ISRCTN15851697 https://doi.org/10.1186/ISRCTN15851697

Helping alleviate the longer-term consequences of COVID-19

Submission date
01/04/2021

Recruitment status
No longer recruiting

Registration date
21/04/2021

Overall study status
Completed

Last Edited
15/01/2024

Condition category
Infections and Infestations

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
COVID-19 is an infectious disease caused by the virus SARS-CoV-2, which has spread across the world since December 2019. The effects of COVID-19 in the early stages of illness are now well known, and research projects have identified new treatments to help patients at this early stage. 1 in 10 patients die 3 months after being discharged from hospital. There is now evidence that around 20% of COVID-19 patients develop new or worsened symptoms, often involving their heart, lungs and circulation, after discharge from hospital. These symptoms are often grouped together as part of a syndrome known as “Long COVID”. Because COVID-19 is a new disease, there is still a lot that we do not know, particularly about the longer-term effects. The aim of this study is to compare different treatments that could prevent or reduce long-term symptoms in COVID-19 patients. The main objective is to determine whether the treatments used improve longer-term outcomes for COVID-19 patients.

Who can participate?
Patients who have been admitted to hospital with COVID-19

What does the study involve?
Participants will be randomly allocated to receive:
1. Apixaban, an anticoagulant or “blood thinner”, twice a day for 2 weeks or
2. Atorvastatin, a statin with anti-inflammatory properties, once a day for 12 months or
3. The usual standard care offered by their hospital, as appropriate to their symptoms and conditions
The researchers will collect a small amount of medical data from the hospital where the participant is being treated, and will also request data from routine health records held by NHS Digital or the equivalent organisations in the devolved nations. This data will be collected for 12 months from the day the participant enters the study, and may include hospital visits, GP visits, referrals, prescriptions and information about deaths.
Participants will also be invited to complete follow-up surveys. This is optional. Surveys can be completed via an app on a smartphone or tablet, or over the phone with a researcher. The surveys will be sent no more frequently than once a week, and include questions relating to symptoms, quality of life, resource use and experience of participating in research.

What are the possible benefits and risks of participating?
Apixaban and atorvastatin have been chosen because patients with Long COVID can have symptoms caused by inflammation and excess clotting. There is potential that the treatment patients are given as part of the study may improve their symptoms and help them recover from their COVID-19 illness more quickly. Though the medications used in HEAL-COVID are well-established treatments with a known profile of safety, like most medication, they also have potential side effects.

Where is the study run from?
Cambridge University Hospitals NHS Foundation Trust and The University of Cambridge jointly Sponsor this study and are responsible for managing it. They are based in the United Kingdom. They have asked that the day-to-day running of the study be carried out by a team based at the Liverpool Clinical Trials Centre (LCTC, part of the University of Liverpool).
Any hospital in the UK looking after COVID patients can take part.

When is the study starting and how long is it expected to run for?
January 2021 to January 2025

Who is funding the study?
National Institute for Health Research (NIHR) (UK)

Who is the main contact?
trial.team@heal-covid.net

Unfortunately, this study is not recruiting public volunteers at this time. This is because the research isn't ready for volunteers yet or the researchers are directly identifying volunteers in certain areas or hospitals. Please do not contact the research team as they will not be able to respond. For more information about COVID-19 research, visit the Be Part of Research homepage.

Contact information

Type(s)
Scientific

Contact name
Dr Charlotte Summers

ORCID ID
https://orcid.org/0000-0002-7269-2873

Contact details
Chief Investigator
University of Cambridge
Department of Medicine
Box 157, Level 5, Addenbrooke's Hospital
Biomedical Campus
Hills Road
Cambridge
United Kingdom
CB2 0QQ

-
trial.team@heal-covid.net

Additional identifiers

ClinicalTrials.gov (NCT)
NCT04801940

Clinical Trials Information System (CTIS)
2021-001187-25

Integrated Research Application System (IRAS)
294861

Central Portfolio Management System (CPMS)
48890

Study information

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

Acronym
HEAL-COVID

Study objectives
Interventions in the post-hospital (convalescent) phase of COVID-19 improve longer-term mortality/morbidity outcomes.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 07/04/2021, South Central - Berkshire Research Ethics Committee (Bristol REC Centre, Whitefriars, Level 3, Block B, Lewins Mead, Bristol, BS1 2NT, UK; +44 (0)207 104 8224, +44 (0)207 104 8270; berkshire.rec@hra.nhs.uk), REC ref: 21/SC/0121

