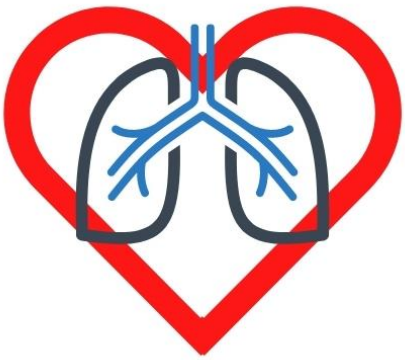

HEAL-COVID

HElping Alleviate the Longer-term consequences of COVID-19 (HEAL-COVID): a national platform trial

HEAL-COVID Protocol

V5.0, 19/08/2021

Joint study Sponsors:
Cambridge University Hospitals NHS Foundation Trust and University of Cambridge
R&D Department,
Box 277,
Cambridge Biomedical Campus,
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UNIVERSITY OF CAMBRIDGE

LIVERPOOL CLINICAL TRIALS CENTRE LCTC

UNIVERSITY OF LIVERPOOL

NIHR | Cambridge Biomedical Research Centre

FUNDED BY

NIHR | National Institute for Health Research

1 PROTOCOL APPROVALS

I, the undersigned, hereby approve this clinical study protocol:

Authorised by Chief Investigator:

Signature: _____ **Date:** Aug 19, 2021

Dr Charlotte Summers

Reader in Intensive Care Medicine, University of Cambridge.

Authorised by Lead Investigator:

Signature: Mark Toshner (Aug 20, 2021 12:29 GMT+1) **Date:** Aug 20, 2021

Dr Mark Toshner

University Lecturer in Translational Respiratory Medicine, University of Cambridge

Authorised on behalf of the Lead Statistician:

Signature: Prof Carrol Gamble (Aug 20, 2021 13:23 GMT+1) **Date:** Aug 20, 2021

Professor Carrol Gamble

Director of Liverpool Clinical Trials Centre & Prof of Biostatistics, University of Liverpool

2 GENERAL INFORMATION

This document describes the HEAL-COVID trial including detailed information about procedures and recruitment. The protocol should not be used as an aide-memoir or guide for the treatment of other patients. Every care was taken in its drafting, but corrections or amendments may be necessary. Any amendments will be notified to the investigators participating in the trial, but sites are advised to consult the HEAL-COVID website to confirm they have the most up to date version. Clinical problems relating to this trial should be referred to Dr Charlotte Summers (Chief Investigator) and Dr Mark Toshner (Lead Investigator), via the CTU.

This protocol defines the participant characteristics required for study entry and the schedule of treatment and follow-up. Participant recruitment will be undertaken in compliance with this document and applicable regulatory and governance requirements. Waivers to authorise non-compliance are not permitted.

Incidence of protocol non-compliance whether reported prospectively (e.g. where a treatment cannot be administered on a scheduled date as a result of public holidays) or retrospectively noted (e.g. as a result of central monitoring) are recorded as protocol deviations. These are monitored and reported to trial oversight committees.

The protocol content is consistent with the SPIRIT (Standard Protocol Item: Recommendations for Interventional Trials 2013), guidelines for inclusion of Patient-Reported Outcomes in clinical trial protocols: the SPIRIT-PRO Extension 2018[1]) and has regard for the Health Research Authority guidance. Regulatory and ethical compliance information is located in section 19.

The Liverpool Clinical Trials Centre is built on the experience of the Liverpool Trials Collaborative which has held full registration status with the UK Clinical Research Collaboration CTU network since its establishment in 2007. Attainment of full registration status follows assessment of standards and systems by an international review panel as reaching the highest quality. The Liverpool Clinical Trials Centre has a diverse trial portfolio underpinned by methodological rigour, a GCP compliant data management system, and quality management system.

3 CONTACT DETAILS

The contact details for the Sponsors, Chief Investigator, Lead Investigator and trial staff involved in trial management, monitoring and analysis, oversight committee members and participating centres are detailed in documents supplementary to the protocol and stored in the Trial Master File.

4 TABLE OF CONTENTS

5 GLOSSARY

AE	Adverse Event
APPT	Activated Partial Thromboplastin Time
APR	Annual Progress Report
AR	Adverse Reaction
CHI	Community Health Index
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CI	Chief Investigator
CK	Creatine kinase
CONSORT	Consolidated Standards of Reporting Trials
CPAP	Continuous Positive Airway Pressure
CRF	Case Report Form
CRN	Clinical Research Network
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trials of an Investigational Medicinal Product
CTU	Clinical Trials Unit
DOAC	Direct oral anticoagulants
DSUR	Developmental Safety Update Reports
ECMO	Extra Corporeal Membrane Oxygenation
EMEA	European Medicines Agency
EQ-5D	EuroQol-5D
ESRD	end-stage renal disease
EU	European Union
EUCTD	European Clinical Trials Directive
EUDRACT	European Clinical Trials Database
FACIT-Fatigue	The Functional Assessment of Chronic Illness Therapy – Fatigue Scale
FACT-GP5	Functional Assessment of Cancer Therapy - Item GP5
FDA	U.S Food and Drug Administration
GAD-2	Generalised Anxiety Disorder -2
GCP	Good Clinical Practice

GP	General Practitioner
HCP	Health Care Professional
HRA	Health Research Authority
IB	Investigator's Brochure
ICER	Incremental cost-effectiveness ratios
ICH	International Conference on Harmonisation
ICHOM	International Consortium for Health Outcomes Measurement
ICU	Intensive Care Unit
IDSMC	Independent Data and Safety and Monitoring Committee
IMNM	Immune-mediated necrotizing myopathy
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
ISF	Investigator Site File (part of the Trial Master File)
ISO	International Organisation for Standardisation
ISRCTN	International Standard Randomised Controlled Trials Number
IWRS	Interactive Web Response System
LCTC	Liverpool Clinical Trials Centre
MA	Marketing Authorisation
MHRA	Medicines and Health Care Products Regulatory Agency
ModRUM	Modular resource use measure
MRC	Medical Research Council
NICE	National Institute for Health and Care Excellence
NHS	National Health Service
NIHR	National Institute for Health Research
NIMP	Non-Investigational Medicinal Product
NRES	National Research Ethics Service
NO	Nitric oxide
NSAIDS	Non-steroidal anti-inflammatory medicinal products
PCL-C	PTSD Checklist – Civilian version
PHQ-2	Patient Health Questionnaire -2
PI	Principal Investigator

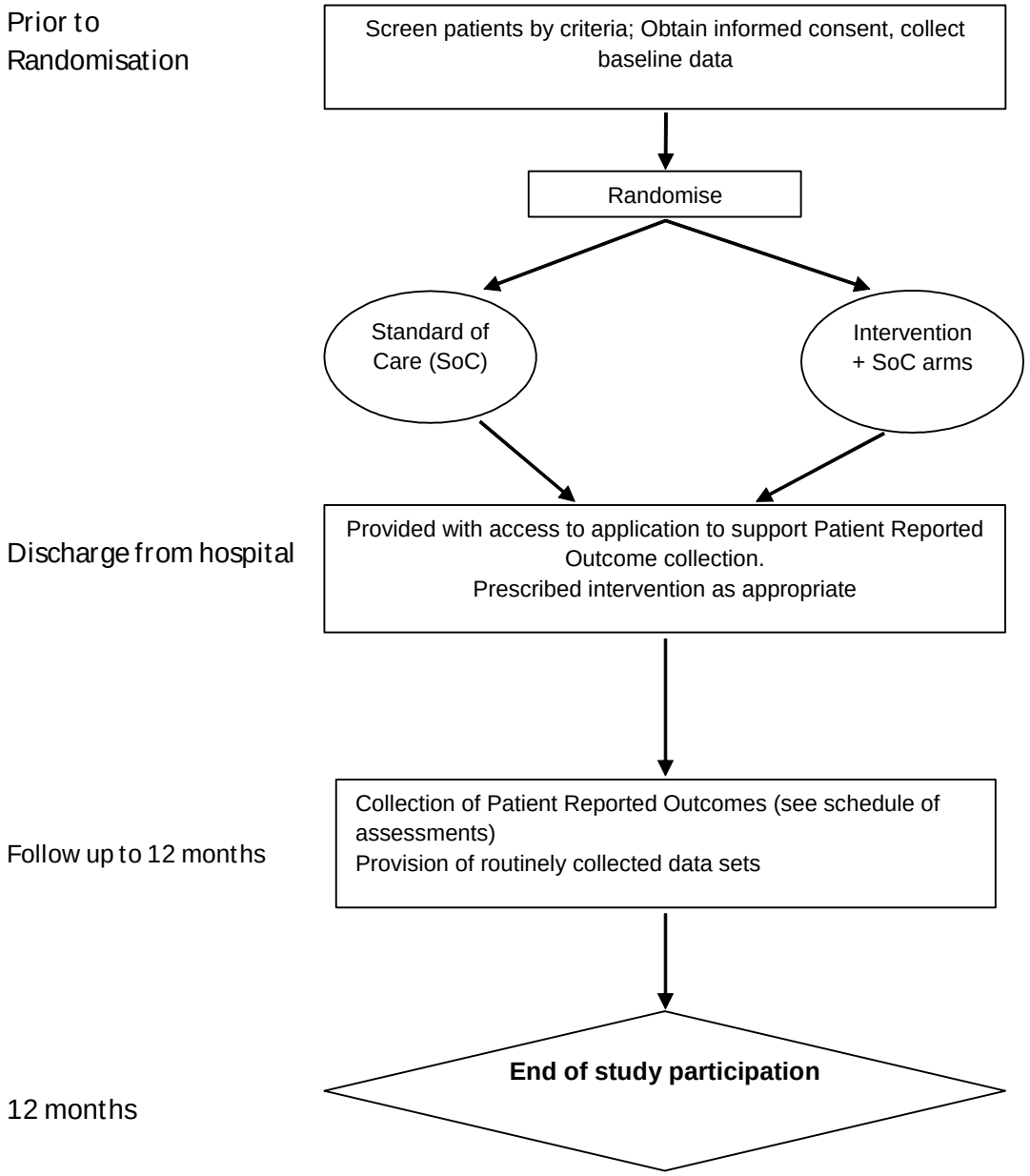
PPI	Public and Patient Involvement
PRO	Patient Reported Outcome
PSF	Pharmacy Site File
PT	Prothrombin Time
PTSD	Post Traumatic Stress Disorder
QA	Quality Assurance
QALY	Quality-Adjusted Life Year
QC	Quality Control
R&D	Research & Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RN	Research Nurse (Registered)
RSI	Reference Safety Information
RSO	Research Support Office
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SmPC	Summary of Product Characteristics
SoC	Standard of Care
SOP	Standard Operating Procedure
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction

6 PROTOCOL OVERVIEW

Full title:	HElping Alleviate the Longer-term consequences of COVID-19: a national platform trial
Acronym:	HEAL-COVID
Phase:	III
Target population:	Hospitalised patients with COVID-19
Sample size:	362 events in total in total for each comparison (approximately 877 patients per arm)
Inclusion criteria:	(i) Greater than or equal to 18 years of age (ii) A hospitalised patient approaching the end of their admission (estimated hospital discharge due at any point within the next 5 days) (iii) SARS-CoV-2 infection associated disease (positive SARS-CoV-2 test relating to this hospital admission) (iv) Written informed consent obtained from participant or participant's legal representative
Generic exclusion criteria:	(i) Known hypersensitivity to trial medication (patient will be excluded from specific arm) (ii) Treatment of COVID-19 related conditions post discharge with any of the trial medications (iii) Long-term pre-hospital administration of trial medication (patient will be excluded from specific arm) (iv) Previous medical history of significant complication (s)/allergies with trial medication or trial medication drug class (v) Medical history that might, in the opinion of the attending clinician, put the patient at significant risk if he/she were to participate in the trial. (vi) Participant not expected to survive 14 days from hospital discharge

Treatment specific exclusion criteria	**Apixaban exclusion criteria** (i) Active clinically significant bleeding (ii) Childs-Pugh C, or worse, chronic liver disease (iii) Known pregnancy or breast-feeding (iv) Coagulopathy: INR known to be greater than 1.7 or platelet count below 70 (v) Known lesion or condition considered by the investigator as a significant risk factor for major bleeding. This may include recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms, or major intraspinal or intracerebral vascular abnormalities (vi) Long-term pre-hospital administration of any other anticoagulant agent to be continued on discharge for non-COVID-19 indications, including but not limited to unfractionated heparin, low molecular weight heparins (e.g. enoxaparin, dalteparin), heparin derivatives (e.g. fondaparinux), and other oral anticoagulants (e.g. warfarin, rivaroxaban, dabigatran **Atorvastatin exclusion criteria** (i) Childs-Pugh C, or worse, chronic liver disease (ii) Unexplained persistent elevation of serum transaminases exceeding five times the upper limit of normal (iii) Known pregnancy or breast-feeding (iv) Treatment with the hepatitis C antivirals glecaprevir/pibrentasvir, ciclosporin, or HIV protease inhibitors (v) Serum creatine kinase concentration known to be in excess of 10 times the upper limit of normal (vi) Long term pre-hospital administration of any statin therapy to be continued on discharge for non-COVID-19 indications
Study Duration	01/02/2021- 31/01/2024
Description of IMP / Intervention:	**Intervention:** (i) Apixaban 2.5mg twice a day for 2 weeks (ii) Atorvastatin 40mg a day for 12 months
	Comparator: Usual standard of care
Primary objective	To determine whether interventions in the post-acute (convalescent) phase of COVID-19 improve longer-term mortality/morbidity outcomes.
Secondary objective	To determine and evaluate treatment-specific and patient-reported outcomes of COVID-19 and their response to intervention. To estimate the cost-effectiveness of treatments.

6.1 Schematic of Study Design



7 ROLES AND RESPONSIBILITIES

7.1 Sponsor

The Cambridge University Hospitals NHS Foundation Trust and University of Cambridge are legally responsible for the study. They will formally delegate specific Sponsoring roles to the Chief Investigator and the Clinical Trials Unit.

7.2 Funder

This study is funded by National Institute for Health Research (NIHR) and the NIHR Cambridge Biomedical Research Centre. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Funder(s)	Financial and Non-financial Support Given	Role
NIHR	£3, 583, 668	This funding source had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results for publication.
NIHR Cambridge Biomedical Research Centre	£160,000	This funding was provided by the Sponsoring institutions of the study to support study set-up and delivery, but has no role in the analysis or interpretation of the data, or the decision to submit results for publication.

Chief Investigator: Charlotte Summers is the Chief Investigator (CI) for the trial and is responsible for overall design and conduct of the trial in collaboration with other members of the study team.

Lead Investigator: Mark Toshner is the Lead Investigator for the trial, and along with the CI is responsible for overall design and conduct of the trial.

Principal Investigators: In each participating centre, a Principal Investigator will be identified to be responsible for the identification and recruitment of study participants, data collection and completion of CRFs, along with follow-up of study patients and adherence to study protocol at site. They will also be responsible for safety reporting and processing any applicable safety information.

Clinical Trials Unit: LCTC at the University of Liverpool, in collaboration with the Chief Investigators, will have overall management responsibility and will be responsible for trial management activities including (but not limited to) study planning, Trial Master File management, safety reporting, data management, randomisation, statistical analysis and participating site coordination.

Patient reported outcome collection: Aparito will provide the digital platform to be used for patient reported outcomes. They are accredited by NHS Digital and have ISO and FDA accreditation. Aparito will provide technical support to trial participants.

7.3 Oversight Committees

HEAL-COVID is subject to oversight from the following committees:

7.3.1 Trial Management Group (TMG)

A Trial Management Group (TMG) will be formed. The TMG are responsible for monitoring all aspects of the progress and conduct of the trial, and will be responsible for the running and management of the trial. The TMG will meet at least monthly unless more frequent meetings are required. Membership of the TMG will be specified in a separate TMG terms and conditions document.

7.3.2 Independent Data and Safety Monitoring Committee (IDSMC)

The role, composition and constitution of the IDSMC will follow NIHR governance guidance (https://www.nihr.ac.uk/documents/research-governance-guidelines/12154 [2]). In the event that adaptations to this guidance are required to support effective trial oversight during a global pandemic, these will be agreed with the funder in advance. Membership of the IDSMC will be specified in a separate document. An IDSMC Charter will be agreed and signed by appointed members.

7.3.3 Trial Steering Committee (TSC)

The role, composition and constitution of the TSC will follow NIHR governance guidance (https://www.nihr.ac.uk/documents/research-governance-guidelines/12154 [2]). In the event that adaptations to this guidance are required to support effective trial oversight during a global pandemic, these will be agreed with the funder in advance. Membership of the TSC will be specified in a separate document. A Terms of Reference will be agreed and signed by appointed members.

7.4 Protocol contributors

Name	Affiliations	Contribution to protocol
Charlotte Summers	University of Cambridge	Study design and protocol drafting
Mark Toshner	University of Cambridge	Study design and protocol drafting
Carrol Gamble	University of Liverpool	Study design, methodology, statistical content, protocol drafting and study conduct
Thomas Jaki	University of Cambridge	Study design, methodology and statistical content and protocol drafting
Martin Landray	University of Oxford	Study design
Danny McAuley	Queen's University of Belfast	Study design
Gisli Jenkins	University of Nottingham	Study design
J Kenneth Baillie	University of Edinburgh	Study design
Emma Bedson	University of Liverpool	Trial management, protocol drafting and regulatory content
Elin Haf Davies	Aparito	Aparito App content
Duncan Richards	University of Oxford	Therapeutic rationale
Melanie Calvert	University of Birmingham	Patient reported outcomes
Paul Wicks	Wicks Digital Health	PPI input and patient reported outcomes
Clare Jackson	University of Liverpool	Data management and monitoring content
Annemarie Docherty	University of Edinburgh	Data linkage
Dyfrig Hughes	Bangor University	Health economics

8 INTRODUCTION

8.1 Background

In December 2019, a cluster of patients with pneumonia of unknown cause was described in Wuhan, China [3]. Named SARS-CoV-2 due to its resemblance to the coronavirus responsible for severe acute respiratory syndrome (SARS-CoV), COVID-19 is the infectious disease caused by SARS-CoV-2. Despite historically unprecedented public health measures, SARS-CoV-2 has rapidly spread across the world. The WHO declared the COVID-19 outbreak a public health emergency of international concern on 30th January 2020.

The acute effects of COVID-19 are now well described. Evidence is emerging of serious longer-term complications occurring in the convalescent phase of the illness in a significant proportion of patients. COVID-19 is a new disease, the natural history of which remains uncertain. Recent data highlight that ~20% of patients develop new or worsened cardiopulmonary symptoms at 40-60-days after hospital discharge [4]. A unique feature of COVID-19 is the high incidence of these cardiovascular and pulmonary complications that may carry long-term implications for morbidity and mortality including venous thromboembolism, persistent lung inflammation, and pulmonary fibrosis; increasingly it appears these may not be confined to the acute phase of the illness, but rather may also occur during the convalescent phase of the illness, thus providing a major contribution to the ill-defined syndrome “Long COVID”.

“Long COVID” is likely to include a constellation of different conditions traversing post-ICU syndromes, significant cardiopulmonary complications, post-viral syndromes and exacerbations of underlying conditions. Patients have reported a range of long-term symptoms associated with Long COVID that have significant impact on their quality of life [5-8]. Though there have been effective acute treatments, there has been little work evaluating longer-term treatment aimed at reducing longer-term complications.

To investigate the role of medium-term convalescent treatment targeting known and emerging complications, an adaptive platform trial will enrol patients at the point of hospital discharge from across centres in the UK.

8.2 Rationale

The trial rationale is that post-hospital outcomes in COVID-19 are potentially modifiable by targeting known pathophysiology. Early intervention post-hospitalisation may reduce morbidity and mortality, reduce symptom burden and improve quality of life. The initial domains of “Long COVID” appropriate for intervention which will be considered are thrombosis, fibrosis and inflammation, but alternative domains may be included as more data relating to the natural history of the disease becomes available. The design is adaptable to fit the interventions and domain of action being tested. Specifically, it allows for:

- a broad range of patients to be enrolled in large numbers
- treatment arms to be added or removed
- shared standard of care (SoC, control) arm so that more patients receive experimental treatments. Eligibility to randomisation to specific treatment arms is based on treatment specific inclusion/exclusion criteria and all comparisons to SoC are within the same eligibility set and concurrent randomisation

8.3 Risk and Benefits

The benefits of participating in this trial outweigh any potential for harm as there are no known treatments, there is significant post-hospital mortality and morbidity due to COVID-19. All treatments included within this trial are repurposed with known safety profiles. Any risks are mitigated by the inclusion and exclusion criteria applicable to that treatment arm. The rationale for each treatment is described within section 12.

8.4 Objectives

The Protocol describes an adaptive platform trial design to provide reliable evidence on the efficacy of post-hospitalisation treatments aiming to improve longer-term clinical outcomes from COVID-19.

In early 2021, when the trial commenced, there were no treatments being assessed in randomised controlled trials targeting the post-hospital convalescent phase of COVID-19. Long-term outcomes for COVID-19 are currently unclear, but early data suggests a significant burden of mortality and morbidity. In this situation, even treatments with only a moderate impact on survival or on hospital resource use are worthwhile. Therefore, the focus of HEAL-COVID is the impact of candidate treatments on mortality and the need for re-hospitalisation.

8.4.1 Primary Objective

The primary objective of HEAL-COVID is to determine whether interventions in the post-hospital (convalescent) phase of COVID-19 improve longer-term mortality/morbidity outcomes.

8.4.2 Secondary Objective(s)

The secondary objectives of HEAL-COVID are to evaluate treatment-specific and patient-reported outcomes of COVID-19 and their response to intervention. An additional objective is to estimate the cost-effectiveness of treatments.

9 OUTCOMES

Outcome selection was informed by the Core Outcome Set developed by Tong et al 2020 [6]. All outcomes relevant to post-discharge are included.

9.1 Primary Outcome

The primary outcome of this study is hospital-free survival, collected through NHS Digital routine health record data. Modifications to the primary outcome for future comparisons may be considered on the basis of emerging data and intervention-specific considerations.

9.2 Economic Outcomes

Incremental cost-effectiveness, from the perspective of NHS resource use and based on quality-adjusted life years estimated from responses to the EQ-5D-5L.

9.3 Secondary Outcomes

Secondary outcomes include:

(i) Days alive and out of hospital

(ii) All-cause mortality

(iii) Hospital readmission after discharge from index hospital admission

(iv) Suspected Serious Adverse Reactions

9.3.1 Patient Reported Outcomes

Patient-reported outcomes assessed using the following measures:

a. FACIT-Fatigue

b. modified MRC Dyspnoea Scale

c. COVID-19 core outcome measure for recovery [9],

d. Patient Health Questionnaire-2 (PHQ-2)

e. Generalized Anxiety Disorder-2 (GAD-2)

f. PTSD Checklist (PCL-2)

g. Quality of life using the EQ5D-5L

h. Intervention tolerability using the FACT-GP5

i. Additional disease specific systemic symptoms

The selection of appropriate patient-reported outcome measures has been informed by: i) the likely mechanism of action in the target population and hypothesised effect (e.g. symptom improvement); ii) outcomes that matter to patients identified through relevant literature [5-8] , and iii) discussions with the HEAL-COVID Patient Participation and Involvement group. Tools are unlikely to be validated in the trial population; however, the team have selected tools that have demonstrated good psychometric properties in other clinical populations. To maximise patient engagement with the study, we have reduced the burden of trial participation on patients and investigators as far as practicable, and have dedicated central team members focussed on patient engagement and support. Additional intervention-specific outcome measures may be added as appropriate for the mechanism of action/ intervention and/ or as emerging knowledge for the natural history of COVID-19 emerges.

The Functional Assessment of Chronic Illness Therapy –Fatigue Scale (FACIT-Fatigue) is a 13-item measure that assesses self-reported fatigue and its impact upon daily activities and function. It has been validated for use across a range of populations [10]. The FACIT-Fatigue has a 7-day recall period and is scored on a 5-point Likert Scale from “0-Not at all”- to “4-Very much”. Individual items scores are summed (2 items of are reversed scored), multiplied by 13 and then divided by the number of items answered with a higher score indicating less fatigue and better quality of life. It takes less than 5 min to complete [11].

The modified MRC Dyspnoea Scale [9] is a modification to the widely used MRC Dyspnoea scale. The item has a 24-hour recall period and is scored on a 5-point Likert scale from “0 - I only get breathless with strenuous exercise” to “4 - I was breathless when dressing, talking or at rest”. It is a new measure developed specifically for COVID-19 trials, but has a high degree of conceptual overlap with its parent clinical measure, the MRC Dyspnoea scale, which is in widescale clinical practice.

The COVID-19 core outcome measure for recovery is a single item intending to measure a return to the pre-illness state. The item has a same day recall period and is scored on a 5-point Likert scale from “0 - Completely recovered” to “4 - Not recovered at all”. It is a new measure developed specifically for COVID-19 trials, but is similar to widely used global clinical impression scales common to many clinical trials.

The Euroqol EQ-5D-5L comprises 5 items plus 1 visual analogue scale. It has been widely validated across a range of diseases and used to assess health outcome from a wide variety of interventions on a common scale, for purposes of evaluation, allocation and monitoring. It is used by the National Institute for Health and Care Excellence (NICE) in health technology assessment [12]. EQ-5D-5L, takes only a few minutes to complete and has a same day recall period [13]. Utilities may be estimated from responses to the EQ-5D-5L, and applying the 3L cross-walk value set [14].

The GAD-2 is a screening tool for generalised anxiety disorder derived from the GAD-7. It comprises the first 2 items of the GAD-7, which are considered as the core anxiety symptoms [15] (“feeling nervous, anxious or on edge”/Not being able to stop or control worrying”). The GAD-2 performs well as a screening tool for three other common anxiety disorders (panic disorder, social anxiety disorder, and PTSD). It has a recall period of two weeks. The GAD-2 has a global score (0-6, no weighting). A higher score indicates increased likeliness of underlying anxiety disorder. The recommended cut-off score for further investigation is ≥ 3. The GAD-2 has been validated in many studies [16] and has retained the same psychometrics properties of the GAD-7 (86% sensitivity/83% specificity).

The PHQ-2 is a screening tool for depression derived from the PHQ-9. It comprises the first 2 items of the PHQ-9 (depressed mood and anhedonia). The PHQ-2 has a recall period of 2 weeks. It has a global score (0-6, no weighting). A higher score indicates increased likeliness of underlying depressive disorder. The recommended cut-off score for further investigation is ≥ 3. The PHQ-2 has been validated in many studies and has shown sensitivity of 83% and specificity of 92% [17].

The PCL-2 is an abbreviated version of the PTSD Checklist – Civilian version (PCL-C) and is used to screen people for PTSD. It comprises 2 items (intrusive memories/distress associated with reminders of the traumatic event). It has a recall period of one month. An individual is considered to have screened positive if the sum of these two items is ≥ 4 [18]. Previous studies have shown that the PCL-2 has good psychometric properties and have shown sensitivity of 0.97 and specificity of 0.58 [18].

The single FACT-G item, GP5, "I am bothered by side effects of treatment," is a summary measure of the overall impact of treatment, based upon its association with the number and degree of adverse events in clinical trials. The single item has demonstrated a significant relationship to overall quality of life as indicated by ability to enjoy life. It has a 7-day recall period and is scored on a 5-point Likert Scale from "0-Not at all"- to "4-Very much" and take less than 1 minute to complete.

Additional disease specific symptomatic questions are informed by data from the ONS [19] and the Long-COVID research group (https://patientresearchcovid19.com).

All PROs will be used in accordance with user manuals, where available.

10 STUDY DESIGN

HEAL-COVID is designed as an adaptive randomised, open label multicentre superiority platform trial. The study is designed using a platform structure that allows multiple different treatments to be evaluated simultaneously and new treatments can be added to the platform. Randomisation will use equal probability between all active treatments a given patient is eligible for and Standard of Care (SoC) as the control arm (i.e. a patient that is eligible for 2 treatments and control will be randomized 1:1:1 between the three arms). All comparative analyses will be based on contemporaneously enrolled patients that were eligible to receive the treatment in this comparison. Random permuted block randomization will be used. To ensure that the platform delivers answers regarding whether treatments are effective in a timely manner, the number of active treatments that are actively recruiting will be limited to three at any point. This is to ensure that a sufficient number of participants can be recruited to the platform as well as limiting the duration required to determine an answer for each intervention.

To further increase the efficiency of the design, treatments will be evaluated for lack of benefit with assessment based on hospital-free survival once half of the required number of events have been observed.

10.1 Blinding

This is an open label study with no blinding requirements. All researchers and participants know which treatment / intervention is being administered.

10.2 Study Setting

Participants will be identified and recruited from hospitals throughout the UK that admit patients with COVID-19. Follow-up data will be collected through data-linkage to routine clinical data sources, and by patient entered data collected via an app/web-based approach.

10.3 Selection of Participating Sites

Criteria for the selection of centres will be described in a separate document 'HEAL-COVID Expression of Interest Form' maintained in the Trial Master File (TMF).

To participate, sites must have equipoise regarding the use of the treatments being tested in HEAL-COVID during the post-hospital phase of COVID-19, and be willing to randomise to all active arms of the study.

Sites fulfilling the trial-specific criteria will be selected to be recruitment centres for the HEAL-COVID trial and will be opened to recruitment upon successful completion of all study-specific conditions. Initiation of sites will be undertaken in accordance with LCTC internal processes. Conditions and documentation required will be detailed on a LCTC Green Light Checklist maintained in the TMF and must be fully completed prior to opening sites to recruitment.

10.4 Selection of Principal Investigators

Principal Investigators will be required to demonstrate relevant experience and commitment during early-stage feasibility assessment. All investigators will have the particular medical expertise necessary to conduct the study in accordance to the protocol and all regulatory and ethical requirements. Written agreement to conduct research as such will be obtained prior to site initiation.

11 ELIGIBILITY CRITERIA

The HEAL-COVID trial aims to recruit 877 patients per active arm and an equal number of matched controls based on sample size calculations described in Section 17.2. All patients or a representative must provide written, informed consent before any study procedures occur (see Section 13.2 for more information regarding informed consent processes) and must meet all eligibility criteria as described below.

11.1 Generic eligibility criteria

11.1.1 Inclusion Criteria

To be included in the trial the participant must be:

(i) greater than or equal to 18 years of age.

(ii) a hospitalised patient approaching the end of their admission (estimated planned discharge at any point within the next 5 days)

(iii) SARS-CoV-2 infection associated disease (positive SARS-CoV-2 test relating to this hospital admission).

(iv) written informed consent obtained from participant or participant's legal representative.

11.1.2 Exclusion Criteria

The presence of any of the following will preclude participant inclusion:

(i) known hypersensitivity to trial medication (patient will be excluded from specific arm).

(ii) treatment of COVID-19 related conditions post discharge with any of the trial medications

(iii) long-term pre-hospital administration of trial medication (patient will be excluded from specific arm).

(iv) previous medical history of significant complication (s)/allergies with trial medication or trial medication drug class.

(v) medical history that might, in the opinion of the attending clinician, put the patient at significant risk if he/she were to participate in the trial.

(vi) participant not expected to survive 14 days from hospital discharge.

11.2 Treatment Specific exclusion criteria

11.2.1 Apixaban exclusion criteria

The presence of any of the following will preclude participant inclusion in the apixaban arm:

(i) active clinically significant bleeding.

(ii) Childs-Pugh C, or worse, chronic liver disease

(iii) known pregnancy or breast-feeding

(iv) coagulopathy: INR known to be greater than 1.7 or platelet count below 70

(v) known lesion or condition considered by the investigator as a significant risk factor for major bleeding. This may include recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms, or major intraspinal or intracerebral vascular abnormalities.

(vi) long term pre-hospitalisation administration with any other anticoagulant agent to be continued on discharge for non-COVID-19 indications including but not limited to unfractionated heparin, low molecular weight heparins (e.g. enoxaparin, dalteparin), heparin derivatives (e.g. fondaparinux), and other oral anticoagulants (e.g. warfarin, rivaroxaban, dabigatran).

11.2.2 Atorvastatin exclusion criteria

The presence of any of the following will preclude participant inclusion in the atorvastatin arm:

(i) Childs-Pugh C, or worse, chronic liver disease

(ii) unexplained persistent elevations of serum transaminases exceeding five times the upper limit of normal.

(iii) known pregnancy or breast-feeding.

(iv) treatment with the hepatitis C antivirals glecaprevir/pibrentasvir, ciclosporin or HIV protease inhibitors.

(v) serum creatine kinase concentration known to be in excess of 10 times the upper limit of normal.

(vi) Long term pre hospital administration of any statin therapy to be continued on discharge for non-COVID-19 indications

11.3 Co-enrolment Guidelines

Where recruitment into another trial is considered to be appropriate and without having any detrimental effect on the HEAL-COVID trial, co-enrolment is permissible. These should be discussed with the CI so that the detrimental effect can be explored and agreed present/absent.

12 TRIAL TREATMENT

12.1 Introduction

Eligible participants will be randomised between standard of care and the currently enrolling arms for which a participant meets the inclusion criteria and none of the exclusion criteria.

IMP will be supplied by the hospital pharmacy in accordance with all applicable guidelines. All therapeutic arms will be commenced on the advice of the UK COVID-19 Therapeutics Advisory Panel, in discussion with the Chief Medical Officer for England. The Chief Investigator and Lead Investigator retain the absolute right not to incorporate recommended therapies into HEAL-COVID.

12.2 Standard of Care

Standard of care will align with contemporaneous best practice and include therapies patients would receive outside of the framework of the trial.

12.3 Apixaban

12.3.1 Rationale and description

COVID-19 is associated with a prothrombotic state that is multifactorial and persists following discharge from hospital [20]. Endothelial dysfunction is likely to be a contributing factor, but other mechanisms are also plausible [21, 22]. For this reason, a thrombosis-specific intervention is included in the study. The available evidence is that venous (as opposed to arterial) thrombosis is the predominant clinical presentation [23, 24]. There is no definitive data to guide drug selection in COVID but trials assessing extended low molecular weight heparin prophylaxis in hospital-associated thrombosis reported no net benefit due to a reduction in venous thromboembolism, with an increased bleeding risk the longer anticoagulation is administered [25], others assessing direct oral anticoagulants (DOACs) have shown a net benefit [26-28]. DOACs are associated with a bleeding risk, but this is lower than warfarin and related anticoagulants. Apixaban is widely used and has a good safety profile including a low incidence of minor adverse effects. On this basis, apixaban 2.5 mg twice a day for 14 days is considered a rational choice to test the potential of DOAC therapy in the post-hospital discharge setting.

Brand name / Active ingredient:	Eliquis / Apixaban
Formulation:	Film-coated tablet
Manufacturer:	Bristol-Myers Squibb-Pfizer
Packaging, storage and stability:	This medicinal product does not require any special storage conditions.
Supplier's name:	Local pharmacy stock
Regulatory Status:	Market Authorised

12.3.2 Preparation, Dosage and Administration

Apixaban 2.5 mg to be taken orally, twice daily, with water, with or without food 14 days only. The site pharmacy will dispense the full course of treatment.

Participants should be given an anticoagulant alert card to carry at all times as per local guidelines.

If a dose is missed, the patient should be instructed to take a tablet immediately and then continue with twice daily intake as before.

For patients who are unable to swallow whole tablets, tablets may be crushed and suspended in water, or 5% glucose in water, or apple juice, or mixed with apple puree and immediately administered orally.

12.3.3 Concomitant Medications/Treatments and Specific Restrictions

Concomitant medications and treatment will be recorded at baseline and for any SSARs.

Special caution is to be taken if patients are treated concomitantly with selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), or non-steroidal anti-inflammatory medicinal products (NSAIDs), including acetylsalicylic acid. Concomitant administration of an anti-platelet agent increases the bleeding risk and appropriate caution should be taken.

Treatment with strong inhibitors of both CYP3A4 and P-gp, such as azole-antimycotics (e.g., ketoconazole, itraconazole, voriconazole and posaconazole) and HIV protease inhibitors (e.g., ritonavir) may increase apixaban exposure by up to 2-fold.

12.3.4 Overdose

Overdose of apixaban may result in a higher risk of bleeding. In the event of haemorrhagic complications, treatment must be discontinued and the source of bleeding investigated. The initiation of appropriate treatment, e.g. surgical haemostasis, the transfusion of fresh frozen plasma or the administration of a reversal agent for factor Xa inhibitors (andexanet alfa) should be considered. Consultation of a coagulation expert should be considered in case of major bleeding. Haemodialysis decreased apixaban AUC by 14% in subjects with end-stage renal disease (ESRD), when a single dose of apixaban 5 mg was administered orally. Therefore, haemodialysis is unlikely to be an effective means of managing apixaban overdose.

12.4 Atorvastatin

12.4.1 Rationale and Description

Follow-up data for those discharged from hospital following admission for COVID-19 shows a substantial risk of death or readmission in the months immediately following admission. The largest available dataset comes from the UK Office for National Statistics; of 47,780 individuals (mean age 65 years, 55% male) followed for a mean of 140 days 29.4% were re-admitted and 12.3% died following discharge [19]. Smaller cohorts from the USA and Spain show that after infectious complication the most common causes of mortality and morbidity are cardiovascular and thrombotic [29, 30]. Prior data relating to other causes of severe respiratory tract infection is consistent with this, and shows that the risk is greatest in the first month following discharge but persists for at least 90 days [31].

Endothelial dysfunction is a cardinal feature of COVID-19 and is a likely contributor to the observed increased morbidity and mortality [32]. Of the available interventions that have potential to ameliorate endothelial dysfunction, the statin class of drugs is considered to have the most suitable profile for evaluation in HEAL-COVID. Other interventions targeting endothelial dysfunction such as ACE inhibitors and ARBs are less suitable for a significant proportion of the target population.

The primary pharmacology of statins is that they inhibit the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, a critical step in the synthesis of endogenous cholesterol [33]. Mevalonate – the product of the HMG-CoA reductase reaction – is also the precursor for many other non-steroidal compounds including moieties used in post-translational modification of proteins. As such, HMG-CoA inhibition impacts a multitude of downstream pathways including inflammatory, thrombotic, anti-microbial and endothelial regulation. In this context statins have been shown *in vitro* to reverse the down regulation of production of nitric oxide (NO) associated with endothelial dysfunction [34, 35]. In hypercholesterolemic, postmenopausal women atorvastatin (10 mg/day) for 8 weeks significantly increased endothelium-dependent dilation as assessed by flow mediated vasodilation of the brachial artery after only two weeks, with further increases after four and eight weeks [36]. In hypercholesterolemic patients with perfusion abnormalities, 12 weeks of treatment with fluvastatin (40 to 80 mg/day) significantly increased myocardial perfusion in ischemic segments by 30% ($p<0.001$). In normal segments, perfusion increased by only 5% ($p<0.005$) [37]. Similarly, vasodilator response to acetylcholine patients with moderately elevated cholesterol levels were significantly increased within 1 month of treatment with simvastatin 20 mg/day, an improvement which was further enhanced after 3 months [38].

The dose-response characteristics for these secondary actions of statins are less well described than the primary pharmacology, but are generally associated with higher dose levels. A wide range of statin drugs is available. Atorvastatin 40 mg/day has been selected on the basis of its very extensive clinical use and widespread availability. It is subject to a modest number of contraindications, warnings and precautions, and has limited potential for drug interactions at the 40 mg/day dose level. Atorvastatin 40 mg/day is therefore considered a rational choice to test the potential therapeutic potential of statins in the post discharge environment.

Active ingredient:	Atorvastatin
Formulation:	Tablet
Manufacturer:	Any brand within NHS stock
Packaging, storage and stability:	This medicinal product does not require any special storage conditions.
Regulatory Status:	Market authorised

12.4.2 Preparation, Dosage and Administration

Atorvastatin 40mg to be taken orally, once daily, for 12 months. Tablets should be swallowed whole with water and can be taken at any time of day, with or without food.

The site pharmacy will dispense at least one month's course of treatment and the remainder of the 12-month course will be prescribed by the participant's GP, or hospital prescribers, depending on local research prescribing policies and capacity.

12.4.3 Concomitant Medications/Treatments and Specific Restrictions

Atorvastatin, like other HMG-CoA reductase inhibitors, may in rare occasions affect the skeletal muscle and cause myalgia, myositis, and myopathy that may progress to rhabdomyolysis. The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of systemic fusidic acid with statins. Fusidic acid should be avoided for the duration of the trial and if necessary atorvastatin should be withheld during administration.

Atorvastatin is metabolised by cytochrome P450 3A4 (CYP3A4) and is a substrate of the hepatic transporters, organic anion-transporting polypeptide 1B1 (OATP1B1) and 1B3 (OATP1B3) transporter. Metabolites of atorvastatin are substrates of OATP1B1. Concomitant administration of medicinal products that are inhibitors of CYP3A4 or transport proteins may lead to increased plasma concentrations of atorvastatin and an increased risk of myopathy. Care should therefore be taken when co-administering atorvastatin with e.g. telithromycin, clarithromycin, rifampicin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole and posaconazole. In cases where co-administration of these medicinal products with atorvastatin is necessary, the benefit and the risk of concurrent treatment should be carefully considered. The risk of myopathy may also be increased with the concomitant use of gemfibrozil and other fibric acid derivates, erythromycin, niacin and ezetimibe. The risk might also be increased at concomitant administration of atorvastatin with other medicinal products that have a potential to induce myopathy, such as fibric acid derivates and ezetimibe. If possible, alternative (non-interacting) therapies should be considered and in the case of short-term treatment of up to 2 weeks atorvastatin should be withheld during administration.

Steady-state digoxin concentrations may increase slightly with co-administration with atorvastatin. Patients taking digoxin should be monitored appropriately.

Co-administration of atorvastatin with an oral contraceptive produced increases in plasma concentrations of norethindrone and ethinyl oestradiol. Women of child-bearing potential should use appropriate contraceptive measures during treatment with atorvastatin.

Although only very rare cases of clinically significant anticoagulant interactions have been reported, prothrombin time as per protocol should be determined before starting atorvastatin in patients taking coumarin anticoagulants and frequently enough during early therapy to ensure there is no significant alteration of prothrombin time.

12.4.3.1 Liver effects

Liver function tests should be performed before the initiation of treatment and periodically thereafter. Patients who develop any signs or symptoms suggestive of liver injury should have liver function tests performed. Patients who develop increased transaminase levels should be monitored until the abnormality resolves. Should an increase in transaminases of greater than five times the upper limit of normal (ULN) be recorded, atorvastatin should be withdrawn.

12.4.3.2 Diabetes Mellitus

Some evidence suggests that statins as a class raise blood glucose. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment, Patients at risk (fasting

glucose 5.6 to 6.9 mmol/L, BMI>30kg/m^2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

12.4.3.3 Miscellaneous

Concomitant intake of large quantities of grapefruit juice and atorvastatin is not recommended.

12.4.4 Overdose

Specific treatment is not available for atorvastatin overdose. Should an overdose occur, the patient should be treated symptomatically and supportive measures instituted, as required. Liver function tests should be performed and serum CK levels should be monitored. Due to extensive atorvastatin binding to plasma proteins, haemodialysis is not expected to significantly enhance atorvastatin clearance.

12.5 Accountability Procedures

For licensed and repurposed treatments, all aspects of treatment supply, storage, and management will be in accordance with standard local policy and practice for prescription medications. Treatment issued to randomised participants will be by prescription, which can be prescribed at the direction of the study site team by any appropriately qualified prescriber. Such study treatments will not be labelled other than as required for routine clinical use. They will be stored alongside other routine medications with no additional monitoring. No accountability records will be kept beyond those used for routine prescriptions.

12.6 Assessment of Compliance

Dispensing data will be collected routinely via NHS Digital and equivalents in the devolved nations.

13 PARTICIPANT TIMELINES AND ASSESSMENTS

13.1 Participant Identification and Screening

Participants will be identified by the study team and participant care teams.

13.2 Informed Consent

The Informed Consent form must be approved by the REC and must comply with GCP, local regulatory and legal requirements. The investigator or designee must ensure that each trial participant, or his/her legally acceptable representative, is fully informed about the nature and objectives of the trial and possible risks associated with their participation. Personal legal representatives (e.g. family member or friend) may be referred to as "Guardian", "Welfare Attorney" or "Nearest Relative" at sites in Scotland.

The investigator or designee will obtain written informed consent from each participant, or telephone consent from the participant's legally acceptable representative before any trial-specific activity is performed. Telephone consent will be followed by written consent by patient/legal representative. The informed consent form used for this trial and any change made during the course of this trial, must be prospectively approved by the REC. The site Principal Investigator will retain the original of each participant signed informed consent form.

Participants can choose not to complete the questionnaires and this will not exclude them from participating in the trial.

Participant information sheets, consent forms and other trial literature are available in a range of languages.

13.2.1 Loss / Regain of capacity.

If a patient who has consented subsequently becomes unable to give informed consent, the previously obtained consent remains valid. If their legally acceptable representative raises concerns regarding their continued participation, this will prompt a reconsideration of their continued participation by the site Principal Investigator.

When consent for a participant's enrolment in the study has been provided by a legal representative and the participant then regains capacity while an inpatient at their recruiting hospital, the research team will provide the participant information sheet and request consent from the participant. Participants will be advised that consent is voluntary and they may withdraw without any detriment to their care. If they choose to continue to participate in the trial they will be requested to sign the consent form.

If a participant for whom consent has been provided by a legal representative regains capacity **after** hospital discharge, the research team will not be aware of this as there are no follow-up visits. As such it will not be possible to approach the participant to provide consent for continued participation. Participants who regain capacity remain able to withdraw from participation if they so wish, without giving a reason and without detriment to their care.

13.3 Eligibility Assessment

Randomisation can be undertaken by any appropriately trained trial team member. Determination of eligibility requires review by individual with prescribing responsibility. The name of the person providing this review must be documented within the randomisation system. Eligibility criteria are described in detail in Section 11.

