaplan-Meier plots and summarised by percentiles of the Kaplan-Meier estimates where available.

9.7 Missing Data

The number and percentage of missing data will be reported for all baseline covariates and outcomes. Where any values have been imputed, this will be reported along with the method of imputation.

References

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ASCOT-ADAPT

Anticoagulation Domain Statistical Analysis Plan

Australasian COVID-19 Trial: An Adaptive Platform Trial

16 May 2022

Anticoagulation SAP Version: 1.0

Protocol Version: ASCOT-ADAPT 6.0

PROTOCOL TITLE	Australasian COVID-19 Trial - Adaptive Platform Trial (ASCOT-ADAPT)
PROTOCOL NUMBER	ERM62646-A
PROTOCOL VERSION	Version 6.0 - 30 Mar 2022
TRIAL REGISTRATION	ACTRN12620000445976
COORDINATING PRINCIPAL INVESTIGATORS	A\Prof Steven Tong[1,2,3] A\Prof Justin Denholm[1,2,4] Professor Joshua Davis[3,5] Professor Bala Venkatesh[6,7,8] Dr Susan Morpeth[9]
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PREPARED BY	Statistical Analysis Committee: ▪ James Totterdell (initial draft) ▪ Mark Jones (subsequent revisions)

Contents

Version History

Version 0.1

May 2021: Draft anticoagulation statistical analysis plan (JT)

Version 0.2

April 2022: Restructuring content and adding additional detail throughout (MJ)

Version 1.0

May 2022: Release for imminent analyses of anticoagulation domain (MJ)

Abbreviations

Abbreviation	Definition
COVID-19	Coronavirus Disease-19
CRF	Case report form
DSA	Domain-specific appendix
FAS	Full analysis set
ISTH	International Society of Thrombosis and Haemostasis
ITT	Intention-to-treat
MCMC	Markov chain Monte Carlo
mMRC	Modified Medical Research Council
PP	Per-protocol
RAR	Response-adaptive randomisation
RT-PCR	Reverse transcription - polymerase chain reaction
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SAR	Serious Adverse Reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
TMT	Trial Management Team

Domain-specific synopsis

TITLE	Australasian COVID-19 Trial: An Adaptive Platform Trial (ASCOT-ADAPT). A multi-centre randomised adaptive platform clinical trial to assess clinical, virological and immunological outcomes in patients with SARS-CoV-2 infection (COVID-19)
PRIMARY OUTCOME	As per the core protocol - a binary variable indicating: ▪ Death from any cause, or ▪ Requirement of new intensive respiratory support (invasive or non-invasive ventilation), or ▪ Vasopressor/inotropic support in the 28 days after randomisation.
SECONDARY OUTCOMES	As per the core protocol: 1. Time to clinical recovery during the first 28 days after enrolment 2. WHO 8-point ordinal outcome scale at day 28 3. All-cause mortality at 28 and 90 days. 4. Days alive and free of hospital by 28 days. 5. Days alive and free of ventilation by 28 days. 6. Presence of patient reported outcome of shortness of breath at days 28 and 90. 7. Quality of life as measured by EQ-5D-5L questionnaire at days 28 and 90.

DOMAIN-SPECIFIC SECONDARY OUTCOMES	1. Confirmed deep venous thrombosis up to 28 days after randomisation 2. Confirmed pulmonary embolus up to 28 days after randomisation 3. Confirmed acute myocardial infarction up to 28 days after randomisation 4. Confirmed ischemic cerebrovascular event up to 28 days after randomisation 5. Any clinically relevant bleeding (non-major or worse), censored at 28 days after randomisation 6. Major bleeding (as defined by ISTH), censored at 28 days after randomisation 7. Clinically relevant non-major bleeding (as defined by the ISTH), censored at 28 days after randomisation 8. Heparin-induced thrombocytopenia during index hospitalisation, censored at 28 days after randomisation 9. Other confirmed thrombotic event up to 28 days after randomisation 10. Any confirmed thrombotic event up to 28 days after randomisation
STUDY DOMAINS	The following domains were open to recruitment at participating sites: 1. Antiviral 2. Anticoagulation
STUDY DURATION	November 2020 onward

SAMPLE SIZE	Flexible (see protocol and statistical appendices for details)
INCLUSION CRITERIA	1. Age ≥ 18 years 2. Admitted to an acute-care hospital 3. Confirmed SARS-CoV-2 by nucleic acid testing in the past 14 days 4. Able to be randomised within 14 days of symptom onset 5. At least one symptom or sign attributable to SARS-CoV-2 infection
EXCLUSION CRITERIA	1. Currently receiving acute intensive respiratory support (invasive or non-invasive ventilation) or vasopressor/inotropic support 2. Previous participation in the trial 3. Treating team deems enrolment in the study is not in the best interest of the patient 4. Death is deemed to be imminent and inevitable within the next 24 hours 5. Either the patient or their primary treating clinician are not committed to active treatment
DOMAIN-SPECIFIC INCLUSION CRITERIA	None

DOMAIN-SPECIFIC EXCLUSION CRITERIA	1. Receiving dual antiplatelet therapy 2. The treating clinician intends to continue or commence therapeutic anticoagulation 3. Contraindication to receiving low molecular weight heparin or unfractionated heparin, including the known or suspected history of heparin exposure such as hypersensitivity 4. Severe thrombocytopenia (platelet count less than 30×10^9/L) 5. History of intracranial haemorrhage in the previous 3 months 6. Severe renal impairment, defined as estimated glomerular filtration rate less than $15/\text{ml/min}/1.73^2$ 7. A current or recurrent condition with a high risk of major bleeding (e.g. bleeding disorder), or a baseline coagulation profile (within the previous 3 days) that indicates a high risk of bleeding, that would be considered a contraindication to receive thromboprophylaxis
BLINDING	This will be an open-label study.