Primary study design
Interventional

Study design
Randomized; Interventional; Design type: Treatment, Drug

Study type(s)
Treatment

Health condition(s) or problem(s) studied
COVID-19 (SARS-CoV-2 infection)

Interventions

The HEAL-COVID trial is an adaptive platform trial that will enrol patients at the point of hospital discharge from centres across the UK. This study will test different treatments among adult patients hospitalised with COVID-19 disease, to investigate whether these treatments can prevent or treat the longer-term symptoms of COVID-19.

Many patients experience new or worsened symptoms after their acute COVID-19 illness, including thrombosis, fibrosis and inflammation, often described as the ill-defined syndrome "Long COVID".

The rationale is that early intervention post-hospitalisation may reduce morbidity and mortality, reduce symptom burden for patients and improve their quality of life.

Patients will be recruited in hospital but treatment will commence on discharge. Two treatments will be examined initially (Apixaban and Atorvastatin), with new treatments to be added via substantial amendments at the direction of the UKCTAP. These treatments have been chosen due to their proven histories as a safe and effective anticoagulant (blood thinner) and anti-inflammatory.

Each treatment arm (initially apixaban and atorvastatin) will be compared to the 'standard care' arm, with the null hypothesis that there is no difference in outcome between the treatments. 877 participants are required for each treatment arm.

The control arm is 'standard care' because there are no known treatments that influence outcomes in COVID-19 disease. All participants in the trial will receive the best available standard care available for any long-term symptoms they develop.

The control arm is shared so that more patients receive experimental treatments, and the randomisation system includes the capability to exclude patients from one treatment arm only if they do not meet the treatment specific exclusion criteria (e.g. hypersensitivity to the drug).

A randomised controlled platform trial design has been chosen as it is the most reliable way to assess the effects of treatment. The design is adaptable in order to allow a broad range of patients to be enrolled in large numbers, with treatment arms to be added or removed. The trial is not blinded and there is no placebo because it is not practical to blind in a multi-arm platform trial and it would add significant complexity to a trial that will need to operate in a very busy clinical environment. It is also not necessary as the primary outcome is hospital-free survival.

Participants will be recruited shortly before discharge from hospital for their initial COVID-19 admission. They will receive the study treatments by prescription from a doctor or prescribing nurse as part of their routine care.

There are no follow-up visits, with primary outcome data being sought from NHS Digital (and the equivalent organisations in Scotland, Wales & Northern Ireland). Secondary outcome data including resource use and patient-reported symptoms/quality of life will be collected via questionnaires completed via a smartphone application or over the phone. EQ5D-5L and resource use questionnaires will be completed monthly. The timing of the other patient-reported questionnaires will be determined by randomisation (either 1:weekly for 4 weeks then monthly or 2:weekly for 12 weeks then monthly).

It is intended that all patients admitted to hospital with COVID-19 who meet the eligibility criteria will be invited to participate Patient groups have been involved in the development of

study materials, including the patient information sheet, poster, website content and survey frequency design.

It is intended that results be published as soon as possible when any treatment arm is removed, either due to clear efficacy or a clear indication that the treatment is no better than standard care. Interim analyses will take place on a regular basis, with an Independent Data & Safety Monitoring Committee meeting monthly to review preliminary data and make recommendations about trial progress.

The results from this study have the potential to change standard care for post-hospital COVID-19 patients as there
are currently no known treatments. As such the publication of these results in a timely manner is a priority.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Apixaban, atorvastatin

Primary outcome(s)
Hospital-free survival collected via linkage to electronic health records or case report form up to 12 months after randomisation.