Eligibility confirmation must be documented in the participant's medical notes. Details must include at a minimum who confirmed full eligibility, when this was confirmed, and when the participant was formally entered into the trial (e.g. randomisation).

13.4 Baseline Assessments

The medical records are source data for baseline assessments. The following information will be recorded on the electronic case report form by the attending clinician or delegate:

- Participants details (e.g. name or initials [depending on privacy requirements], NHS/CHI number [UK only] or medical records number including, date of birth, sex, ethnicity, contact details including email and phone number)
- Legal representative contact details
- Clinician details (name)
- Participant's height and weight
- COVID-19 symptom onset date
- Maximum COVID-19 severity as assessed by need for supplemental oxygen, nasal high flow oxygen, non-invasive ventilation, continuous positive airway pressure (CPAP), invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
- Oxygen saturations on air at time of study randomisation
- Closest routine measurement at point of enrolment of creatinine, urea, liver transaminases (ALT/AST), C-reactive protein, haemoglobin, white cell counts, platelets, APPT, INR or PT, D-dimer, and serum creatine kinase (where available) with date of measurement. N.B. Some blood tests are only undertaken by sites if clinically indicated. Where clinically indicated and undertaken, results should be provided. Additional blood tests for research purposes only are not required.
- Pregnancy test (for women of childbearing potential)
- SARS-CoV-2 test result and date of test
- Major co-morbidities (e.g. chronic cardiac disease, chronic non-asthmatic pulmonary disease, chronic kidney disease, obesity, chronic neurological disorder such as stroke, dementia, malignancy, and liver disease)
- List of medications used to treat COVID-19 (e.g. remdesivir, dexamethasone, tocilizumab)

- Enrolment in CTIMP study during hospital admission (record therapeutic arm if known)
- Date of hospital admission, and date of ICU admission, if applicable
- Contraindication to the study treatment regimens (in the opinion of the attending clinician)
- Smoking status
- Residence in care home
- Functional status
- Confinement (shielding) status
- Vaccination status
- Baseline quality of life/symptom data and resource use data using 10 short questionnaires.
- Name of person completing the form
- The person completing the form will then be asked to confirm that they wish to randomise the patient and will be required to enter their name and e-mail address.

The above list incorporates the requirements of the NIHR Urgent Public Health research programme, and any future amendments to the required characteristics will be enacted.

13.5 Randomisation

Randomisation must only take place following provision of documented informed consent.

The secure randomisation system will confirm eligibility of patients to enter HEAL-COVID and determine which arms the participant may be randomised to. Randomisation will use permuted blocks of equal ratio to each trial arm to which the participant may be allocated.

A username and password, provided by the LCTC will be required to access the randomisation system. Designated research staff will be given access upon completion of training available on the trial website (www.heal-covid.net).

Randomisation: web access http://www.heal-covid.net

If there are any problems with the randomisation systems contact the coordinating CTU on 0151 794 0222, *or via email to trial.team@heal-covid.net*

(Note that the coordinating CTU is open from 0900–1700, Monday–Friday, excluding public holidays)

Following randomisation, the system will send automated emails to the following: PI at site, the person randomising and LCTC. The emails will document the name of the person randomising, the name of the person who confirmed eligibility, the participant's trial identification number, their allocation, and the date/time of randomisation for central monitoring purposes.

Where possible, participants who have opted to complete the patient reported questionnaires should not be notified of their treatment allocation until baseline questionnaires have been completed. Patients should receive their randomised treatment allocation as described in Section 12.

13.6 Baseline Patient Reported Outcomes

Patient-reported outcomes will be collected using the Aparito Atom5 application available for use on Android or iOS operating systems. Baseline completion will usually be in hospital, but with baseline/follow up permitted in all settings (home, hospital, care home, other). The order of administration will be standardised. Participants will be sent reminders, and both research personnel and participants will be provided with training resources to help minimise missing data. For participants who are unable to use the app (due to preference, language or other requirements) nurse interview-led completion (telephone or video conference) will be offered, with translators as required. Alternative language versions of each PRO will be provided when validated translations exist. Participants will be advised that the PRO data will not directly inform their clinical care or be reviewed by the clinical team. Proxy-completion will be permitted if the participant is unable to complete the PRO, will be documented and will be attributable by the provision of a unique onboarding code to use the application.

13.7 Intervention

Once the research team are made aware of the treatment allocation, participants will receive their allocated treatment from the point of hospital discharge. This will be administered as described in Section 12.

13.8 Schedule for Assessments and Follow-up.

All assessments and follow-up are to be conducted in line with the Schedule of Assessments below:

13.8.1 Schedule of Assessments

Procedures		Screening	Baseline	Variable frequency until week 12 **	Monthly	End of trial
Signed Consent Form		X				
Assessment of Eligibility Criteria		X				
Review of Medical History		X				
Review of Concomitant Medications		X				
Participant characteristics			X			
Randomisation		X				
Study Intervention			X			
Clinical Laboratory results^	Creatinine, Urea, ALT/AST, C-reactive protein	X				
	Haemoglobin, white cell count, platelets, D-dimer, APPT and INR or PT, serum creatine kinase, pregnancy test (if applicable)	X				
Patient reported outcomes (if applicable)	FACIT-Fatigue		X	X	X	
	Modified MRC Dyspnoea Scale		X	X	X	
	COVID-19 core outcome measure for recovery		X	X	X	
	Patient Health Questionnaire-2 PHQ		X	X	X	
	Generalized Anxiety Disorder-2 (GAD-2)		X	X	X	
	PTSD Checklist (PCL-2)		X	X	X	
	EQ5D-5L		X		X	
	Tolerability FACT-GP5		X	X	X	
	Additional disease specific systemic symptoms		X	X	X	
	Resource use				X	
NHS Digital and equivalents	Routine digital data				X	X

(X) – As indicated/appropriate.

^ most recent prior to enrolment blood results (dated), where they are available from routine clinical care.

Order of PRO questionnaires will be standardised.

**Highest frequency is weekly during the early stages of the study where the greatest clinical changes are anticipated

All follow-up data will be collected remotely. Participants will not be required to attend any appointments. PROs will be collected using the Aparito ATOM5 app or by telephone/video call whereby the caller will enter the data into the

Aparito database via secure web interface with unique username and password per person. When PROs are collected weekly, there is a window of ±2 days maximum, and when collected monthly this increases to ± 7 days.

Routine data will be collected via NHS Digital and equivalents in the devolved nations. The data collected will include information regarding mortality, hospital readmission, outpatient attendance, study treatment dispensing and resource use over the participant lifespan and beyond.

A non-study specific questionnaire (NIHR Patient Experience Questionnaire) will be completed at months 3 and 12. Participants will be provided with a link to complete the questionnaire that will direct them to the NIHR website/data collection tool. This questionnaire is about their experience of participating in research and does not evaluate the treatments being considered.

13.9 Intervention Discontinuation and Participant Discontinuation/Withdrawal

In consenting to the trial, participants/legal representative agree to all trial activities including administration of trial intervention and treatment and data collection. Every effort should be made to facilitate the completion of these for every recruited participant. If it is not possible to complete these activities (or it is deemed inappropriate) the reasons why should be documented. The following sub-sections describe the different levels of discontinuation/withdrawal.

For participants who lack capacity, if their legal representative withdraws consent for treatment or methods of follow-up then these activities would cease.

13.9.1 Premature Discontinuation of Trial Intervention

The participants may discontinue treatment for reasons including, but not limited to:

(i) Participant-led i.e. request by the participant / legal representative / consultee

(ii) Unacceptable toxicity

(iii) Intercurrent illness preventing further treatment

(iv) Death

(v) Clinician-led:

a. Any change in the participant's condition that justifies the discontinuation of treatment in the clinician's opinion

b. Reasons of non-adherence or non-compliance with treatment or other trial procedures

c. Participant meets an exclusion criterion (either newly developed or not previously recognised)

A decision by a participant (or their legal representative) that they no longer wish to continue receiving study treatment should not be considered to be a withdrawal of consent for follow-up, including patient-reported outcome assessment. However, participants (or their legal representative) are free to withdraw consent for some or

all aspects of the study at any time if they wish to do so. In accordance with regulatory guidance, de-identified data that have already been collected and incorporated in the study database will continue to be used.

13.9.2 Participant Withdrawal from Follow Up

Participants/Legal Representatives are free to withdraw from follow up at any time without providing a reason, though a reason should be recorded if one is given. Those who wish to withdraw from further follow-up will have the data collected up to the point of that withdrawal included in the analyses. The participant will not contribute further data to the study and the CTU should be informed via email to the CTU and via completion of a Withdrawal CRF to be returned to the CTU within 7 days.

If participants/Legal Representatives express a wish to withdraw from follow up, the research team at site should ascertain if this is for all elements of trial follow-up, for example participants may decide to stop completing the questionnaires but still allow routine data capture to be collected for the trial.

In the case of ongoing adverse events, participants should be given appropriate care under medical supervision until the symptoms of any adverse event resolve or the patient's condition becomes stable. Any SSARs will be notifiable to the CTU via processes detailed in Section 15 even if a participant has withdrawn from follow up.

13.10 End of Trial

The end of the trial is defined to be the date on which data for all participants is frozen and data entry privileges are withdrawn from the trial database. The trial may be closed prematurely by the Trial Steering Committee (TSC), on the recommendation of the Independent Data and Safety Monitoring Committee (IDSMC).

Site and closure activities will be centrally coordinated and conducted in accordance with CTU processes regardless of whether the trial closes as planned or prematurely. This includes activities such as:

- End of Trial notification to REC and MHRA
- All site data entered onto the study database, discrepancies raised and satisfactory responses received
- Quality Control checks of the Trial Master File as appropriate

14 SUB-STUDIES

A sub-study asks a separate research question from the parent protocol and does not contribute to the parent protocol's objectives, but uses all or a subset of study participants or samples. As an adaptive design, as further data emerges on complications of COVID-19, the study will explicitly retain the ability to add sub-studies and including recall studies. Ancillary studies will be optional and may require separate consent. These will require additional amendments.

14.1 Frequency of questionnaires

Completion of questionnaires is a challenge faced in many trials. It is important to ensure enough data is collected without over burdening participants. There is little evidence about the timing of questionnaires to ensure optimal completion. A randomised controlled trial will be embedded within HEAL-COVID to look at the impact of questionnaire frequency on questionnaire completion. Participants will be randomised to receive questionnaires at different frequencies. Participants will be randomised to receive questionnaires at either 1) weekly for 4 weeks and then monthly, or 2) weekly for 12 weeks and then monthly.

15 SAFETY REPORTING

Safety reporting in clinical trials is a legal and ethical requirement and it is imperative that all applicable requirements detailed here are followed during the trial.

HEAL-COVID will **only** report Serious Adverse Events that are believed with a reasonable probability to be due to one of the study treatments i.e. a Suspected Serious Adverse Reactions (SSAR).

15.1 Assessment of Safety

The assessment of seriousness of safety events should be performed by an appropriately delegated, medically qualified member of the site research team.

A safety event is assessed as serious if it:

- Results in death;
- Is life threatening (i.e. the investigator considers the event places the subject at immediate risk of death from the experience as it occurred (this does not include an adverse experience that, had it occurred in a more severe form, might have cause death));
- Requires hospitalisation or prolongation of existing hospitalisation (hospitalisation is defined as an in-patient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SSAR);
- Results in persistent or significant disability or incapacity (substantial disruption of one's ability to conduct normal life functions);
- Consists of a congenital anomaly or birth defect (in offspring of subjects, or their partners, taking the IMP regardless of time of diagnosis).

15.2 Assessment of "Causality" - Relationship to Trial Treatment/Intervention

The assignment of the causality should be made using the definitions in the table below:

Table 2: Definitions of Causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship.
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possibly	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probably	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Almost certainly	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

HEAL-COVID will only report events that are assessed as being possibly, probably or almost certainly related to the trial treatment.

In making this assessment, there should be consideration of the probability of an alternative cause (for example, COVID-19 itself or some other condition preceding randomisation), the timing of the event with respect to study treatment, the response to withdrawal of the study treatment, and (where appropriate) the response to subsequent re-challenge.

If any doubt about the causality exists the local investigator should inform the LCTC who will notify the CI. If causality is not determined by the investigator, the causality is considered as related and then the Sponsor representative will add a second causality assessment. The opinion of the treating investigator will never be downgraded.

15.3 Assessment of Expectedness

The Chief Investigator and Lead Investigator for the HEAL-COVID trial are responsible for assessing whether a safety event is expected or unexpected, however the Chief or Lead Investigator will not assess their own patients. There is no requirement for a reporting investigator to assess expectedness.

An event will be considered unexpected if it is not listed within the current and approved reference safety information (RSI) (see section 15.3.1) for the study at the time of the event's onset. The nature, severity, or frequency of the event should be considered–if this is not consistent with that described for the type of event in the RSI the event should be assessed as unexpected.

15.3.1 Reference Safety Information / Information used to Assess Expectedness

Section 4.8 of the summary of product characteristics will be used as the Reference Safety Information (RSI) for HEAL-COVID.

15.4 Time period for Active Monitoring of Safety Events

Active monitoring of safety events experienced by trial participants will be from the period of randomisation until 30 days from last administration of IMP.

Pregnant women will be followed up until the outcome of the birth (see Section 15.5 for more information on reporting pregnancy).

15.5 Reporting of Pregnancy

If pregnancy occurs during either the intervention or follow up period of the trial, this must be notified to the LCTC using the appropriate CRF within 24 hours of the site research team becoming aware. The pregnancy must be followed up by the site research team until outcome and reported to LCTC.

Any pregnancies that result in a safety event assessed as "serious" (e.g. birth defect) must also be reported separately on the appropriate SSAR CRFs. All pregnancies and outcomes reported to LCTC will be notified to the study Sponsor and monitored by trial oversight committees.

All pregnancies and outcomes reported to LCTC will be notified to the study Sponsor and monitored by trial oversight committees.

15.6 Reporting death

If the research team become aware of the death of a participant (whether related to the trial or not) this should be notified to the LCTC using the appropriate CRF.

15.7 Notes on safety reporting

The focus of safety reporting will be on those events that, based on a single case, are likely to be related to the study medication. To this end, anticipated events that are either study efficacy endpoints, consequences of the underlying disease, or common in the study population will be exempted from expedited reporting. Thus, the following events will be exempted from expedited reporting:

(i) Events that are the consequence of COVID-19

(ii) Common events that are the consequence of conditions present preceding randomisation

Any SSARs that are not exempt will be reviewed by the CI (or delegate) and an assessment made of whether the event is "expected" or not (assessed against the RSI). Any SSARs that are not expected would be considered a Suspected Unexpected Serious Adverse Reaction (SUSAR).

15.8 Reporting Procedures

All safety events which are recorded for the study should be reported following the procedures detailed below. The occurrence of a safety event may come to the attention of research staff during routine study visits, from the participant's notes, directly from the participant or by other means.

15.8.1 Investigator Reporting Responsibilities

The PI is responsible for ensuring that all SSARs requiring recording during this study, which the local research team become aware of, are reported to LCTC. It is the responsibility of the PI or delegate to assess the seriousness and causality of events. When LCTC receive the SSAR this will be MedDRA coded and provided to the Chief Investigator for agreement along with the RSI to assess causality and expectedness.

Safety events which meet the definition of a SSAR must be reported to the LCTC on an SSAR form and reported immediately and in no circumstances later than 24 hours from becoming aware where they will be appropriately processed.

The SSAR form should be completed by an appropriately delegated member of the research team; the assessments of seriousness and causality must be performed by an appropriately medically qualified person. Minimum reporting information must be provided in initial reports for all studies.

15.8.2 Reporting an initial or follow-up SSAR

The PI or delegate should ensure the actions below are completed for SSARs:

(i) Research sites should telephone the LCTC on telephone number 0151 794 0222 prior to submitting a SSAR report

(ii) The SSAR form should be transferred securely within 24 hours to the LCTC Central Safety Team (CST) via email lctcsafe@liverpool.ac.uk

(iii) The responsible investigator must notify their R&D department of the event (as per standard local governance procedures)

(iv) The participant must be identified by trial number, age or month and year of birth and initials only. The patient's name should not be used on any correspondence

(v) SSARs must be subsequently followed up in line with the processes below:

- Follow up must continue until clinical recovery is complete and laboratory results have returned to normal, or until the event has stabilised. N.B. Follow-up may continue after completion of protocol treatment if necessary

- Follow-up information is noted on a new SSAR form to be transferred securely to the LCTC as soon as more information becomes available

- Tick the appropriate box on the new SSAR form to identify the type of report; this is dependent on resolution status of the SSAR e.g. follow-up / final

Extra, annotated information and/or copies of pseudonymised test results may be requested from LCTC if required.

15.9 LCTC Responsibilities

All SSARs will be forwarded to the Chief Investigator by LCTC within 24 hours of receiving the minimum information from site. The CI (or delegate) will review information provided by site and for all events assessed as "related" will provide an assessment of "expectedness".

Safety events which are assessed as "serious", "related" and "unexpected" will be expedited to the MHRA as a SUSAR within the following timeframes:

- SUSARs which are fatal or life-threatening – as soon as possible and in any case no later than 7 days after the LCTC is first aware of the event. If the initial report is incomplete, a complete report will be submitted within an additional 8 days.

- SUSARs that are not fatal or life-threatening – within 15 days of the LCTC first becoming aware of the event.

Additionally, SUSARs will be reported to the trial Sponsors and Principal Investigators of participating sites within 14 days.

The LCTC will submit an Annual Safety Report to REC and a Development Safety Update Report to the MHRA on an annual basis.

The PIs at all institutions participating in the trial will be notified of any SUSARs within a reasonable timeline, and if appropriate, accompanied by a summary of the evolving safety profile of the IMP.

Any concerns raised by the TMG/IDSMC or inconsistencies regarding safety reporting noted at a given site may prompt additional training at sites, with the potential for the LCTC to carry out monitoring visits if there is suspicion of unreported SSAR in patient case notes. Additional training will also be provided if there are unacceptable delays in safety reporting timelines.

15.9.1 Safety Reports

Safety reports will be generated during the course of the trial which allows for monitoring of SSARs including reporting rates and SSARs by arm. The LCTC will send annual developmental safety update reports (DSURs)/Annual Progress Reports (APRs) containing a list of all SSARs to the IDSMC, MHRA and main REC. If any safety reports identify issues that have implications for the safety of trial participants, the PIs at all institutions participating in the trial will be notified.

15.9.2 Urgent Safety Measures (USMs)

An urgent safety measure (USM) is a procedure to protect clinical trial participants from any immediate hazard to their health and safety but has not previously been defined by the protocol. It can be put in place prior to authorisation by the REC and the MHRA.

The Sponsor/LCTC will notify the MHRA and REC immediately and, in any event, within three days that such a measure has been taken and the reasons why it has been taken. The initial notification to the REC and MHRA will be by telephone (ideally within 24 hours) and a notice in writing will be sent within three days, setting out the reasons for the USM and the plan for further action. After discussion with the REC and MHRA, further action will be agreed, which may include submission of a substantial amendment, a temporary halt, or permanent termination of the trial.

Following notification, if a substantial amendment is required this must be submitted as soon as possible to the REC and ideally within two weeks to the MHRA. If the study is temporarily halted it may not recommence until authorised to do so by the REC/MHRA. If the study is permanently terminated before the date specified for its conclusion (in the original applications to REC and MHRA), the Sponsor should notify the REC and MHRA within 15 days of the date of termination by submitting the formal End of Trial Notification.

15.10 Contact Details and Out-of-hours Medical Cover

As this study is pragmatic of treatments with well-established safety profiles, emergency and out-of-hours medical care will be in line with usual NHS arrangements and local standard practice; no special provision is required for HEAL-COVID participants. All participants will be provided with a copy of the information sheet, which includes information about their participation and contact details for the local research team who may be contacted if necessary. During office hours (9am-5pm), the CI or delegate are able to provide medical advice in relation to participation by contacting the trial manager on 0151 794 0222

16 ECONOMIC CONSIDERATIONS

16.1 Summary

An economic analysis, adopting the perspective of the NHS, will be conducted in accordance with NICE methods [39], to estimate the cost-effectiveness of the medicines being assessed. The primary economic outcome will be the incremental cost per quality-adjusted life year (QALY) gained, using a trial-based analysis of each "non-futile" intervention over a 12-month time horizon. A health economic analysis plan will be specified, and the economic findings will be reported in accordance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guideline [40].

16.2 Data

Primary care consultations, dispensed medicines and secondary care (Accident and Emergency, Admitted Patient Care, Adult Critical Care, Outpatients) resource use will be based on linked Hospital Episode Statistics and electronic primary care data from NHS-Digital and equivalents in the devolved nations. Participant's use of primary care, secondary care, as well as indirect costs (impact on employment), and out of pocket expenses, will also be measured using the core module of ModRUM (the modular resource use measure [41]), administered via the ATOM5 platform. Unit cost data will be obtained from the most recent versions of NHS reference costs [42], the British National Formulary [43], and the annual compendium of unit costs of health and social care [44].

QALYs will be estimated from responses to the EQ-5D-5L, and applying the 3L cross-walk value set [14]. The number of QALYs experienced by each patient will be calculated as the area under the curve, using the trapezoidal rule.

16.3 Economic Analysis

Mean total costs and QALYs will be used to calculate the incremental cost-effectiveness ratio. Where appropriate, missing resource use or health outcome data will be imputed [45] . Non-parametric, bootstrapped 95% confidence intervals for items of resource use, costs and QALYs will be estimated (10,000 replicates). Estimates of ICERs will be compared with the NICE £20,000 to £30,000 per QALY threshold of cost-effectiveness, and analyses will be conducted to assess scenarios such as different costing perspective, and the sensitivity of the ICER to changes in parameter estimates. Multivariate sensitivity analyses will be applied where interaction effects are suspected, and the joint uncertainty in costs and benefits will be considered through application of bootstrapping and estimation of cost-effectiveness acceptability curves [46].

In a secondary analysis, a lifetime horizon will be considered using a decision analytic model. Survival curves will be extrapolated using accepted methods [47]; and costs and QALY decrements will be estimated from regression models of trial data, supplemented in the case of QALYs, by population statistics [48]. Costs and benefits accruing after the first year will be discounted at 3.5% per annum.

17 STATISTICAL CONSIDERATIONS

17.1 Summary

All analyses for primary and secondary outcomes will be prepared by LCTC and made publicly available within reports, presentations and publications . A more detailed statistical analysis plan [49] developed by the investigators will be available on the study website. The analysis and reporting of the trial will be in accordance with CONSORT guidelines for adaptive designs [50] and CONSORT-PRO [51].

17.2 Sample Size

Using a two-sided log-rank test with a significance level of 1% and a hazard ratio of 1.5 implies that 362 events (re-hospitalisation or death) need to be observed to achieve 90% power for a 1:1 allocation ratio comparing a single active treatment vs SoC. Assuming no drop outs and an event rate of 25% [19] in the SoC arm means that a total of 1754 patients (877 per arm) need to be recruited for one comparison. The significance level has been adjusted to allow for multiplicity. The Table below gives the power for this event rate for different assumptions about the true hazard ratio whilst maintaining the required number of events (362). No adjustment for dropouts has been made due to the use of routine data to ascertain events.

Table 1: Power for a 2 treatment comparison when 362 events have been observed for different true outcomes.

	Hazard ratio				
	1.30	1.35	1.40	1.45	1.50
Power (%)	47.0	61.1	73.5	83.2	90.0

17.3 Method of Randomisation

17.3.1 Allocation Sequence Generation

A randomisation specification document will be written detailing the requirements for the trial according to the Standard Operating Procedures of LCTC. The permuted block randomisation sequence will be generated using STATA version 14 [52]. Allocation ratios will be set to be equal for each trial arm a participant is eligible to be allocated to. Access to the randomisation specification and the allocation sequences generated will be controlled by the LCTC randomisation team.

17.3.2 Concealment and Implementation of Allocation Sequence

Patient allocations will be irrevocably generated upon completion of the central randomisation form by a delegated member of the trial research team. Allocation concealment will be ensured as the service will not release the randomisation code until the patient has been recruited into the trial; this takes place after confirmation of eligibility has been completed. Following randomisation, the system will provide the allocation and participant trial identifier sending automated emails of the same for central monitoring purposes.

17.4 Interim Analyses

For each comparison, an interim analysis will be undertaken once 181 events have been observed across both arms in this comparison. A Cox proportional hazards model will be fit on and the treatment effect estimated. If the treatment effect indicates that the active treatment is no better than control (i.e. if the test statistic is zero or worse) the IDSMC may recommend that the study be stopped for futility and recruitment to this treatment will stop. Treatment of all participants already randomised to this comparison will continue until the planned end point to enable meaningful 12 months outcome data to be collected. No early stopping for benefit is planned unless indicated by the Independent Data Monitoring Committee (IDSMC) if the result is likely to convince a broad range of clinicians including participants in the trial and the general clinical community. The IDMC may, at any point, determine there is a safety concern and require a treatment arm to be stopped immediately.

At the interim review point, a sample size re-estimation will be undertaken. The event rate of re-hospitalisation or death will be estimated for the control group and the sample size may be updated on the basis of the new estimate.

Analyses of the accumulating data will be performed at regular intervals (initially at least monthly with frequency under review by the IDSMC) for review by the IDSMC. These analyses will be performed at the LCTC. The IDSMC will be asked to give advice on whether the accumulated data from the trial, together with results from other relevant trials, justifies continuing recruitment of further patients or further follow-up.

17.5 Adding of arms

New treatments will be added to the platform by recruiting additional participants to the study. When a new potential treatment is to be included in the platform, following regulatory approval of a substantial amendment to the MHRA, it will be added immediately provided that no more than two active treatments currently recruiting to the platform. If the study is already recruiting to three active treatments, then inclusion of a new treatment in the platform will be delayed until one of the current treatment comparisons has reached its recruitment target or has been discontinued for lack of benefit or safety.

17.6 Statistical Analysis Plan

A full statistical analysis plan (SAP) will be written prior to the recruitment of the first participant. The SAP will be version controlled and changes to the SAP documented with rationale for the change. Any changes required to the SAP will be implemented by a statistician who has not had access to the trial database or seen comparative summaries of the data accrued to date.

The main features of the SAP are summarised below:

- Analysis will be by the intention to treat principle (ITT)
- Baseline characteristics will be summarized using descriptive statistics only, formal statistical comparisons will not be made
- The primary outcome will be analysed using a Cox proportional hazards model and the assumption of proportional hazards investigated. The primary outcome is specified as time to event, with secondary interpretation of hospital free survival days. The primary outcome must be interpreted in the light of the

secondary outcome specified as the number of days alive and out of hospital at 12 months (60 days for purposes of interim analysis).

- Secondary outcomes will be analysed where appropriate using regression models dependent on data type (binary, categorical, continuous etc.)
- Hospital outpatient attendance, speciality and reason, cause specific mortality and reasons for readmission will be summarised as per baseline characteristics
- Any subgroup analyses will be prespecified in the statistical analysis plan in light of accumulating evidence. Pre-specified subgroup analysis of the primary outcome will use the same approach to the analysis
- Point estimates will be reported together with 99% confidence intervals
- As much information as possible will be collected about the reasons for missing outcome data; this will be used to inform any imputation approaches employed in the analysis

18 DATA MANAGEMENT AND TRIAL MONITORING

For the HEAL-COVID trial, the responsibilities for Data Management and monitoring are detailed in separate Data Management and Trial Monitoring Plans. These provide details including the internal processes that will be conducted at the CTU throughout the trial. Justification for the level of monitoring is provided within those documents and the trial-specific risk assessment. All data will be managed as per LCTC processes and in line with all relevant regulatory, ethical and legal obligations.

18.1 Source Documents

The case report form (CRF) will be considered the source document for data where no prior record exists and that is recorded directly in the CRF or Aparito App.

Date(s) of informed consent processes (including date of provision of participant information, randomisation number and the fact that the participant is enrolled in a clinical trial (including possible treatment arms) should be added to the patient's medical record chronologically.

18.2 Data Collection Methods

Data will be collected by using web-based applications, and may include additional paper CRFs. All data will be sent to LCTC where it will be securely stored and used for the purposes of monitoring and final analyses. Data will be collected via the following systems:

- **ATOM5 platform (Aparito);** an NHS Digital approved, ISO13485, ISO/IEC 27001:2013 Accreditation and FDA CFR21 Part 11 compliant digital data collection platform designed specifically for clinical trials. Trial participants will be able to submit data via smart phone or web-portal, and data entry will be possible in multiple languages. A dedicated Aparito team member will be available via telephone to assist trial participants with any technical issues they experience with the platform or entering their data. Given the age profile of patients admitted to hospital with COVID-19, consideration has been given to their likely preference/ability for submitting patient reported data via smartphone/website. Patients or their proxy who do not have access to/cannot use a smartphone or internet, will be contacted by a member of the core study research team to determine their preference of format in which they wish to submit patient-reported data (written or via telephone interview), and will be supported to do so in the chosen manner.

- **NHS Digital and the equivalent bodies in the devolved nations**. Patients' randomisation numbers, NHS numbers/CHI numbers, DOBs, randomisation dates and end of participation dates will be sent to NHS Digital (English data), Public Health Scotland's electronic Data Research and Innovation Service (eDRIS) (Scottish data), and the Secure Anonymised Information Linkage (SAIL) databank (Welsh data), where they will be linked with routine healthcare data regarding mortality and hospital readmissions. The NHS/CHI numbers will then be removed, and the linked data will be securely transferred to the LCTC for storage and analysis.

  As there is no equivalent to NHS Digital in Northern Ireland, Northern Ireland sites will provide critical routine healthcare data directly to LCTC.

- **Public Health Scotland Safe Haven.** At the end of the trial, the data from HEAL-COVID will be stored in the PHS National Safe Haven to allow data linkage with other COVID trials.

- Randomisation information will be held within the trial specific randomisation system at LCTC. All routine medical data collected will be stored within a password protected study specific database with audit trail functionality. Delegated LCTC staff will only have access to view data in order to perform monitoring and analysis. Any data transfers will be undertaken using secure methods. Additional detail will be outlined in the Data Management Plan.

18.3 Monitoring

Monitoring is conducted to ensure protection of the participants within the trial, and that all aspects of the trial (procedures, laboratory, trial intervention administration and data collection) are of high quality and conducted in accordance with Sponsor and regulatory requirements.

A detailed Trial Monitoring Plan will be developed and agreed by the TMG and CI to describe who will conduct the monitoring, the frequency, and what level of detail monitoring will be conducted. Monitoring will be dependent on the documented risk assessment of the trial, which determines the level and type of monitoring required for specific hazards. All processes may be subject to monitoring, e.g. enrolment, consent, adherence to trial interventions, accuracy and timeliness of data collection etc.

Trial Oversight Committees related to the monitoring of the trial are detailed in Roles and Responsibilities see section 7.

18.3.1 Central Monitoring

There are a number of monitoring features in place at the CTU to ensure reliability and validity of the trial data, to be detailed in the Trial Monitoring Plan. Data will be checked for missing or unusual values (range checks) and for consistency within participants over time. Other data checks relevant to participant rights and safety will also be regularly performed as per CTU processes. Any suspect data will be queried with sites within the trial database. Individual sites will respond to the queries providing an explanation/resolution to the discrepancies and update the data in the database (where appropriate).

It is noted that there will be limited opportunity for resolution of data queries due to time frames and site capacity. Therefore, all systems used to capture data will have data validations built in to raise warnings at the point of data entry. Any additional data cleaning will be restricted to key data items pertaining to safety and primary outcome.

Site monitoring visits may be 'triggered' in response to concerns regarding study conduct, participant recruitment, outlier data or other factors as appropriate.

18.3.2 Clinical Site Monitoring

All monitoring within HEAL-COVID will be done remotely.

18.4 Risk Assessment

A full and comprehensive risk assessment will be conducted for HEAL-COVID with a monitoring plan developed appropriate to risks identified. Given the adaptive nature of the trial the risk assessment will be reviewed following removal or addition of trial interventions.

18.5 Confidentiality

This trial will collect personal data (e.g. participant names), including special category personal data (i.e. participant medical information) and this will be handled in accordance with all applicable data protection legislation. Data (including special category) will only be collected, used and stored if necessary for the trial (e.g. evidencing provision of consent, for data management and central monitoring, statistical analysis, regulatory reporting, etc.). At all times, this data will be handled confidentially and securely.

CRFs will be labelled with a unique trial screening and/or randomisation number. Verification that appropriate informed consent is obtained will be enabled by sites confirming on the randomisation system that valid consent has been given.

Site-specific study-related information will be stored securely and confidentially at sites and all local relevant data protection policies will be adhered to.

The LCTC as part of The University of Liverpool will preserve the confidentiality of participants taking part in the study. The Cambridge University Hospitals NHS Foundation Trust, University of Cambridge and University of Liverpool are joint data controllers and are registered as Data Controllers with the Information Commissioners Office.

Breaches of data protection principles or regulations identified by LCTC will be notified promptly to the trial Sponsors and The University of Liverpool's Data Protection Officer and appropriate processes followed.

18.6 Quality Assurance and Control

To assure protocol compliance, ethical standards, regulatory compliance and data quality, as a minimum, the following will occur:

(i) The PI and other key staff from each centre will receive initiation training, which will incorporate elements of trial-specific training necessary to fulfil the requirements of the protocol

(ii) The Trial Manager at the LCTC will verify appropriate approvals are in place prior to initiation of a centre and the relevant personnel have completed trial specific training. A greenlight checklist will verify all approvals are in place prior to trial initiation at LCTC and the individual centre

(iii) The trial will be conducted in accordance with procedures identified in the protocol

(iv) The IDSMC, TSC and TMG will provide oversight of the trial

(v) The TMG will monitor screening, randomisation and consent rates between centres and compliance with the protocol

(vi) Data quality checks and monitoring procedures will be undertaken in line with the trial Data Management Plan

18.7 Records Retention

The retention period for the HEAL-COVID research data and information is 10 years from the official End of Trial date.

The PI at each investigational site must make arrangements to store the essential trial documents (as defined by ICH GCP guidelines) including the Investigator Site File and the applicable participant medical records for the full length of the trial's retention period, and will arrange for confidential destruction at the end of this period as instructed by the Sponsor / CTU.

The PI is also responsible for archiving all relevant source documents so that the trial data can be compared against source data after completion of the trial (e.g. in case of inspection from authorities). They must ensure the continued storage of the documents, even if they, for example, leave the clinic/practice or retire before the end of required storage period. Delegation of responsibility for this must be documented in writing.

All other persons and organisations involved in the trial will be responsible for storing and archiving the parts of the TMF relevant to their delegated duties.

The LCTC undertakes to archive as per their contractual requirements; documents will be archived in compliance with the principles of GCP. All electronic CRFs and trial data will be archived onto an appropriate media for long term accessible storage. Hard copies of data will be boxed and transferred to secure premises where unique reference numbers are applied to enable confidentiality, tracking and retrieval.

19 REGULATORY AND ETHICAL CONSIDERATIONS

19.1 Statement of Compliance

The trial will comply with the relevant regulatory processes including The Medicines for Human Use (Clinical Trials) Regulations 2004 (and subsequent amendments) and the established Principles of GCP.

19.2 Ethical Considerations

The trial will abide by the principles of the World Medical Association Declaration of Helsinki and has been designed to be as pragmatic as possible.

19.3 Peer Review

The trial has been peer reviewed by the NIHR Programme.

19.4 Patient and public involvement (PPI)

We are acutely aware of the value of patient and public involvement (PPI) in the design and delivery of the HEAL-COVID study. Meaningful PPI will help us to ensure that the study remains rooted in and connected to the needs, experience and expertise of the people it is designed to serve. To maximise patient engagement with the study, we have reduced the burden of trial participation on patients as far as practicable, and have dedicated team members focussed on patient engagement and support.

Members of the Cambridge University Hospital PPI Group have helped shape the patient facing documents by reviewing materials including the patient information sheet and consent form, posters and questionnaires indicating preferred options and providing feedback on making the process easier for patients recovering from COVID-19.

A dedicated HEAL-COVID PPI Panel will be convened, ensuring a diverse membership including those representing communities disproportionately affected by COVID-19, who are typically under-served by and have low participation rates in research (and who are often under-represented in PPI networks). We aim to recruit patients and carers with experience of Long-COVID and will consult with them to ensure that we find ways of working that are accessible to them. We anticipate that this group will develop a close relationship with the research team, responding to specific tasks and providing critique and insight on the study design, materials and dissemination.

19.5 GCP Training

All PIs must hold evidence of appropriate GCP training or undergo GCP training prior to undertaking any responsibilities on this trial. This training should be updated as appropriate or in accordance with the PIs' Trust's policy. Full GCP training is not mandatory for other site staff. The practical aspects of GCP are covered in the trial specific training that must be completed by staff before taking part in the trial.

19.6 Approvals

The protocol, PIS, consent/assent forms and any proposed public-facing material will be submitted to an appropriate Research Ethics Committee (REC), MHRA, Health Research Authority (HRA) and host institution(s) for written approval.

Any substantial amendments to the original approved documents will be submitted and, where necessary, approved by the above parties before use.

19.7 Protocol Deviation and Serious Breaches

Deviations from, breaches or violations of, or non-compliance to either the protocol, the conditions or principles of GCP, and MHRA and REC requirements are handled based on their nature and severity.

19.7.1 Non-Serious breaches

Protocol deviations and other non-serious breaches of GCP etc. will be managed according to local site and LCTC procedures as appropriate. They will be reported to trial oversight committees.

19.7.2 Serious breaches

A breach of the protocol or GCP is 'serious' if it meets the definition of being "likely to affect to a significant degree the safety or physical or mental integrity of the trial participants, or the scientific value of the trial". This assessment can only be determined by the Sponsor.

If any persons involved in the conduct of the trial become aware of a potential serious breach, they must immediately report this to the LCTC who will in turn notify the Sponsor. The Sponsor will assess the breach and determine if it meets the criteria of a 'serious' breach.

The Sponsor may seek advice from medical expert members of the TMG and/or of the independent oversight committees (IDSMC) in determining whether or not the breach is likely to affect to a significant degree the safety, physical or mental integrity of participants.

The Sponsor may seek advice from the Trial Statistician in determining whether or not the breach is likely to significantly affect the scientific value of the trial. However, the Sponsor retains responsibility for the assessment of whether or not a breach meets the definition of 'serious' and is subject to expedited reporting to MHRA and REC.

Breaches confirmed as 'serious' will be reported to MHRA and REC within seven days by the CTU on behalf of the Sponsor and notified to the TMG and IDSMC at their next meeting.

Any requests for additional information from the Sponsor, TMG, IDSMC, MHRA, or REC, will be promptly actioned by the relevant member(s) of the research team and open communication will be maintained to ensure appropriate corrective actions are taken and documented.

Incidents of protocol non-compliance will be recorded as protocol deviations, the incidence of which are monitored and reported to trial oversight committees.

20 INDEMNITY

Cambridge University Hospitals NHS Foundation Trust, as a member of the NHS Clinical Negligence Scheme for Trusts, will accept full financial liability for harm caused to participants in the clinical trial caused through the negligence of its employees and honorary contract holders. There are no specific arrangements for compensation should a participant be harmed through participation in the trial, but no-one has acted negligently.

The University of Cambridge will arrange insurance for negligent harm caused as a result of protocol design and for non-negligent harm arising through participation in the clinical trial.

21 PUBLICATION AND DISSEMINATION

21.1 Publication Policy

A separate Publication Policy document will be produced.

21.2 Dissemination to Key Stakeholders

On completion of the research, a Final Trial Report will be prepared and submitted to the MHRA and REC. The results of HEAL-COVID will be made publicly available following NIHR approval, as outlined in the Dissemination Plan.

21.3 Data Sharing

At the end of the trial, after the primary results have been published, all requests for access to trial data will be reviewed by the TMG and where at all possible access will be granted.

22 CHRONOLOGY OF PROTOCOL AMENDMENTS

Version 5 (13/08/2021)

Summary of Amendments from Protocol V4.0 to Protocol V5.0		
Protocol Section Number	**Protocol Section Title**	**Summary of Changes**
Front page	N/A	ISRCTN and clinicaltrials.gov registration numbers added. Research Ethics Reference number added.
2	Protocol Approvals	Amended the Chief Investigator's job title
6	Protocol Overview	Generic inclusion criteria ii) and iii) wording amended for clarification. Generic exclusion criterion ii) added to provide further clarification that when sites, as part of standard of care, treat patients with COVID-19 with any of the trial treatments post discharge, participants should be excluded from the trial. Added allergies to exclusion criterion iv). Apixaban exclusion criterion iv) and v) amended for clarification. Criterion vi amended to clarify that patients with long term pre-hospital administration with any other anticoagulant agent to be continued on discharge for non-COVID-19 indications must be excluded from the apixaban arm. Atorvastatin exclusion criterion v) and vi) amended to clarify that patients with long term pre-hospital administration with any statin therapy to be continued on discharge for non-COVID-19 indications must be excluded from the atorvastatin arm.
8.2	Rationale	Minor amendment for clarification to refer to COVID as COVID-19.
9.3	Secondary outcomes	Days alive and out of hospital added as a secondary outcome
9.3.1	Patient Reported Outcomes	Minor amendment for clarification to refer to COVID as COVID-19. COVID-19 outcome measure for recovery upper limit corrected from 5 to 4.
10.3	Selection of Participating Sites	Amendment to clarify that sites will complete an expression of interest form to confirm site suitability. Sites must express equipoise for the treatments in the hospital phase.

11.1.1	Inclusion criteria	Generic inclusion criteria iii) wording amended for clarification.
11.1.2	Exclusion criteria	Generic exclusion criterion ii amended to ensure that when sites, as part of standard of care, treat patients with COVID-19 with any of the trial treatments post discharge, participants should be excluded from the trial. Added allergies to exclusion criterion iv).
11.2.1	Apixaban exclusion criteria	Apixaban exclusion criterion iv) and v) amended for clarification. Apixaban exclusion criterion vi amended to clarify that patients with long term pre-hospital administration with any other anticoagulant agent to be continued on discharge for non-COVID-19 indications must be excluded from the apixaban arm.
11.2.2	Atorvastatin exclusion criteria	Atorvastatin exclusion criterion v amended for clarification. Criterion vi amended to clarify that patients with long term pre-hospital administration with any statin therapy to be continued on discharge for non-COVID-19 indications must be excluded from the atorvastatin arm.
12.3.1	Rationale and description	Typographical error corrected to clarify that apixaban 2.5mg twice a day for 14 days was chosen as a treatment arm for the trial.
12.4.2	Preparation, Dosage and Administration	Section corrected to clarify that atorvastatin can be taken with or without food. Section amended to allow GPs or hospital prescribers to prescribe atorvastatin the remainder of the 12 months course, depending on local research prescribing policies and capacity.
12.5	Accountability Procedures	Wording added to clarify that the trial treatment can be prescribed at the direction of the study site team by any appropriately qualified prescriber.
13.4	Baseline Assessments	Wording has been added to clarify that serum creatine kinase is collected if clinically indicated as part of the eligibility criteria. Wording to clarify that blood test results are only required if available and clinically indicated. Wording added to clarify that pregnancy tests should be given to women of childbearing potential.
13.7	Intervention	Section corrected in line with the flow chart to clarify that treatment should be given from the point of discharge.
13.8.1	Schedule of assessments	Serum creatine kinase has been added to clarify that this should be provided if clinically indicated as part of the eligibility criteria.

17.1	Statistical considerations summary	Minor amendments to clarify that analyses will be made publicly available within reports, presentations, publications.
17.6	Statistical Analysis Plan	Additional information provided regarding the interpretation of the primary outcome. As it must be interpreted in the light of the secondary outcome specified as the number of days alive and out of hospital at 12 months (60 days for purposes of interim analysis).
18.2	Data Collection Methods	Clarified that for Northern Ireland sites, as there is no equivalent to NHS Digital, sites will provide critical routine healthcare data directly to LCTC.
23	References	References now published have been updated.

Version 4.0 (01/04/2021)

Summary of Amendments from Protocol V3.0 to Protocol V4.0		
Protocol Section Number	**Protocol Section Title**	**Summary of Changes**
Front page	CTA reference number	CTA reference number has been added.
6.1	Schematic of Study Design	Flow chart amended to clarify that all the participants will receive the usual Standard of Care and some will also receive the intervention.
13.4	Baseline Assessments	Collection of current medications has been removed as requirement from the baseline assessments. Sites will check the patient's current medication in reference to the exclusion criteria but the data is not required for the analysis.
22	Chronology of protocol amendments	Included a summary of the protocol changes made from v2.0 to v3.0 and v3.0 to v4.0.

Version 3 (24/03/2021)

Summary of Amendments from Protocol V2.0 to Protocol V3.0		
Protocol Section Number	**Protocol Section Title**	**Summary of Changes**
12.4.2	Preparation, dosage and administration	A sentence added to clarify that women of child-bearing potential should use appropriate contraceptive measures during treatment with atorvastatin.
12.4.3.1	Liver effects	Section amended to clarify that should an increase in transaminases of greater than five times the upper limit of normal (ULN) be recorded, atorvastatin should be withdrawn.
15.2	Assessment of "causality" – relationship to trial treatment/intervention	Additional wording included to clarify that if any doubt exists about the causality of an event the local investigator will inform the LCTC. If causality is not determined by the investigator, the causality is considered as related and then the Sponsor representative will add a second causality assessment. The opinion of the treating investigator will never be downgraded.

Version 2 (17/03/2021)

Version 2 was submitted to REC and MHRA and further amendments were requested.

Version 1.0 (15/03/2021)

Version 1 was not submitted to REC or MHRA for approval.

23 REFERENCES

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24 DOCUMENTS SUPPLEMENTARY TO THE PROTOCOL

Documents referenced within the protocol are separately maintained and version controlled. Any of the supplementary documents subject to MHRA and / or Ethical review are submitted as separate version-controlled documents.