1 Introduction

1.1 Background

ASCOT-ADAPT is an investigator-initiated, multi-centre, open-label, randomised controlled Bayesian adaptive platform trial. Patients enrolled in ASCOT-ADAPT and who progress to requiring invasive or non-invasive ventilation can be enrolled in REMAP-CAP (with follow-up data continuing to be collected from these patients for ASCOT).

The anticoagulation domain was developed because COVID-19 is associated with a prothrombotic state, which can manifest as microvascular thrombosis, venous or arterial thrombosis. Identifying interventions that reduce thrombotic complications is therefore a management priority. Specifically, in ASCOT-ADAPT, eligible patients enrolled within the anticoagulation domain are administered low molecular weight heparin at varying dosage. Recent meta-analyses have summarised the knowledge on higher-dose anticoagulation therapy for COVID-19 (Jorda et al., 2022; Kow et al., 2022; Reis et al., 2022; Yasuda et al., n.d.) with Jorda et al. (2022) suggesting: *"there is currently insufficient evidence of survival benefit of therapeutic-dose or intermediate-dose anticoagulation compared with prophylactic-dose anticoagulation in non-critically ill and in critically ill patients hospitalised with COVID-19"*.

1.2 Objectives of domain

The primary objective of the anticoagulation domain is to determine the effectiveness of anticoagulation therapy for patients with COVID-19. Specifically, we hypothesise that the proportion of patients alive and not requiring intensive respiratory or vasopressor support at 28 days after enrolment (primary endpoint for ASCOT-ADAPT) will vary according to anticoagulation dose.

The domain includes a pre-specified objective of evaluating the interactions associated with the combined delivery of anticoagulation and antiviral therapy, which is still active. Therefore, given the relative sample size randomised within each domain, it is more appropriate to report the interaction at the time of revealing the antiviral domain. Additionally, combined reporting would result in the potential risk of revealing information that may compromise the antiviral domain.

1.3 Status

Figure 1 provides a summary of the cumulative enrolment into ASCOT-ADAPT and the progression of the treatment arms for the anticoagulation domain. Nearly all participants in the platform have been randomised within the anticoagulation domain. The vertical dashed lines indicate the times that the interim analyses occurred, which also corresponds to the (approximate) times at which updates to the response adaptive randomisation could be made. The horizontal lines in the lower panel represent the period that each arm was open to enrolment.

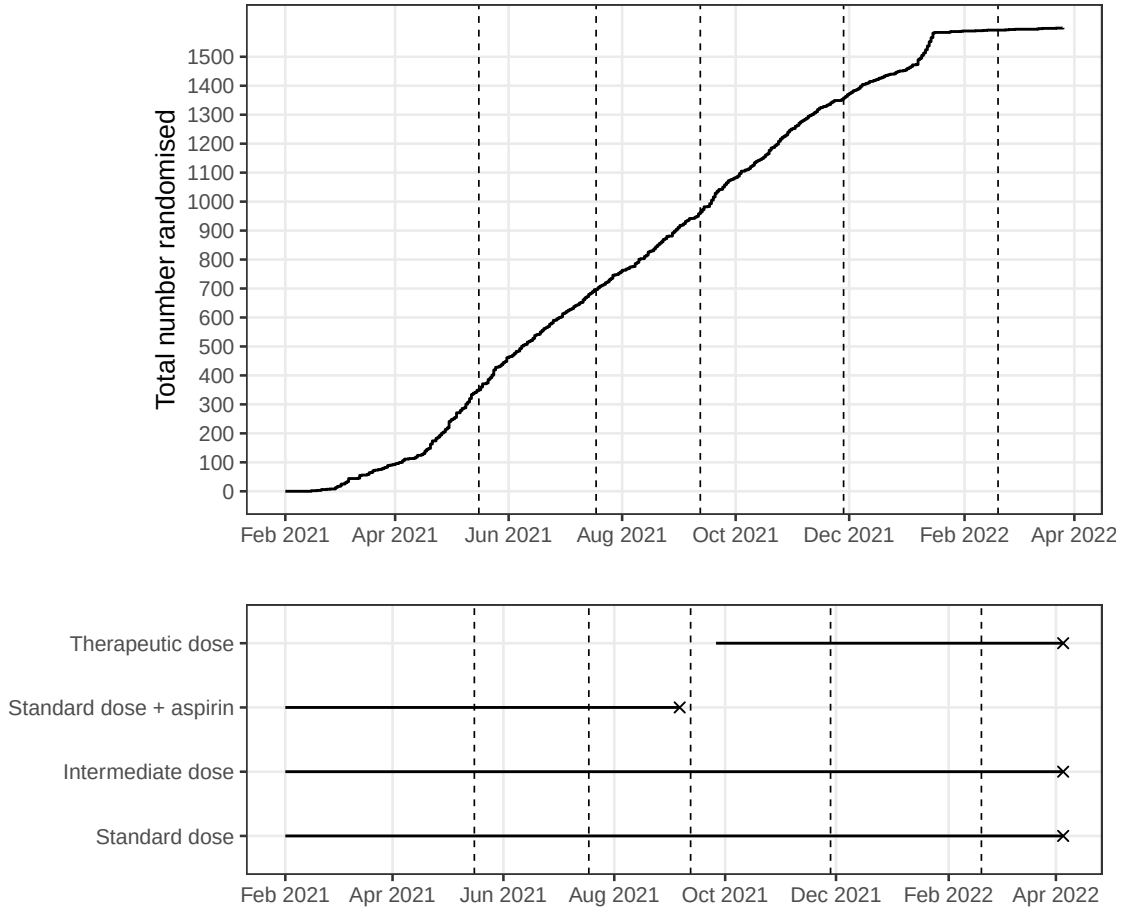

Figure 1: Evolution of anticoagulation domain - dates and adaptation points (vertical lines show time of interim analyses, crosses show time at which arm stopped).

The anticoagulation domain opened for enrolment on 4 Feb 2021 and included treatment arms: standard (prophylactic) dose thromboprophylaxis, intermediate dose thromboprophylaxis and standard dose thromboprophylaxis co-administered with aspirin. On 10 Sept 2021, the prophylactic dose with

aspirin was stopped as a result of external evidence[1] of no benefit (RECOVERY Collaborative Group, 2021). An intermediate dose with aspirin and therapeutic anticoagulation were both proposed, but only therapeutic anticoagulation was activated (late Sep 2021). The introduction of the therapeutic anticoagulation arm was motivated by the findings from the ATTACC, ACTIV-4a and REMAP-CAP collaboration (ATTACC Investigators et al., 2021). On 3 March 2022, the DSMB met and requested that the unblinded DSMB statistician perform a predictive probability assessment of the trial being able to meet pre-specified decision criteria with the scenarios of an additional 260 (expected maximal enrolment with existing funding) or 1,440 (expected maximal enrolment if additional funding secured) enrolments within the anticoagulation domain. Based on these simulations, the DSMB recommended on 21 Mach 2022 that the therapeutic anticoagulation arm be stopped. On 8 April 2022, as a combined result of funding constraints and likely futility, the TMT made the decision to stop enrolment to the anticoagulation domain and complete a definitive analysis for this domain. At the time of the decision, the antiviral (nafamostat and standard of care) and the anticoagulation domains were active, the antiviral domain had enrolled approximately 149 participants and the anticoagulation domain had enrolled 1575 participants. The database components related to the anticoagulant domain will be locked when the last enrolled participant in the anticoagulant domain has reached the 28 day follow up and the data checks/cleaning are completed.

1.4 Purpose and scope of plan

This domain-specific statistical analysis plan (SAP) identifies the data and outlines the procedures for assessing the effectiveness and safety of the anticoagulation domain in ASCOT-ADAPT. The domain-specific SAP is not a standalone document; it is intended to be read in conjunction with the core protocol, the domain specific protocol and the statistical appendix to the core protocol (versions below) all of which are publicly available at the trial website (https://www.ascot-trial.edu.au/pages/resources). The primary analysis, the core secondary analyses and the domain-specific secondary analyses all fall within the scope of this plan. The planned analyses will be included in future trial reports and manuscripts. Exploratory analyses not necessarily identified in this SAP may be performed to support the planned analyses. However, any *post-hoc* or unplanned analyses not

[1]The following reference is the original pre-print source.

specified herein will be identified as such in any statistical reports and manuscripts for publication.

This SAP was written and reviewed by members of the statistical committee and comments were also provided by the trial management team and the domain specific working group members. All contributors were blinded to individual treatment allocations and to the results from each interim analysis that are reported to the Data Safety and Monitoring Board (DSMB) at the time of their contributions.

The following documents were reviewed when preparing this SAP:

- Core protocol for ASCOT-ADAPT Version 6.0
- ASCOT-ADAPT Statistical Analysis Appendix Version 2.2
- Domain-specific appendices to the core protocol
  - Anticoagulation Version 5.0
  - Antiviral Version 5.0

As noted, this SAP is not a standalone document and readers are therefore encouraged to read the core protocol and associated appendices for further details on the conduct of this study, the operational aspects of clinical assessments, the timing for completing a patient in this study, and other design aspects.

2 Study design

2.1 Overview

The generalised study design is outlined in the core protocol and further details are provided in the statistical appendix to the core protocol. The design adopts a Bayesian framework for all analyses. The statistical model (and extensions) for the primary analysis is specified in the statistical appendix to the core protocol. Decision criteria based on posterior probabilities associated with primary analysis model parameters drive all trial adaptations. The primary model will be used in reporting the results for the anticoagulation domain. While there are no within-domain interactions for this domain, an interaction between the anticoagulation and antiviral (nafamostat) domains was pre-specified. However, given that the antiviral domain is still actively recruiting, the between-domain interaction will not be incorporated into the primary model for reporting the anticoagulation domain.

In the statistical appendix to the core protocol, the following statistical decision rules were defined as applicable for adaptations in all domains in the trial:

- **Domain Superiority**: if a single intervention within a domain has posterior probability of being in the best regimen exceeding 99%, then a decision of superiority will be made for that intervention in the domain.
- **Intervention Effectiveness**: if a single non-control intervention within a domain has posterior probability of being more effective than control exceeding 99%, then a decision of effectiveness will be made for that intervention.
- **Intervention Futility**: if a single non-control intervention within a domain has posterior probability less than 5% of being more effective than control by at least an odds ratio of 1.2, then a decision of futility will be made for that intervention.
- **Intervention Equivalence**: if two non-control interventions have a 90% posterior probability of equivalence (odds ratio between $1/1.2$ and 1.2), then a decision of equivalence may be made for those two interventions.

With the exception of the equivalence criteria, the actions associated with each of these decision rules are outlined in the statistical appendix to the core protocol. The decision rule thresholds

were selected accounting for the multiple interim analyses and interventions, based on average trial operating characteristics over a range of trial scenarios generated by statistical simulation and documented in the statistical appendix.

Statistical decisions trigger reporting to the DSMB in closed sessions, who then determine whether the proposed action should be taken, or if there is justification for delaying the action in light of the existing data and/or external evidence. However, while the decision rules direct adaptation, in settings where stopping arises due to other reasons (such as evidence that is external to the trial) emphasis will be placed on the posterior probabilities and parameter summaries.

2.2 Study population

For the platform eligibility, refer to the synopsis presented earlier, the core protocol and the domain-specific appendix. There are no domain-specific inclusion criteria beyond those defined in the core protocol, however, there are domain specific exclusion criteria for the anticoagulation domain. These exclusion criteria apply in addition to those criteria listed in the core protocol. Specifically, participants will be excluded from the anticoagulation domain if any of the following are met:

- Receiving dual antiplatelet therapy
- The treating clinician intends to continue or commence therapeutic anticoagulation
- Contraindication to receiving low molecular weight heparin or unfractionated heparin, including the known or suspected history of heparin exposure such as hypersensitivity.
- Severe thrombocytopenia (platelet count less than 30 $\times 10^9$/L)
- History of intracranial haemorrhage in the previous 3 months
- Severe renal impairment, defined as estimated glomerular filtration rate less than $15/\text{ml}/\text{min}/1.73^2$.
- A current or recurrent condition with a high risk of major bleeding (e.g. bleeding disorder), or a baseline coagulation profile (within the previous 3 days) that indicates a high risk of bleeding, that would be considered a contraindication to receive thromboprophylaxis.

There are also intervention specific exclusion criteria for the standard thromboprophylaxis plus aspirin arm:

- Receiving an antiplatelet agent
- Hypersensitivity to aspirin

2.3 Outcomes

For all core outcomes, refer to the synopsis presented earlier, the core protocol and the domain-specific appendix. In addition to the core outcomes, the domain-specific outcomes (all of which will consider death when reported) include:

- Confirmed deep venous thrombosis (DVT) up to 28 days after randomisation
- Confirmed pulmonary embolus (PE) up to 28 days
- Confirmed acute myocardial infarction up to 28 days
- Confirmed ischemic cerebrovascular event up to 28 days
- Major bleeding (as defined by ISTH) censored at 28 days after randomisation
- Clinically relevant non-major bleeding (as defined by ISTH), censored at 28 days
- Heparin-induced thrombocytopenia during index hospitalisation, censored at 28 days
- Other confirmed thrombotic event up to 28 days after randomisation

The clinical criteria for each of the above has been captured in the domain-specific appendix. While it was not defined in the anticoagulation domain specific appendix, two aggregated outcome were defined. The first was *any thrombotic event (or death) up to 28 days after randomisation* corresponding to the occurrence of any of the following:

- Confirmed DVT
- Confirmed PE
- Confirmed ischemic cerebrovascular event
- Confirmed acute myocardial infarction
- Confirmed other thrombotic event

The second was *any clinically relevant bleeding (non-major or worse), up to 28 days after randomisation*.

All of the domain-specific outcomes are binary variables. If patients have been discharged from

hospital before day 28, a history of domain specific secondary outcomes will be sought from the patient, person responsible, or supervising medical practitioner during the day 28 follow-up telephone call. Confirmation of diagnosis will be required from hospital medical records, radiological reports, or a supervising medical practitioner.

In addition to core serious adverse reactions, domain-specific adverse events that should be reported as serious adverse reaction (SAR) include:

- Major bleeding (as defined by ISTH definition)
- Heparin-induced thrombocytopenia (HIT)

2.4 Subgroups

The following subgroups (replicated from the statistical appendix to the core protocol) include:

- country/region
- days since symptom onset $\leq$ 7 days or $>$ 7 days
- $<$ 60 years of age or $\geq$ 60 years of age
- receipt of corticosteroid
- receipt of remdesivir
- receipt of other agent intended to be an antiviral agent against SARS-CoV-2
- required supplemental oxygen at time of randomisation or oxygen saturation less than 94% at room air
- participants receiving ACE inhibitor/ATII blocker therapy at the time of presentation

However, we note that data on ACE inhibitor/ATII blocker therapy was not collected.

Pre-specified domain-specific patient subgroups of interest to be explored in the context of the primary analysis include:

- D-dimer above (versus below) upper limit of normal at baseline
- Weight less than 120kg versus greater than 120kg
- Patients already on aspirin or not on aspirin at enrolment

3 Analysis sets

3.1 General principles

The primary analysis population consists of all participants that are randomised to at least one of the interventions in the **anticoagulation domain** and have passed 28 days after randomisation with their primary endpoint status either known or known to be missing. The definitive analysis (that will be reported as the primary result) will be based on both concurrent and non-concurrent controls, using model-based approaches to bridge the overlap between multiple treatments arms, adjust for time trends and make appropriate comparisons (see statistical appendix to the core protocol for detail). However, only the data for those participants who were enrolled into the domain prior to the date that the domain closed will be used. This primary analysis population will be used for all outcomes with participants analysed by the regimen to which they were assigned (see ACS-ITT below).

When a platform conclusion is reached for a specific intervention within the anticoagulation domain, and randomisation to that intervention stops, follow-up of participants receiving that intervention will be completed to day 28 and a definitive analysis undertaken for the domain.

For each of the analysis sets (ITT and per protocol) described below, there may be a subset used for the definitive analysis of an intervention. These subsets are determined by the participants randomisation date, eligibility criteria and the platform conclusion date.

3.2 Intention-to-treat

The intention-to-treat (ITT) population is intended to represent patients reflective of what might be seen if the treatment was used in clinical practice. In the ITT analyses, participants will be analysed according to the regimen and interventions to which they were randomised, irrespective of what they received and their adherence. Participants who were randomised to at least one domain will be included in the Full Analysis Set (FAS) ITT dataset. Participants who were randomised in a specific domain, but subsequently found to be ineligible will be included in the ITT set for that domain.

The datasets applicable to the anticoagulation domain analyses are listed in Table 1. When epoch-specific datasets need to be referred to, we will denote them using a subscript. For example, ACS-ITT$_{t=1}$ denotes the subset of the FAS-ITT dataset that were randomised within the anticoagulation domain in the most recent epoch relative to the current time (each epoch spans a 4 week window, counting backwards in time). The intersection between the anticoagulation and antiviral sets (those that were assigned to both domains) is relevant primarily for the evaluation of the interactions between the anticoagulation and antiviral domains. However, as noted earlier, as the antiviral domain is ongoing, the interaction will be reported in the publication of that domain.

3.3 Per-protocol

The per-protocol (PP) population aims to support identifying treatment effects under ideal (or at least near-ideal) conditions. The domain-specific appendix has outlined how the intervention should be delivered (in terms of dose and duration). The per-protocol population will be represented as participants who were commenced on their allocated treatment arm and received the expected dose on more than 75% of study days. Participants who discontinued their allocated treatment arm due to death, requirement for intensive respiratory or inotropic support, clinically significant bleeding or suspected or confirmed thrombosis are included in the per protocol population (as this was allowed in the protocol).

The datasets applicable to the anticoagulation analyses are listed in Table 2. Epoch-specific datasets are denoted in an analogous manner to those for the ITT datasets.

3.4 Sample size

As the aim of the platform was for perpetual recruitment until a conclusion could be made for all interventions under consideration, no pre-specified sample size was defined. Additionally, given the adaptive design, sample size is a random variable that is conditional on the realised/observed design. To evaluate the platform operating characteristics, simulations assumed a maximum total sample size of 5000 participants.

Table 1: Dataset definitions for use in intention-to-treat analyses.

Name	Abbreviation	Description
Full Analysis Set (ITT)	FAS-ITT	All participants who were randomised to at least one study domain. Participants will be analysed as randomised, irrespective of withdrawal, treatment compliance, or other protocol deviations.
Anticoagulation Set	ACS-ITT	Subset of FAS-ITT who were randomised to the anticoagulation domain.
Antiviral Set	AVS-ITT	Subset of FAS-ITT who were randomised to the antiviral domain.
Anticoagulation ∩ Antiviral	ACS-AVS-ITT	Intersection of ACS-ITT and AVS-ITT.
Intervention specific set	<Intervention>-ITT	Subset of anticoagulation specific ITT who were eligible to be randomised to the intervention of interest and randomised either to that intervention or control

Table 2: Dataset definitions for use in per-protocol analyses.

Name	Abbreviation	Description
Full Analysis Set (PP)	FAS-PP	All participants who were randomised to at least one study domain and satisfied platform, domain, and intervention protocol requirements.
Anticoagulation Set	ACS-PP	Subset of FAS-PP who were randomised to the anticoagulation domain and completed the treatment originally allocated.
Antiviral Set	AVS-PP	Subset of FAS-PP who were randomised to the antiviral domain.
Anticoagulation ∩ Antiviral	ACS-AVS-PP	Intersection of ACS-PP and AVS-PP.
Intervention specific set	<Intervention>-PP	Subset of anticoagulation specific PP who were eligible to be randomised to the intervention of interest and randomised either to that intervention or control

4 Data management

4.1 Data sources

Data will be cleaned blind by members of the TMT and access/extracts will be provided to the analytic team following the protocols used to date for interim analyses.

5 Analysis - general considerations

In the interests of time, the primary analysis and all 28 day secondary outcomes will be implemented and reported publicly prior to all participants reaching the 90 day endpoints. The 90 day outcomes will be analysed subsequently, as soon as practical after the data is available.

5.1 Participant progression

A CONSORT (CONsolidated Standards of Reporting Trials) diagram will be used to show the patient progression for the anticoagulation domain (specific details on other domains will be omitted). A summary of the screening information will be provided dependent on availability. Number (and percentage) of participants randomised to each intervention will be given for all randomised participants by interim analysis. Reasons for ineligibility to the platform and anticoagulation domain and domain-specific interventions will be tabulated. Reasons for study withdrawal will be presented by intervention group.

5.2 Enrolment

Enrolment by site and domain-specific intervention will be tabulated.

5.3 Participant characteristics

Baseline data, as per the statistical appendix to the core protocol will be summarised by domain-specific intervention, including demographics, co-morbidities and prognostic variables (see table template section 12.3). Grouping will be based on the treatments arms involved in the anticoagulation domain and overall.

5.4 Protocol adherence

The protocols for intervention dosing are provided in the relevant sections of the anticoagulation domain appendix to the core protocol. Adherence to the intervention protocol will be summarised

descriptively for each intervention in the domain.

5.5 Visual summaries

Visual summaries will be provided for:

- Cumulative frequency of participants randomised and timepoints at which adaptations occurred (per Figure 1)
- Proportion with the primary outcome by interim analysis and anticoagulant intervention group (showing date of analysis and number of new enrolments) based on concurrent controls and cumulative non-concurrent controls
- Cumulative randomisation charts (overall and by study site)
- Age class distribution
- Temporal evolution of the empirical distribution of the WHO eight-point ordinal outcome scale
- Forest plot of primary outcome in pre-defined subgroups

Additional visual summaries may be requested to support reports or publications.

5.6 Descriptive statistics

Descriptive summaries will be provided for:

- All primary and secondary outcomes
  - Descriptive statistics will be provided for components that make up composite outcomes. For example, the primary outcome is a composite and so descriptive summaries will be provided for the variables that make up the composite, namely, the number of participants requiring vasopressor/inotropic support, the number requiring new intensive respiratory support and the number of deaths.
- Drugs received during hospital stay (participants with discharge records)
- Discharge outcomes

Dichotomous outcomes will be summarised by counts and proportions in each category. Ordinal outcomes will be summarised by the frequency and proportions in each outcome category. Time-

to-event outcomes will be presented using Kaplan-Meier plots and summarised by percentiles of the Kaplan-Meier estimates where available and appropriate.

5.7 Model summaries

Model outputs for each parameter estimate in the linear predictor will be the mean, median, standard deviation, and 95% credible intervals (all credible intervals be equal-tailed percentiles, e.g. 95% credible intervals will range from the 2.5th percentile to the 97.5th percentile). For tabulated summaries, random effects may be integrated out. While model parameters will be adjusted for assignment in other domains, the only intervention effects to be reported will relate to the anticoagulation domain.

The extent of overlap will be considered in comparisons between treatment arms. For example, there is no temporal overlap between the standard dose + aspirin arm and the therapeutic arms.

All models will be parameterised so that an odds-ratio (or relevant parameter) greater than 1 (or other appropriate reference value) indicates that there is an increase in the likelihood of the outcome.

5.8 Missing data

Missingness in the participant characteristics will be explored and reported. Patterns and number of missing data for the primary, secondary and domain specific outcomes will be reported/visualised. Patterns and number of missing data for the covariates involved in the primary model linear predictor will also be reported/visualised. Variables with missingness in excess of 10% will be identified, but no formal imputation model developed. Exploratory analyses examining the associations attributed to missingness may be implemented. For example, intervention specific missingness may be considered. Worst/best scenarios may be assessed for the primary outcome (see 10).

5.9 Diagnostics

Where possible, models will be validated on simulated data. Convergence of MCMC chains will be inspected using standard approaches including traceplots and the Gelman-Rubin diagnostic (R-hat values). Diagnostics reported by Stan (e.g. divergent transitions) will be addressed. Posterior

predictive checks will be used to scrutinise relevant aspects of the models. Should model specification or other issues/concerns arise, the analysts have discretion to make necessary adjustments, subject to ensuring that all changes or updates to the pre-specified models are documented in the clinical trial report and manuscripts.

5.10 Quality assurance

Data verification will be implemented (blinded) via a combination of manual and scripted (automated) checks. All code associated with the analyses will be reviewed by a second unblinded statistician. Results from analyses documented within the trial report will be reviewed and discussed by the statistics WG.

5.11 Software

All data analyses will be performed using R (R Core Team, 2022). Models will be fit in R using Stan (Carpenter et al., 2017) via the `rstan` or `cmdstanr` packages.

6 Primary analysis

The primary analysis (including the priors) will be implemented and reported as specified in the statistical appendix to the core protocol and run on the ACS-ITT population (see earlier). In brief, the primary analysis model is a Bayesian logistic regression model for the binary primary endpoint. The linear predictor includes terms for:

- treatment (all domains)
- ineligibility
- region
- site
- time
- age

For further detail, refer to the statistical appendix to the core protocol. While the model parameters are conditional on intervention assignment within other domains, only intervention contrasts relating to the anticoagulation domain will be made available.

The probabilities for each decision criteria (2.1) will be computed, that is, we will provide the probability of effectiveness, futility, superiority and inferiority based on the pre-specified definitions of these quantities. In addition, the probabilities of each arm being the best intervention in the domain will be provided.

As a minimum, we will also produce summaries of model estimates for comparisons between:

- standard dose vs standard dose + aspirin
- standard dose vs intermediate
- standard dose vs therapeutic
- intermediate vs therapeutic

Other comparisons such as standard vs (pooled intermediate & therapeutic) and therapeutic vs (pooled standard & intermediate) may be produced.

No interactions between intervention domains will be included in the linear predictor.

7 Secondary analysis

Secondary analyses will adopt a linear predictor that has an analogous structure to that used in the primary analysis.

7.1 Time to clinical recovery during the first 28 days after enrolment

Per the core protocol, clinical recovery is defined as the first day, during the 28 days after enrolment, on which a patient satisfies categories 1, 2, or 3 on the WHO eight-point ordinal outcome scale (it will be assumed that the participant is not hospitalised on the first day following discharge and that on the day of discharge the participant is still considered hospitalised but not requiring supplemental oxygen nor ongoing medical care if the site has mistakenly indicated the patient was not hospitalised). This outcome will be modelled per the statistical appendix to the core protocol, specifically, we will use a discrete-time-to-event proportional continuation ratio logistic model.

7.2 WHO 8-point ordinal outcome scale at day 28 after randomisation

The WHO 8-point ordinal outcome ranges from "Not hospitalised, no limitations on activities" (1) to "Death" (8) assessed at day 28 of follow up. Note that admission to a Hospital in the Home unit is not counted as hospitalisation for the purposes of this ordinal scale. Additionally, patients who have been admitted to hospital and transferred to a Hospital in the Home unit will be assessed as either ordinal score 1 or 2. This outcome will be modelled per the statistical appendix to the core protocol, specifically, we will use a cumulative logistic regression model. The proportional odds assumption will be assessed by fitting independent logistic regression models to successive cutpoints.

7.3 All-cause mortality at 28 and 90 days after randomisation

The outcomes was defined as death with the relevant time window and will be modelled per the statistical appendix to the core protocol. Specifically, we will use a logistic regression model.

7.4 Days alive and free of hospital by 28 days after randomisation

This outcome was defined as the number of days alive and free of hospital from randomisation to 28 days, calculated as 28 minus the number of days in the hospital. All patients dying within 28 days will be assigned zero free days. Note that days spent in a Hospital in the Home unit will not be counted as days in hospital as hospital means 'acute-care hospital' for the purposes of this endpoint. The outcome will be modelled per the statistical appendix to the core protocol, specifically, we will use a cumulative logistic regression model. The proportional odds assumption will be assessed by fitting independent logistic regression models to successive cutpoints.

7.5 Days alive and free of invasive or non-invasive ventilation by 28 days after randomisation

This outcome was defined as the number of days alive and free of positive pressure ventilation (invasive or noon-invasive) to 28 days, calculated as 28 minus the number of days on ventilatory support. All patients dying within 28 days will be assigned zero free days. The outcome will be modelled per the statistical appendix to the core protocol, specifically, we will use a cumulative logistic regression model. The proportional odds assumption will be assessed by fitting independent logistic regression models to successive cutpoints.

7.6 Presence of patient reported outcome of shortness of breath at days 28 and 90 post randomisation

This outcome will be modelled per the statistical appendix to the core protocol, specifically, we will use a logistic regression model.

7.7 Modified Medical Research Council (mMRC) breathlessness scale at days 28 and 90 post randomisation

The Medical Research Council (mMRC) breathlessness scale ordinal outcome ranges from "I only get breathless with strenuous exercise" (0) to "I am too breathless to leave the house or I am breathless

when dressing or undressing" (4). This outcome will be modelled per the statistical appendix to the core protocol, specifically, we will use a cumulative logistic regression model. The proportional odds assumption will be assessed by fitting independent logistic regression models to successive cutpoints.

7.8 Quality of life as measured by EQ-5D-5L questionnaire at days 28 and 90 post randomisation

Health-Related Quality of Life (HRQoL) as measured by the EuroQol 5 dimension, 5 level (EQ-5D-5L) questionnaire, and the visual analogue scale (VAS), will be reported descriptively. HRQoL utility values will be calculated using the appropriate population algorithms.

8 Domain-specific secondary analysis

8.1 Any thrombotic event (or death) to day 28

This outcome corresponds to the occurrence of any of the following thrombotic events:

- DVT
- PE
- Acute myocardial infarction
- Ischemic cerebrovascular event
- Other thrombotic event

and will account for the risk of death. This outcome will be reported descriptively and analysed by logistic regression.

8.2 Confirmed deep venous thrombosis up to 28 days

This outcome will be reported descriptively.

8.3 Confirmed pulmonary embolus up to 28 days

This outcome will be reported descriptively.

8.4 Confirmed acute myocardial infarction up to 28 days

This outcome will be reported descriptively.

8.5 Confirmed ischemic cerebrovascular event up to 28 days

This outcome will be reported descriptively.

8.6 Any clinically relevant bleeding (non-major or worse), censored at 28 days after randomisation

This outcome will be analysed by logistic regression.

8.7 Major bleeding (as defined by ISTH) censored at 28 days

This outcome will be reported descriptively.

8.8 Clinically relevant non-major bleeding (as defined by ISTH), censored at 28 days

This outcome will be reported descriptively.

8.9 Heparin-induced thrombocytopenia during index hospitalisation, censored at 28 days

This outcome will be reported descriptively.

8.10 Other confirmed thrombotic event up to 28 days after randomisation

This outcome will be reported descriptively.

9 Safety analyses

Safety analyses will be restricted to descriptive summaries by domain-specific intervention group and overall.

10 Sensitivity analyses

Several sensitivity analyses were identified in the statistical appendix to the core protocol. For this domain, we will run the following sensitivities:

- The primary analysis will be re-run based on the FAS-ITT dataset
- The primary analysis will be re-run based solely on those participants eligible for all interventions in the anticoagulation domain
- The primary analysis will be re-run based solely on concurrently randomised controls
- The primary analysis will be re-run under worst-case scenarios whereby all participants with missing primary outcomes will be set to having met the primary outcome (death or requirement of new intensive respiratory support or vasopressor/inotropic support)
- The primary analysis will be re-run under best-case scenarios whereby all participants with missing primary outcomes will be set to having NOT met the primary outcome (death or requirement of new intensive respiratory support or vasopressor/inotropic support)
- The primary analysis will be re-run on the ACS-PP population (see earlier)
- Secondary analyses will be re-run based solely on contemporaneous controls
- Domain-specific secondary analyses will be re-run based solely on contemporaneous controls

Deviations from the above are at the analysts' discretion but must be reported with a reason for the deviation.

11 Subgroup analyses

Subgroups (see 2.4) will be analysed for the primary outcome per the approach detailed in the statistical appendix to the core protocol. Any additional subgroup analyses will be considered *post-*

hoc and reported as such.

As noted earlier, subgroups analyses are (a) subject to analyst discretion based on their assessment of the suitability of the data (b) will not be explored in any secondary outcome and (c) not contingent on the results from the primary analysis. The rationale for any variation to the approach will be documented in the trial report.

12 Reporting

In the interests of time, the primary results will report only the primary outcome and the 28 day secondary outcomes. The 90 day outcomes will be reported in subsequent manuscripts.

12.1 Blinding

Only information pertaining to the anticoagulation domain will be reported. For example, information on the proportions allocated to other domains will not be disclosed when reporting baseline characteristics.

12.2 Clinical trial report

All results will be documented in a single clinical trial report, which will be used as the basis for the content in all manuscripts to be published.

12.3 Tables

An **indicative** set of shell tables to be reported are specified in the following sections. Statistical tests for comparisons of groups will not be provided.

12.3.1 Participant characteristics at baseline

Table 3: Participant characteristics at baseline

Variable	Std (n = xx)	Std+Aspirin (n = xx)	Int (n = xx)	Thera (n = xx)	Overall (n = xx)
Age					
Median (IQR)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Sex					
Male, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Female, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Weight					
Median, (IQR)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Missing, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Vaccinated					
Yes, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Missing, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Ethnicity					
Indian, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Asian, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
etc, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Smoking					
Current, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Former, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Never, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Missing, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

12.3.2 Baseline co-morbidities

Table 4: Baseline co-morbidities

Variable	Std (n = xx)	Std+Aspirin (n = xx)	Int (n = xx)	Thera (n = xx)	Overall (n = xx)
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Hypertension, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Diabetes, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Obesity, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Asthma, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Chronic lung disease, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Chronic cardiac disease, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Obstructive sleep apnoea, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Iatrogenic immunosuppression, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Chronic kidney disease, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Malignant neoplasm, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate or severe liver disease, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Dialysis, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
HIV infection, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Dementia, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Missing, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

12.3.3 Baseline prognostic variables

Table 5: Baseline prognostic variables

Variable	Std (n = xx)	Std+Aspirin (n = xx)	Int (n = xx)	Thera (n = xx)	Overall (n = xx)
Was the patient on room air for any of the preceding 24 hours?					
Yes, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Missing, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Was the patient's GCS < 15?					
Yes, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Missing, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Peripheral oxygen saturation (SpO2) on room air (Lowest)					
Median (IQR)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Missing, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Highest respiratory rate (breaths/minute)					
Median (IQR)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Missing, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Highest recorded Urea in the last 24 hours (mmol/L)					
Median (IQR)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Missing, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Highest recorded CRP in the last 24 hours (mg/L)					
Median (IQR)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Missing, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
APTT					
Median (IQR)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Missing, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
INR					
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Missing, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Fibrinogen1 (g/L)					
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Missing, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Prothrombin time (sec)					
Median (IQR)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Missing, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Taking aspirin					
Yes, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Missing, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Interventions					
None	xx	xx	xx	xx	xx
Antiviral	xx	xx	xx	xx	xx
Corticosteroids	xx	xx	xx	xx	xx
Anti-inflammatory	xx	xx	xx	xx	xx
Time from onset of symptoms to hospitalisation					
Median (IQR)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)

Table 5: Baseline prognostic variables *(continued)*

Variable	Std (n = xx)	Std+Aspirin (n = xx)	Int (n = xx)	Thera (n = xx)	Overall (n = xx)
Time from hospitalisation to randomisation					
Median (IQR)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)

12.3.4 Summary of primary outcome observations

Table 6: Summary of primary outcome observations

Event	Std (n = xx)	Std+Aspirin (n = xx)	Int (n = xx)	Thera (n = xx)	Overall (n = xx)
Overall (n = xx)					
Proportion with primary outcome	xx.x	xx.x	xx.x	xx.x	xx.x
Death, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Intensive respiratory support, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Vasopressor/inotropic support, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Interim 1 (n = xx)					
Proportion with primary outcome	xx.x	xx.x	xx.x	xx.x	xx.x
Death, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Intensive respiratory support, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Vasopressor/inotropic support, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Interim 2 (n = xx)					
Proportion with primary outcome	xx.x	xx.x	xx.x	xx.x	xx.x
Death, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Intensive respiratory support, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Vasopressor/inotropic support, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note:

Interim sections show primary outcome for those enrolled in the current interval.

12.3.5 Compliance to study drug

Table 7: Compliance to study drug

Variable	Std (n = xx)	Std+Aspirin (n = xx)	Int (n = xx)	Thera (n = xx)	Overall (n = xx)
Time from randomisation to administration of study drug					
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Missing, n (%)	xx (x)	xx (x)	xx (x)	xx (x)	xx (x)
Time on study treatment (days)					
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Missing, n (%)	xx (x)	xx (x)	xx (x)	xx (x)	xx (x)
Cumulative dose of study drug received (ml)					
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Missing, n (%)	xx (x)	xx (x)	xx (x)	xx (x)	xx (x)
Cumulative dose duration (hours)					
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Missing, n (%)	xx (x)	xx (x)	xx (x)	xx (x)	xx (x)
Overall compliance (%)					
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Missing, n (%)	xx (x)	xx (x)	xx (x)	xx (x)	xx (x)

12.3.6 Summary of secondary outcomes for anticoagulation domain

Table 8: Summary of secondary outcomes for anticoagulation domain

Event	Std (n = xx)	Std+Aspirin (n = xx)	Int (n = xx)	Thera (n = xx)	Overall (n = xx)
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Died on or prior to day 28, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Acute myocardial infarction, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Ischemic cerebrovascular event, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Deep vein thrombosis, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Pulmonary embolism, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other thrombotic event (arterial or venous), n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Clinically relevant non-major bleeding, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other thrombotic event, n(%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Unknown, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

12.3.7 Summary of safety outcomes for anticoagulation domain

Table 9: Summary of safety outcomes for anticoagulation domain

Event	Std (n = xx)	Std+Aspirin (n = xx)	Int (n = xx)	Thera (n = xx)	Overall (n = xx)
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Major bleeding as per the ISTH definition, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Clinically relevant non major bleeding, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Heparin-induced thrombocytopenia (HIT), n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Unknown, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note:

Table will be modified as required. For example, serious adverse reactions may be included.

12.3.8 Summary of parameter estimates for primary outcome

Table 10: Summary of parameter estimates for primary outcome

Parameter (Odds-ratio)	Median	95% Credible interval	Mean (SD)	Pr(OR > 1)
Standard + aspirin	x.xx	x.xx - x.xx	0.91 (0.07)	x.xx
Intermedi...	x.xx	x.xx - x.xx	x.xx (x.xx)	x.xx
Therapeutic	x.xx	x.xx - x.xx	x.xx (x.xx)	x.xx
Age >= 60	x.xx	x.xx - x.xx	x.xx (x.xx)	x.xx
Epoch-0 (referant)	x.xx	x.xx - x.xx	x.xx (x.xx)	x.xx
Epoch-1	x.xx	x.xx - x.xx	x.xx (x.xx)	x.xx
...	x.xx	x.xx - x.xx	x.xx (x.xx)	x.xx
Corticosteroids	x.xx	x.xx - x.xx	x.xx (x.xx)	x.xx
Remdesivir	x.xx	x.xx - x.xx	x.xx (x.xx)	x.xx
Standard + aspirin	x.xx	x.xx - x.xx	x.xx (x.xx)	x.xx

Note:

Other contrasts may be reported as will decision summaries.

Analogous tables will be provided for secondary outcomes and decision summaries. Analysts have discretion to vary tables from these definitions where deemed necessary.

12.4 Figures

Figures as listed in 5.5 will be reported.

13 References

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