Key secondary outcome(s)
1. All-cause mortality collected via linkage to electronic health records or case report form up to 12 months after randomisation
2. Hospital readmission after discharge from index hospital admission collected via linkage to electronic health records or case report form up to 12 months after randomisation
3. Suspected serious adverse reactions measured using Case Report Form (CRF) up to 12 months after randomisation
4. Fatigue measured using FACIT-Fatigue collected using the Aparito Atom5 application at baseline, weekly for 4 or 12 weeks, then monthly until 12 months after randomisation
5. Breathlessness measured using the Modified MRC Dyspnoea Scale collected using the Aparito Atom5 application at baseline, weekly for 4 or 12 weeks, then monthly until 12 months after randomisation
6. Return to the pre-illness state measured using COVID-19 core outcome measure for recovery collected using the Aparito Atom5 application at baseline, weekly for 4 or 12 weeks, then monthly until 12 months after randomisation
7. Depression measured using Patient Health Questionnaire-2 (PHQ-2) collected using the Aparito Atom5 application at baseline, weekly for 4 or 12 weeks, then monthly until 12 months after randomisation
8. Generalised anxiety disorder measured using Generalized Anxiety Disorder-2 (GAD-2) collected using the Aparito Atom5 application at baseline, weekly for 4 or 12 weeks, then monthly until 12 months after randomisation
9. PTSD measured using the PTSD Checklist (PCL-2) collected using the Aparito Atom5 application at baseline, weekly for 4 or 12 weeks, then monthly until 12 months after randomisation

10. Quality of life measured using the EQ5D-5L collected using the Aparito Atom5 application at baseline and monthly until 12 months after randomisation
11. Intervention tolerability measured using the FACT-GP5 collected using the Aparito Atom5 application at baseline, weekly for 4 or 12 weeks, then monthly until 12 months after randomisation
12. Additional disease-specific systemic symptoms measured using a bespoke questionnaire collected using the Aparito Atom5 application at baseline, weekly for 4 or 12 weeks, then monthly until 12 months after randomisation

Other outcome measures:
1. Incremental cost-effectiveness ratio based on:
1.1. Quality-adjusted life-years estimated from responses to the EQ-5D-5L collected using the Aparito Atom5 application at baseline and monthly until 12 months after randomisation
1.2. Resource use collected via linkage to electronic health records or case report form up to 12 months after randomisation and collected using the Aparito Atom5 application at baseline and monthly until 12 months after randomisation
1.3 Total cost per patient, from the perspective of the National Health Service based on the sum-product of the numbers of items of resource use, and their respective unit costs

Completion date
31/01/2025

Eligibility

Key inclusion criteria
1. Greater than or equal to 18 years of age
2. Hospitalised patient approaching the end of their admission (estimated planned discharge at any point within the next 5 days)
3. SARS-CoV-2 infection-associated disease (laboratory-confirmed SARS-CoV-2 infection on this hospital admission)
4. Written informed consent obtained from participant or participant’s legal representative

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Total final enrolment
1245

Key exclusion criteria
Generic exclusion criteria:
1. Known hypersensitivity to trial medication (patient will be excluded from specific arm)
2. Long-term pre-hospital administration of trial medication (patient will be excluded from specific arm
3. Previous medical history of significant complication with trial medication or trial medication drug class
4. 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.
5. Participant not expected to survive 14 days from hospital discharge

Apixaban exclusion criteria:
1. Active clinically significant bleeding
2. Childs-Pugh C, or worse, chronic liver disease
3. Known pregnancy or breast-feeding
4. Coagulopathy: INR greater than 1.7 or platelet count below 70
5. 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
6. Concomitant treatment following discharge with any other anticoagulant agent, 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:
1. Childs-Pugh C, or worse, chronic liver disease
2. Unexplained persistent elevation of serum transaminases exceeding five times the upper limit of normal
3. Known pregnancy or breast-feeding.
4. Treatment with the hepatitis C antivirals glecaprevir/pibrentasvir. Ciclosporin, or HIV protease inhibitors
5. Serum creatine kinase concentration exceeding 10 times the upper limit of normal.
6. Long-term pre-hospital administration of any statin therapy

Date of first enrolment
23/04/2021

Date of final enrolment
31/01/2023

Locations

Countries of recruitment
United Kingdom

Study participating centre

Any NHS hospital in the UK that treats COVID patients, a full list of open sites with a map of locations will be available at https://www.heal-covid.net/
United Kingdom
-

Sponsor information

Organisation
Cambridge University Hospitals NHS Foundation Trust

ROR
https://ror.org/04v54gj93

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request. 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. Consent for data sharing for future research is included in the Patient Information Sheet & Consent form, and the trial website will be updated with details of any data sharing activities that take place.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Protocol file	version V4.0	01/04/2021	21/04/2021	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes