Operations Manual for Trial Personnel and Recruiting Sites

Title:	A randomized double-blind placebo-controlled trial of Brensocatib (INS1007) in patients with severe COVID-19		
Short Title:	**STOP-COVID-19: S**uperiority **T**rial **O**f **P**rotease inhibition in **COVID-19**		
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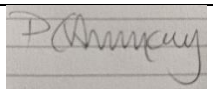
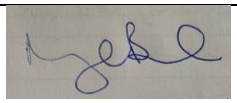
Signature:		Signature:	
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Abbreviations

AE	Adverse Event
AR	Adverse Reaction
CTIMP	Clinical Trial of Investigational Medicinal Product
CTU	Clinical Trials Unit
eCRF	Electronic Case Report Form
IB	Investigator Brochure
ICF	Informed Consent From
ISF	Investigator Site File
GCP	Good Clinical Practice
MHRA	Medicines and Healthcare products Regulatory Agency
NEWS2	National Early Warning Score
PCR	Polymerise chain reaction
PI	Principal Investigator
PIS	Participant Information Sheet
PPE	Personal Protective Equipment
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCTU	Tayside Clinical Trials Unit
TMF	Trial Master File
WPG	Working Practice Guidelines

Contents

1 Recruiting a participant

1.1 Identifying participants

- Participants will be identified following admission to hospital, with either suspected or confirmed COVID-19 infection:
  - Positive SARS-CoV-2 PCR (or similar lab test)
  - Clinically suspected COVID-19
  - Identification may occur in A&E and COVID-19 treatment units, or general hospital wards/units for people who are admitted to hospital for other reasons and may have contracted COVID-19 infection during their stay
- After identification and obtaining permission from the clinical care team, medical records will be screened to assess STOP-COVID19 eligibility:
  - Retrospective review of medical records and routine clinical assessments.
  - Most recent investigation results will be used, within 72 hours of screening assessment and 24 hours of baseline (randomisation).
  - Additional screening investigations will only be carried out where these have not been carried out in the previous 72 hours (and/or where results are not available):
    - After obtaining informed consent the required additional screening investigation (e.g. liver or renal function tests) samples will be requested/collected by the research team and sent to the local laboratory for analysis.
  - Eligible participants will fulfil all inclusion criteria and will not meet any exclusion criteria
    - Stop screening if any exclusion is identified.
  - The Screening Log (excel) will be completed to detail all pre-consent activity; providing the following details:
    - Date of identification, numbers eligible, numbers ineligible and reason for ineligibility.
  - The Enrolment and Randomisation Log will be completed for all consented participants.
  - PI, or medically qualified delegate, will confirm and record eligibly assessment in the medical record before randomisation.

1.2 Recruiting participants

Participants with COVID-19 will be recruited in hospital:

- Appropriately trained and delegated STOP-COVID19 trial team members will recruit participants; the clinical care team may contact the research team to advise of potential participants.
- Recruitment discussions will be face-to-face; trial team members will use appropriate personal protective equipment (PPE).
- Potential participants will be given a copy of the brief Participant Information Sheet (bPIS) and the Participant Information Sheet (PIS). Where potential participants lack capacity, the appropriate representative will be given a copy of the legal representative PIS.
- Translations in the following languages are available on the website if required: Bengali, French, Polish, Portuguese, Punjabi, Urdu
- RECOVERY and STOP-COVID CIs have agreed that:
  - If a patient in randomised to RECOVERY they may then be co-enrolled into STOP-COVID19.
  - If a patient is randomised to STOP-COVID19 they may then be co-enrolled into RECOVERY
  - RECOVERY and STOP-COVID19 will work closely together to share information on participating sites, interventions, and co-enrolments.

- For Co-enrolment Remap Cap and STOP-COVID19 please refer to document “Co-ordination of REMAP-CAP and STOP-COVID19 trials
- For co-enrolment in PRINCIPLE and STOP-COVID19 please refer to document “Co-ordination of PRINCIPLE and STOP-COVID19
- Co-participation in observational studies is allowed.

Potential participants who decline participation will be thanked for their consideration of STOP-COVID19 and made aware that this will not affect their future medical care.

1.3 Recruiting associated documents

- Identification excel spreadsheet: complete for all medical record searches; detail reason for ineligibility.
- Enrolment & Randomisation Log: complete for all consented; detail randomisation or reason for ineligibility.

2 Informed Consent

2.1 Responsibility for taking informed consent

- The PI is responsible for informed consent, activity may be delegated to appropriately trained members of the STOP-COVID19 trial team.
- Informed consent will be obtained by delegated members of the STOP-COVID19 research team, who are:
  - competent and experienced in obtaining informed consent for CTIMPs.
  - following STOP-COVID19 Protocol, principles of Good Clinical Practice and Declaration of Helsinki.
  - following local infection control procedures.
- Where a participant requests to speak with a physician from the trial team, informed consent will be deferred until this has occurred and all questions are satisfactorily answered.
- STOP-COVID19, informed consent and infection control training will be recorded in individual training records.
- Informed consent delegation will be recorded on the Delegation Log, filed within the Investigator Site File.

2.2 Taking Informed Consent

- Informed consent will be taken in an appropriate location, allowing sensitive issues to be discussed, and at a time that gives consideration to the patient's condition and clinical activity.
- If required, translated documents should be used.
- The time and date of the informed consent discussion/s will be recorded in the medical record.
- The participant and trial team member receiving informed consent both sign and date the Informed Consent Form (ICF).
- Informed consent/the signed informed consent form will be witnessed as per protocol or local COVID-19 SOP.
- Where a participant is able to give verbal informed consent but is unable to complete the ICP a witness independent of the research team should sign the witness statement on the ICF, ensure the participant's name is written on the ICF.
- ICF will be handled as per protocol or local COVID-19 SOP (SOP to be sent to Trial Manager). Options include:
  - The signed form remains with the participant and at the time of discharge is destroyed and disposed inside the isolation room/space.
  - The signed form remains with the participant and at discharge is taken home by the participant.
  - The team member obtaining informed consent will place the completed ICF into a clean envelope prior to leaving the room/space. The envelope will be held and sealed by the witness, then retained securely for 7 days before opening and filing in the medical record. Relevant participant information will be printed on the front of the sealed envelope.
- Record ICF completion within medical records as per local COVID-19 infection control policy. Options include:
  - Photograph the ICF through the isolation room window or from a distance of over 2 meters (isolation space).
    - As soon as possible print a copy of the photographed ICF.
    - An independent witness, present during written consent, will complete the witness section on ICF.
    - The ICF copy signed by the witness will be filed in the participant's medical records.
  - Where the ICF will be stored within a sealed envelope for 7 days consent will be recorded in the medical records as soon as possible.
- Where capacity is lost, consent remains legally binding and valid (see Protocol Section 7).
- Where re-consent is required following significant change to the Protocol (substantial amendment) the above procedures will be followed, except where capacity is lost requiring adults with incapacity consent (Section 2.3).
- Date of consent will be recorded on the Enrolment & Randomisation Log, filed within the ISF.

2.3 Adults with Incapacity

See Protocol Section 7

- Where incapacity is suspected:

incapacity will be assessed by the patient's clinician or medically qualified investigator; where an assessment has been completed for prior clinical treatment, the assessment will be documented in the medical record.

- For participants with incapacity to consent, consent will be first sought from a personal legal representative (relative).
  Due to the COVID-19 pandemic, in the majority of cases relatives will not be present in hospital, in these cases informed consent will be given by a professional legal representative. However, **before consent is given by a professional legal representative, the research team will endeavor to contact the participant's relative by phone**.
  - Where the research team are able to contact a relative, they will explain why they have been contacted and explain the trial to them.
  - The option of viewing the Participant Information Sheet (PIS) on the trial website or to emailing a copy of the PIS will be given.
    - If the relative is unable to view the website or receive email the research team member may read the brief PIS to the relative.
    - Where a relative is not able to access the website or does not wish the PIS to be emailed they will be asked if they wish to provide an address for a copy to be posted to them.
      STOP-COVID19 website: https://stop-covid19.org.uk/
  - After discussion about the trial and answering any questions the relative may have, the research team member will ask if they agree to their relative taking part in the trial.
    - This discussion and wishes of the relative will be documented in the participant's medical notes.
  - Where a relative agrees for a participant to take part in the trial written consent will be obtained from a professional legal representative.
    - Discussions with the legal representative where possible should take place in the presence of the participant; if this is not possible the participant should receive information about the trial in keeping with their capacity and if signs of objection are noted the participant will not be enrolled (despite legal representative giving their consent).
  - Where a relative does not agree for their relative to take part in the trial no consent will be sought, and the participant will not be enrolled in the trial.
- Legal representation:
  - In Scotland the Adults with Incapacity (Scotland) Act 2000 applies.
    - Personal legal representative: Welfare Guardian, Welfare Attorney or if not appointed the adult's nearest relative;
      and if neither are reasonably contactable:
    - Professional legal representative: doctor responsible for the adult's medical care who is independent of the trial or person nominated by the NHS board.
  - In England the Mental Capacity Act and Medicines for Human Use (Clinical Trials) Regulations 2004 apply.
    - Personal legal representative: a person not connected with the conduct of the trial who is suitable to act as the legal representative by virtue of their relationship with the adult and is available, and willing to do so.
      If one is not available:
  - Professional legal representative: a doctor responsible for the medical treatment of the adult if they are independent of the trial, or a person nominated by the healthcare provider.

Where capacity is regained, informed consent will be obtained from the participant as soon as is practicable. The participant will be given verbal and written information, appropriate to their condition that allows them to consider their participation to date, ongoing participation or withdrawal. Discussions and consent will be recorded within the medical record (as per Sections 2.1 & 2.2).

2.4 TAYSIDE ONLY Optional Consent: future research using data & biological samples

Participants can choose to give optional consent for:

- The use of participant data and stored specimens, for future research unrelated to COVID-19 and for submission to Professor James Chalmers, Division of Molecular and Clinical Medicine laboratory.

2.5 Informed Consent associated documents

- Identification Log (excel spreadsheet): complete for all medical record searches; detail reason for ineligibility.
- Enrolment & Randomisation Log: complete for all consented; detail randomisation or reason for ineligibility.
- Delegation Log.
- Medical Record.

NOTE: Medical records detailing trial participation and providing source data will be retained for 25 years. Clearly label front of paper records/flag electronic records.

3 Screening

3.1 Informed consent

See Section 2 for more detailed information.

3.2 Combined Screening and Baseline

- Screening and Baseline procedures can be combined and occur on Day 1 where:
  - all screening results are available
  - AND PI (or medically qualified delegate) is available to confirm/sign-off eligibility
  - AND delegated trial staff are available to perform Randomisation
  - AND trial medication is available from Clinical Trial Pharmacy for dosing before 5pm.
- Data will be collected as per Schedule of Procedures: Screening and Baseline.

3.3 Screening Samples

- The following are required to assess eligibility. Where results are not available within 72 hours of Screening the required samples will be requested/collected by the research team and sent to the local laboratory for analysis:
  - Nasal swab for SARS CoV-2 PCR.
  - BLOOD SAMPLES:
    1. SST tube
       - Urea & electrolytes, creatinine and eGFR
       - Liver function tests: ALT and AST.
    2. EDTA tube
       - Full blood count: white cells, haemoglobin, platelets, neutrophils, eosinophils, lymphocytes.
- The most recent results will be used for the screening/baseline assessments; including where a new clinical sample has been obtained further to collecting screening samples.
- Screening test results will be recorded in the medical record and eCRF.
- Refer to Schedule of Procedures.

3.4 Inclusion/exclusion criteria: assessed at Screening

It is likely that assessments will be carried out by the clinical team during routine care. Retrospective collection from medical records is expected, both to reduce duplication and minimise research team COVID-19 exposure. Where assessments have been carried out in the preceding 72 hours, **the most recent results will be used for eligibility assessment**.

Participant must meet **all** inclusion criteria:

- Male or female
  - Women of child-bearing potential will undertake urine or blood pregnancy testing after consent for eligibility assessment (prior to enrolment/randomisation).
- Age ≥ 16 years.
- SARS-COV-2 infection (clinically suspected* or laboratory confirmed*)
- Admitted to hospital as in-patient less than 96 hours prior to ranodisation^.
- illness of any duration, and at least one of the following:
  - Radiographic infiltrates by imaging (e.g. chest x-ray, CT scan)
    OR
  - Evidence of rales/crackles on physical examination
    OR
  - SpO2 ≤94% on room air
    OR
  - Requiring supplemental oxygen
    OR
  - Lymphocyte count <1 x 10^9 cells per L.

NOTE: if participant qualifies based on oxygen supplementation or radiographic infiltrates it is not necessary to perform a physical assessment to confirm presence of rales/crackles.

- Participant (or legally authorised representative) provides written informed consent.
- Able to take oral medication.

- Understands and agrees to comply with planned trial procedures.

*Laboratory-confirmed: SARS-CoV-2 infection as determined by polymerase chain reaction (PCR), or other commercial or public health assay in any specimen < 96 hours prior to randomization.
⁺Clinically suspected: in general, SARS-CoV-2 infection should be suspected when a patient presents with (i) typical symptoms (e.g. influenza-like illness with fever and muscle pain, or respiratory illness with cough and shortness of breath); and (ii) compatible chest X-ray findings (consolidation or ground-glass shadowing); and (iii) alternative causes have been considered unlikely or excluded (e.g. heart failure, influenza). However, the diagnosis remains a clinical one based on the opinion of the managing doctor
^Where a patient has been admitted to hospital for a non COVID-19 reason and develops COVID-19 symptoms whilst an in-patient, randomisation may occur up to 96 hours from onset of symptoms.

Participant must **not meet any** exclusion criteria:
NOTE: Where several results are available the result closest to randomisation should be used.

- ALT and /or AST > 5 times the upper limit of normal within 72 hours of randomisation.
- History of severe liver disease.
- Stage 4 severe chronic kidney disease or requiring dialysis (i.e. eGFR <30): result within 72 hours of randomisation.
- Absolute neutrophil count less than 1.0 x 10^9 cells per L within 72 hours of randomisation (the result closest to randomisation should be used if several results are available).
- Current treatment with potent Cyp3A4 inducers/inhibitors (e.g.itraconazole, ketoconazole, diltiazem, verapamil, phenytoin or rifampicin)
- HIV treatments – current treatment with protease/integrase inhibitors or non-nucleoside reverse transcriptase inhibitors*
- Pregnant or breast feeding.
- Anticipated transfer to another hospital which is not a trial site within 72 hours.
- Allergy to Brensocatib.
- Use of any investigational drug within five times of the elimination half-life after the last trial dose or within 30 days, whichever is longer.

Women of child-bearing potential must be willing to have pregnancy testing prior to trial entry.

*The Liverpool HIV checker (https://www.hiv-druginteractions.org/checker) should be used to check for any HIV drug interactions. Simvastatin could be used as a surrogate for Brensocatib as it metabolised similarly by CYP 3A4 pathway

NOTE: PI, or medically qualified delegate, will complete final review and document eligibility sign-off in the medical record before randomisation.

3.5 Data collection & entry

- Screening will be recorded in the medical record then entered on the STOP-COVID19 database:
  - Retrospective clinical data, within 72 hours of Screening, will be collected from the medical record.
- Optional STOP-COVID19 worksheets may be used.
- The most recent result, closest to the screening assessment time, will be used.
- The following information will be collected:

3.5.1 Demographic, Clinical Information and Measurements

- Collect from the medical/clinical record and record on the eCRF.
  - Demographic information:
    - Age
    - Sex at birth
    - Ethnicity.
- Clinical information and measurements (most recent):
  - Vital signs:

- Blood Pressure mmHg (lying or seated)
- Pulse per minute (lying or seated)
- Oxygen saturation on air or state supplemental oxygen: concentration or litres per minute
- Tympanic temperature degrees Centigrade.

- Clinical support status 7-point scale (the worst score that day – recorded retrospectively):
  1. Not hospitalised, no limitations on activities
  2. Not hospitalised, limitation on activities;
  3. Hospitalised, not requiring supplemental oxygen;
  4. Hospitalised, requiring supplemental oxygen;
  5. Hospitalised, on non-invasive ventilation or high flow oxygen devices;
  6. Hospitalised, on invasive mechanical ventilation or ECMO;
  7. Death.
- NEWS2 (most recent, using clinically recorded parameters).
- 12 lead ECG result.

- Where any result/finding is out-with inclusion/exclusion criteria the participant is not eligible and will not be randomised. Update Enrolment and Randomisation Log with reason for ineligibility.
- Refer to Schedule of Procedures.

3.5.2 Medical history & Physical Examination – other relevant medical conditions

- Obtain from the medical record the following retrospective medical history. Record in the eCRF:
  - Approximate day of onset of COVID-19 symptoms.
  - History of chronic medical conditions related to inclusion and exclusion criteria.
  - Medication allergies – tick where present.
  - Review/record medications and therapies for this current COVID-19 illness.
  - CT scan result (if carried out).
  - Physical examination findings (review for eligibly e.g. respiratory findings).

3.5.3 Concomitant medications

- No concomitant medications will have to be stopped for STOP-COVID19.
- Review concomitant medications; record on the eCRF.
- Females of childbearing potential and males must be willing to use a highly effective method of contraception (hormonal or barrier method of birth control; abstinence). Contraception should be continued until at least 30 days after final dose of IMP taken. Such methods include:
  - combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
    - oral
    - intravaginal
    - transdermal.
  - progestogen-only hormonal contraception associated with inhibition of ovulation
    - oral
    - injectable
    - implantable.
  - intrauterine device (IUD).
  - intrauterine hormone-releasing system (IUS).
  - bilateral tubal occlusion.
  - vasectomised partner.
  - sexual abstinence.

3.6 Screening associated documents

- Identification Log excel spreadsheet: complete for all medical record searches; detail reason for pre-screen ineligibility.
- Enrolment & Randomisation Log: complete for all consented; detail randomisation or reason for ineligibility.
- Screening Worksheet – optional.
- Delegation Log.

4 Baseline & Randomisation

To provide flexibility the Baseline assessments and Randomisation may be combined with, or separated from, Screening. See Section 3 for combined Screening and Baseline.

4.1 Separate Screening and Baseline

Possible reasons to perform separate visits include, for example:
- No availability of trial team to perform Randomisation.
- No availability of screening sample results.
- No availability of PI, or medically qualified delegate, for eligibility sign-off.
- No access to dispense trial medication.

- Baseline/Randomisation can be separated from Screening by up to 24 hours:
  - Date of first dose = day 1
- Data will be collected as per Schedule of Procedures: Baseline.

4.2 Data collection & entry

- Baseline assessments will be recorded in the medical record then entered on the STOP-COVID19 database:
  - Retrospective clinical data, within 24 hours of Baseline, will be collected from the medical record.
- Optional STOP-COVID19 worksheets may be used.
- The following information will be collected:

4.2.1 Baseline assessments

- Where baseline assessments are carried out on a separate day from the screening the following clinical information and measurements, **the most recent results will be used for eligibility and recorded:**
  - Vital signs:
    - Blood Pressure mmHg (lying or seated)
    - Pulse per minute (lying or seated)
    - Oxygen saturation on air or state supplemental oxygen: concentration or litres per minute
    - Tympanic temperature degrees Centigrade.
  - Clinical support status 7-point scale (the worst score that day – recorded retrospectively).
  - NEWS2.
  - CT scan result (if carried out).
  - Changes to concomitant medications (see Section 7).
  - Adverse Events (see Section 12).

- The most recent result will be used for the baseline assessment; including where a new clinical sample has been obtained further to collecting screening samples.
- Where any result/finding is out-with inclusion/exclusion criteria the participant is not eligible and will not be randomised. Update Enrolment and Randomisation Log.
- Refer to Schedule of Procedures.

4.2.2 TAYSIDE ONLY: Baseline samples

- Optional samples, with consent, can be stored for sub-trial and future use.
- Optional sputum and blood samples will be transferred to the Professor James Chalmers Laboratory.
- Samples will be requested/collected by the clinical team and transferred immediately, and within 2 hours, to the laboratory.
- See Separate Tayside Laboratory Manual for more details.
- Refer to Schedule of Procedures.

4.2.3 Pre-randomisation PI sign-off

- PI, or medically qualified delegate, will review all screening and baseline results to assess eligibility.

- Where all inclusion and no exclusion criterion are met the participant is eligible.
- **The medical record must be signed to confirm completion of the eligibility assessment BEFORE randomisation takes place.**

4.2.4 Randomisation

- Following PI assessment and eligibility sign-off, documented in the medical record, randomisation can occur.
- A delegated member of the research team will use TRuST to complete randomisation.
    - See Section 10 for more details.

4.3 Informing a GP about entry into the trial

- Following enrolment and randomisation the GP letter will be sent and a copy filed in the medical record.

4.4 Baseline associated documents

- Enrolment & Randomisation Log: complete for all consented; detail randomisation or reason for ineligibility.
- Baseline Worksheet – optional.
- Delegation Log.
- GP Letter.

5 Follow-up Data Collection

5.1 Adverse events (AE)

- The medical record will be reviewed at each follow-up timepoint.
- The PI or delegate (e.g. Research Nurse) will identify and record AEs.
- **Exceptions:** Expected events that will **not be recorded** as AEs, are:
  - cough
  - pyrexia
  - headache
  - tiredness
  - diarrhoea
  - aches and pains
  - nasal congestion
  - runny nose
  - sore throat
  - anosmia (absent or decreased sense of smell)
  - loss of taste
  - deterioration in renal and or liver function and changes in full blood count parameters.
- All identified AEs will be recorded in the medical record and eCRF.
- See Section 12 for more detail.

5.2 Concomitant medications

- Review concomitant medications; record on the eCRF– tick where present.
- Refer to Schedule of Procedures.

5.3 Data entry

- Follow-up visits will be recorded in the medical record then entered on the STOP-COVID19 database:
  - Clinical data will be collected from the medical record.
  - Optional STOP-COVID19 worksheets may be used.
- All data from participants should be entered on the eCRF within 7 days of the last data collection point for that participant.

5.4 Assessments

- Where assessments have not been carried out that day, they will be carried out by the research team, except for blood tests.
- The following information will be collected:

5.4.1 Daily whilst hospitalised

- The following clinical information and measurements on the assessment day are to be recorded/taken:
  - Clinical support status 7-point scale (the worst score that day – recorded retrospectively)
  - NEWS2 (closest to 8am)
  - CT scan result (if carried out)
  - Adverse Events.

5.4.2 Days 3, 5, and 11

- The following blood results will be recorded where taken for clinical reasons. If not taken for clinical reasons they will not be taken for the trial purposes and this will be classed as not obtained. If more than one result is available for a particular day the result closest to 8am should be recorded.
  - Urea & electrolytes, creatinine and eGFR.
  - Liver function tests: ALT and AST.
  - Full blood count: white cells, haemoglobin, platelets, neutrophils, eosinophils, lymphocytes.
- The following clinical information and measurements will be recorded/taken:
  - Clinical support status 7-point scale (the worst score that day – recorded retrospectively).

- NEWS2 (closest to 8am).
- CT scan result (if carried out).
- Adverse Events.

- Telephone follow-up will be performed/recorded if discharged from hospital. Where it is not possible to carry out the visit on the scheduled date visits may occur +/- 1 day

5.4.3 Day 8

- The following blood results will be recorded where taken for clinical reasons. If not taken for clinical reasons they will not be taken for the trial purposes and this will be classed as not obtained. If more than one result is available for a particular day the result closest to 8am should be recorded.
    - Urea & electrolytes, creatinine and eGFR.
    - Liver function tests: ALT and AST.
    - Full blood count: white cells, haemoglobin, platelets, neutrophils, eosinophils, lymphocytes.
- TAYSIDE ONLY: Sputum OR Endotracheal aspirate (if available) and Blood samples to be obtained – see Tayside Laboratory Manual.
- The following clinical information and measurements will be recorded/taken:
    - Vital signs (closest to 8am)
        - Blood Pressure mmHg (lying or seated)
        - Pulse per minute (lying or seated)
        - Oxygen saturation on air or state supplemental oxygen: concentration or litres per minute
        - Tympanic temperature degrees Centigrade.
    - Clinical support status 7-point scale (the worst score that day – recorded retrospectively).
    - NEWS2 (closest to 8am).
    - CT scan result (if carried out).
    - Adverse events.
    - Concomitant medications.
- Telephone follow-up will be performed/recorded if discharged from hospital.

5.4.4 Day 15

- The following blood results will be recorded where taken for clinical reasons. If not taken for clinical reasons they will not be taken for the trial purposes and this will be classed as not obtained. If more than one result is available for a particular day the result closest to 8am should be recorded.
    - Urea & electrolytes, creatinine and eGFR.
    - Liver function tests: ALT and AST.
    - Full blood count: white cells, haemoglobin, platelets, neutrophils, eosinophils, lymphocytes.
- TAYSIDE ONLY: Nasal swab for SARS CoV-2 PCR, Sputum OR Endotracheal aspirate (if available) and Blood samples – see Tayside Laboratory Manual.
- The following clinical information and measurements will be recorded/taken:
    - Vital signs (closest to 8am):
        - Blood Pressure mmHg (lying or seated)
        - Pulse per minute (lying or seated)
        - Oxygen saturation on air or state supplemental oxygen: concentration or litres per minute
        - Tympanic temperature degrees Centigrade.
    - Clinical support status 7-point scale (the worst score that day – recorded retrospectively).
    - NEWS2 (closest to 8am).
    - CT scan result (if carried out)
    - Adverse events.
    - Concomitant medications.
- Telephone follow-up will be performed/recorded if discharged from hospital.

5.4.5 Day 29

- The following blood results will be recorded where taken for clinical reasons. If not taken for clinical reasons they will not be taken for the trial purposes and this will be classed as not obtained. If more than one result is available for a particular day the result closest to 8am should be recorded.
    - Urea & electrolytes, creatinine and eGFR.
    - Liver function tests: ALT and AST.
    - Full blood count: white cells, haemoglobin, platelets, neutrophils, eosinophils, lymphocytes.
- TAYSIDE/SHEFFIELD ONLY: see Laboratory Manual.
- The following clinical information and measurements will be recorded/taken:
    - Vital signs (closest to 8am):
        - Blood Pressure mmHg (lying or seated)
        - Pulse per minute (lying or seated)
        - Oxygen saturation on air or state supplemental oxygen: concentration or litres per minute
        - Tympanic temperature degrees Centigrade.
    - Clinical support status 7-point scale (the worst score that day – recorded retrospectively).
    - NEWS2 (closest to 8am).
    - CT scan result (if carried out).
    - Adverse events.
    - Concomitant medications.
    - IMP compliance check:
        - Excess IMP/IMP container will be obtained from the clinical team and returned to Clinical Trials Pharmacy (CTP).
        - The prescription chart will be updated to discontinue IMP following 28 days of treatment. No dose will be administered on Day 29.
          NOTE: 35 tablets are supplied however dosing is only for 28 days. The excess tablets will be returned to CTP.
    - EQ-5D Questionnaire (if able):
        - Interviewer administration is detailed on the EQ-5D; question wording will be followed as closely as possible.
        - The response that matches how the participant feels today will be marked.
        - The completed questionnaire is source data and will be filed in the medical record.
        - Responses will be transcribed into the eCRF.
    - Telephone follow-up will be performed/recorded if discharged from hospital except at the TAYSIDE/SHEFFIELD site where discharged participants will attend a Day 29 visit.

5.5 Hospital Discharge

- The research nurse will be responsible to ensure that pre-discharge the participant is provided with:
    - Diary
    - IMP with instruction
        - To continue dosing to day 28
        - Return excess IMP for disposal (post-day 28 dosing)
        - SAE for IMP return to pharmacy
    - Research team contacts
    - Planned follow-up visit calls.
- Re-admitted participants:
    - Collect daily clinical information and measurements (as detailed above and within the Schedule of Procedures) from the day of re-admission
        - Re-admission may not be known until a scheduled follow-up assessment telephone call.
        - Retrospective data collection will be used.
        - Where a clinical assessment has not been performed the result will be recorded as missing; this will not constitute a protocol breach.

5.6 Follow-up Visits associated documents

- Follow-up Worksheets: Daily, Day 3, 5, 8, 11, 15 and 29 – optional
- Diary.

6 Clinical Assessments

Assessments will generally be carried out and recorded by the clinical team during routine care and documented on a NEWS chart.

- Where these assessments have been carried out by the clinical team the results of the assessment **closest to 8am on the day** will be used to prevent duplication and further exposure of the trial team to participants with COVID-19.
- The research team member will record the assessment in the eCRF.
- Where assessments have not been carried out by the clinical team within 24 hours of the visit time these should be carried out by the research team, with the exception of blood samples.
- Any missing assessments will be reported as a breach to protocol, except where participants have been re-admitted and the clinical assessment was not performed (see Section 5.5).

6.1 Vital signs

- Blood Pressure mmHg (lying or seated).
- Pulse per minute (lying or seated).
- Oxygen saturation on air or state supplemental oxygen: concentration - litres per minute.
- Tympanic temperature degrees Centigrade.

6.2 Supplemental Oxygen

- Record in eCRF % or per litre.
- Most recent clinical recording.

6.3 Clinical support status 7-point scale (the worst score that day – recorded retrospectively)

- Collect from the medical/clinical record and record on the eCRF:
  1. Not hospitalised, no limitations on activities
  2. Not hospitalised, limitation on activities;
  3. Hospitalised, not requiring supplemental oxygen;
  4. Hospitalised, requiring supplemental oxygen;
  5. Hospitalised, on non-invasive ventilation or high flow oxygen devices;
  6. Hospitalised, on invasive mechanical ventilation or ECMO;
  7. Death.

6.4 NEWS2

The **NEWS2** is an aggregate **scoring system** in which a **score** is allocated to 7 physiological measurements, already recorded in routine hospital practice.
NEWS2 scoring ranges from 0-20.

- Scoring requires the following clinical assessments:
  - respiration rate
  - oxygen saturation
  - systolic blood pressure
  - pulse rate
  - level of consciousness or new confusion
  - temperature.
  - inspired oxygen.

- Record the clinically calculated NEWS2 score, closest to 8am
  - Where NEWS2 score has not been calculated by the clinical team use NEWS scoring system to calculate NEWS using the closest to 8am recorded clinical assessments.

NEWS2 Scoring System:

Physiological parameter	Score 3	2	1	0	1	2	3
Respiration rate (per minute)	≤8		9–11	12–20		21–24	≥25
SpO_2 Scale 1 (%)	≤91	92–93	94–95	≥96			
Air or oxygen?		Oxygen		Air			
Systolic blood pressure (mmHg)	≤90	91–100	101–110	111–219			≥220
Pulse (per minute)	≤40		41–50	51–90	91–110	111–130	≥131
Consciousness				Alert			CVPU
Temperature (°C)	≤35.0		35.1–36.0	36.1–38.0	38.1–39.0	≥39.1	

NOTES:
1. Sp02: Use Scale 1
2. Consciousness:
    - C: Confusion, new i.e. not participant's normal pre-hospitalisation sate
    - V: Responds only to Voice
    - P: Responds only to Pain
    - U: Unresponsive.

6.5 CT scan result

- Where carried out record results in eCRF.

7 Concomitant medication

7.1 Excluded medications

- Should any of the following excluded medications be commenced trial treatment will be discontinued:
  - Itraconazole
  - Ketoconazole
  - Diltiazem
  - Verapamil.
  - Phenytoin
  - Rifampicin
  - Protease or integrase inhibitors
  - Non-nucleoside reverse transcription inhibitors

7.2 Data entry

Review the medical record for concomitant medications:

- Record on the eCRF– tick where present.
- No concomitant medications will be stopped for STOP-COVID19.

8 Sample Collection

Screening/eligibility:

- Samples will only be taken for trial purposes prior to confirming eligibility if these have not been already carried out by the clinical team within the time limits (96 hours for SARS CoV-2 confirmation, 72 hours for other eligibility criteria).

Follow-up assessment days:

- Clinical sample results will be used at all time points.
- If not taken for clinical reasons they will not be taken for the trial purposes and this will be classed as not obtained.
- If more than one result is available for a particular day the result closest to 8am should be recorded.
- Local reference ranges will be adopted.
- Samples, except for TAYSIDE/SHEFFIELD ONLY research samples (see Tayside Laboratory Handbook), are processed and reported by the local laboratory.

8.1 Nasal swabs

- Nasal swab for SARS CoV-2 PCR.

8.2 Blood samples

- SST
  - Urea & electrolytes, creatinine and eGFR.
  - Liver function tests: ALT and AST.
- EDTA
  - Full blood count.

8.3.1 Order of Draw Table

Order	Blood Sample	Tube	Lab
1	U&Es, creatinine and eGFR; LTFs (ALT, AST),	SST	Local
2	FBC: white cells, haemoglobin, platelets, neutrophils, eosinophils, lymphocytes	EDTA	Local

9 Randomisation

9.1 Randomisation Procedure Summary

- Randomisation will take place following PI, or medically qualified delegate, confirmation of eligibility.
- **The medical record must be signed to confirm completion of the eligibility assessment BEFORE randomisation takes place.**
- A delegated member of the research team performs participant randomisation.
- TRuST (The Tayside Randomisation System) is used.
    - TRuST is a secure, password protected, GCP compliant web-based system and accessible from any web-based device.
    - Full details of the system are provided within the TRuST Randomisation and Emergency Unblinding guides.

9.2 Emergency Unblinding Procedure

- Unblinding will only be carried out where a physician considers that it is necessary for clinical safety.
- Full details are provided within the TRuST unblinding guide.
- The PI or or other research staff listed on the delegation log will use their login to access the 24-hour, web-based TRuST unblinding system.
- The CI will also have access to the 24-hour, web-based TRuST unblinding system. The CI can be contacted should the PI/delegate be unable to perform the required unblinding.
- Unblinding is recorded on the Unblinding Form, providing:
    - Date
    - Reason
    - Treatment allocation.
- Place the Unblinding Form inside a sealed envelope and file in the ISF, Section 9.3
- The PI/delegate will only disclose treatment allocation to relevant clinical team members i.e. individuals involved in the participant's clinical care.
- Where possible the participant will remain in the trial and continue trial procedures.
- The Clinician will decide whether the participant will remain on IMP.

9.3 Randomisation and Unblinding associated documents

- Randomisation Log.
- Emergency Unblinding Form.
- TRuST Randomisation User guide.
- TRuST Emergency Unblinding guide/training.

10 Investigational Medicinal Product (IMP) management

Full details of the IMP management plan are found in the ISF and PSF.

- The IMP are oral tablets. Placebo and active tablets will be identical in appearance.

10.1 Investigator Brochure

- Filed in ISF, Section 12.1

10.2 IMP Manufacture, Packing & Supply

- IMP will be packed and supplied in individual (per participant) bottles.
- Each bottle will contain 35 tablets; only 28 will be taken.

10.3 IMP Storage

- IMP is stored between 2 and 30 degrees Centigrade.

10.4 Requesting IMP

- TRuST randomisation system will provide an immediate treatment allocation on screen and confirmation of allocation will be emailed to PI, individual completing randomisation and the clinical trials pharmacy. The clinical trial manager and CI will also receive email notification.
- Delegated research team member will complete the IMP Request Form.
- IMP Request Form will be signed by a medically qualified Doctor delegated this task on the Delegation Log.
- IMP Request Form will be taken/delivered to Clinical Trials Pharmacy by the research team member along with a copy of the randomisation email.

10.5 Issuing IMP

- IMP will be issued by Clinical Trials Pharmacy at Day 1 (post-randomisation).

10.6 IMP Prescribing

- The medically qualified Doctor, either research or clinical team member, will prescribe IMP on the prescription chart.
- The individual completing randomisation will be responsible for ensuring that IMP is prescribed as per local policy.

10.7 Issuing IMP to the Participant

- Clinical Trials Pharmacy will issue IMP to the research team member:
  - Research nurse/delegated research team member will take IMP to the participant's clinical area as per local CTIMP dispensing procedure.
  - The research nurse/delegated research team member will ensure that the IMP is available for Day 1 dosing.
  - The clinical team will be responsible for IMP storage from receipt until Day 29/discharge.
- IMP will be stored securely under appropriate storage conditions - locked and with limited access storage that is accessible to authorised personnel - within the clinical area as per local policy and procedure.
- IMP labelling specifies storage.

10.8 IMP/Placebo appearance

	Investigational Medicinal Product	Dosage, form and strength	Appearance
Arm 1	Brensocatib	25mg daily	Round, brown film-coated, biconvex tablet
Arm 2	Placebo	No dose	Round, brown film-coated, biconvex tablet

10.9 IMP Dosing

- Once daily dosing for 28 days.
- One tablet to be taken by mouth once daily on Days 1 to Day 28 (inclusive). No dose is taken on Day 29.
- Administration:
  - Administer with water
  - Before breakfast, at approximately the same time each day. There is no requirement for the trial drug to be taken before food if the participant is not eating.
- Day 1 dose should be taken as early as possible (following randomisation) however must be taken before 5pm.
  - Where IMP is not available for dosing before 5pm, Day 0 dosing will be delayed until the following morning.
- Missed dose:
  - if a dose is missed it should be given within 10 hours of the missed dose.
- if more than 10 hours have passed do not dose, wait until the next day.
- Where participant becomes unable to take oral medication nasogastric (NG) administration is permitted:
  - Crush tablet
  - Place crushed tablet in water for 5-10 minutes
  - Draw liquid into syringe (catheter tip syringe or standard syringe with adaptor)
  - Push liquid through NG tube
  - Flush NG tube with 10mL water or saline, then clamp for 30 minutes
  - Release clamp after 30 minutes.

10.10 IMP Treatment

- Treatment is administered for 28 days.
- The Prescription Chart will be completed by a medically qualified individual, detailing:
  - Treatment for 28 days.
  - No treatment on Day 29.
- Clinical staff will record administration on the Prescription Chart
- Day 1 treatment will commence close to randomisation.
- Where a participant is discharged, they will be supplied with IMP and continue with the 28 days of treatment:
  - Delegated research team member will advise participant of once daily oral dosing and storage conditions, as specified on the IMP label.

10.11 IMP Discontinuation

Reasons for discontinuation:

- Persistent adverse effects which are determined to be severe, persistent, treatment related and not responsive to treatment.
- If an allergic reaction to trial drug occurs the trial drug will be stopped, and treatment will be initiated as appropriate.
- Absolute neutrophil count less than 1.0×10^9 cells per L at any time.

10.12 IMP Compliance

- In-hospital Participant Day 29 compliance check:
  - Delegated research team staff will check drug returns (open IMP container, count any remaining tablets) and medication record sheet.
  - Record number of unused tablets on eCRF.
- Discharged Participant Day 29 compliance check:
  - The diary will be issued at discharge to instruct the participant only to take a maximum of 28 doses.
  - The last day the participant should take their tablets should be completed by research team prior to giving to participant.
  - Delegated research team staff will telephone participant to ask how many tablets are remaining.

- Record number of unused tablets on eCRF.
- Discharged participants will return IMP by post except at the Tayside site where discharged participants will return IMP at the Day 29 visit.

10.13 IMP Returns

- In-hospital
  - Unused medication and packaging will be collected from the clinical team and returned to Clinical Trials Pharmacy for accountability check and disposal.
- Discharged participant
  - The trial team should provide a stamped, addresses envelope to participants to return the IMP bottle and remaining tablets.
  - Returns received should be returned to CTP for accountability and disposal.
  - Local infection control procedures should be followed this may include sealing the returned envelope in a bag for 5 days before opening.
  - Stamped envelopes will be supplied to the trial team.

10.14 IMP Destruction

- IMP disposal will be carried out by the Clinical Trial Pharmacy in accordance with local policy and procedures.

11 Adverse events (AE) / Serious Adverse Events (SAE)

11.1 Summary: Identification, recording, assessment and reporting of AEs and SAEs

- AEs occurring from the time a participant consents until the last trial visit will be recorded in the medical record.
- At each scheduled assessment (see Schedule of Procedures) a delegated member of the research team (e.g. Research Nurse) will review the medical record.
- Identified AEs, with the exception of expected events, see section 11.4, will be recorded in the eCRF.
- The PI will assess seriousness, causality and expectedness for all AEs and record this assessment in the medical record.
- SAEs will be reported to Sponsor within 24 hours of becoming aware of the SAE.
  Reporting is via a completed SAE form, which must be signed by the PI/delegate, emailed to tay.pharmacovigilance@nhs.scot and copied to CI and trial manager.
  SAEs will be recorded in the eCRF and medical record.
- AEs/SAEs will be followed up until recovered, recovered with sequelae or death or for 30 days after participant's last visit whichever occurs first.
- Suspected Unexpected Serious Adverse Reaction (SUSARS) will be followed until resolution.

11.2 Defining AE & SAE

Safety reporting will be conducted in compliance with TASC SOP11 Identifying, Recording and Reporting Adverse Events for Clinical Research.

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions. It is important to note that this is entirely separate to the known side effects listed in the SmPC. It is specifically a temporal relationship between taking the drug, the half-life, and the time of the event or any valid alternative etiology that would explain the event.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the reference safety information.

NOTE: to avoid confusion or misunderstanding of the difference between the terms “serious” and “severe”, the following note of clarification is provided: “Severe” is often used to describe intensity of a specific event, which may be of relatively minor medical significance. “Seriousness” is the regulatory definition supplied above.

11.3 Detecting AE & SAE

- All AEs and SAEs must be recorded from the time a participant consents (Day -1) to join the trial until the last trial assessment (Day 29).
- The Investigator, or delegated research team member, will review the medical record for / ask about the occurrence of AEs/SAEs at every assessment time point during the trial (See Schedule of Procedures).
- Discharged participants will be given a diary to record AEs.
  At each telephone follow-up assessment, they will be asked if they have:
  - been re-admitted to hospital
  - had any accidents
  - had any new illnesses or symptoms
  - used any new medicines
  - changed concomitant medication regimens.
- If there is any doubt as to whether a clinical observation is an AE, the event should be recorded.

11.4 Expected events & Operational definitions

- Deterioration of the existing COVID-19 condition, with the exception of death, or known side-effects (below) which will be recorded as primary or secondary endpoints are not reported as (S)AEs or (S)ARs.
- All deaths will be reported as SAEs.
- The following events will be deemed as expected in participants with COVID-19 and will not be recorded as AEs:
  - cough
  - pyrexia
  - headache
  - tiredness
  - diarrhoea
  - aches and pains
  - nasal congestion
  - runny nose
  - sore throat
  - anosmia: reduced or loss of smell
  - loss of taste
  - deterioration in renal and or liver function and changes in full blood count parameters.
- Anticipated AEs for the trial drug are be listed in the Reference Safety Information these would not be considered to be SUSARs unless the severity of the event was considered to be unexpected.
- All SAEs and SARs will be reported to sponsor, see section 11.7, with the exception of hospitalisation as this is recorded as an end point.

11.5 Recording AE & SAE

- Depending on severity, when an AE/SAE occurs, it is the responsibility of the PI/RN to review all documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event.
- All relevant information will be recorded in the medical record, eCRF AE log and if relevant on the SAE form.
- Information to be collected includes:
    - IMP dose, type of event, onset date, Investigator assessment of severity and causality, date of resolution as well as treatment required, investigations needed and outcome.

11.6 Evaluation of AE & SAE

- Seriousness, causality, severity and expectedness will be evaluated as though the participant is taking active drug.
- Reference Safety Information (RSI) is described in the Investigator Brochure Section 6.6.

12.6.1 Assessment of Causality

- The Principal Investigator must make an assessment of whether the AE/SAE is likely to be related to treatment according to the following definitions:
    - Unrelated: where an event is not considered to be related to the trial drug.
    - Possibly: although a relationship to the trial drug cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship make other explanations possible.
    - Probably: the temporal relationship and absence of a more likely explanation suggest the event could be related to the trial drug.
    - Definitely: The known effects of the trial drug or its therapeutic class, or based on challenge testing, suggest that trial drug is the most likely cause.
- All AEs/SAEs judged as having a reasonable suspected causal relationship (e.g. possibly, probably, definitely) to the trial drug will be considered as **ARs/SARs**.
- All AEs/SAEs judged as being related (e.g. possibly, probably, definitely) to an interaction between the trial drug and another drug will also be considered to be **ARs/SARs**.
- Alternative causes such as natural history of the underlying disease, concomitant therapy, other risk factors and the temporal relationship of the event to the treatment should be considered.

12.6.2 Assessment of Severity

- The PI should make an assessment of severity for each AE/SAE and record this on the eCRF according to one of the following categories:
    - Mild: an event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
    - Moderate: an event that is sufficiently discomforting to interfere with normal everyday activities.
    - Severe: an event that prevents normal everyday activities.

The term ‘severe’, used to describe the intensity, should not be confused with ‘serious’ which is a regulatory definition based on participant/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe.

12.6.3 Assessment of Expectedness

If an event is judged to be an AR/SAR, the evaluation of expectedness should be made based on knowledge of the reaction and the relevant product information documented in the IB.

11.7 Reporting of SAE/SUSAR

- Once the Investigator becomes aware that a potential reportable SAE has occurred in a trial participant, they must report the information to the TASC Pharmacovigilance Section and CI within 24 hours of becoming aware of the event as per TASC SOP11.
- The PI/RN will complete the SAE form, which must be completed as thoroughly as possible with all available details of the event, signed by the PI or designee.
- If all the required information is not available at the time of reporting, the PI/RN must ensure that any missing information is provided as soon as this becomes available. It should be indicated on the report that this information is follow-up information of a previously reported event.

- The SAE report must provide an assessment of causality and expectedness at the time of the initial report to the Pharmacovigilance Section according to Section 12.6: Assessment of Causality and Assessment of Expectedness.
  The SAE form will be made available via the Investigator/Researcher section of the trial specific website https://stop-covid19.org.uk/ and should be completed, printed and signed by the PI, and e-mailed to tay.pharmacovigilance@nhs.scot Cc CI and Trial Manager: Stop-coviid19@dundee.ac.uk
- The completed from should be filed in the ISF.

11.8 (S)AE & SUSAR follow-up

- Participants with unresolved (S)AEs at end of trial will be followed up until 30 days after participant's last visit.
- Suspected Unexpected Serious Adverse Reaction (SUSARS) will be followed until resolution. Any SUSAR will be reported to the Sponsor irrespective of how long after IMP administration the reaction has occurred and will be followed up until resolved.

11.9 Notification of Deaths

- All deaths will be reported to the sponsor irrespective of whether the death is related to disease progression, the IMP, or an unrelated event. Reporting of deaths will follow the SAE reporting process (Section 11.7).

11.10 Pregnancy Reporting

- All pregnancies within the trial (either the trial participant or the participant's partner, with participants consent) will be reported to the Chief Investigator and the Sponsor using the relevant TASC Pregnancy Notification Form within 24 hours of notification.
  The TASC Pregnancy Notification Form and submitted to the Sponsor Pharmacovigilance Section tay.pharmacovigilance@nhs.scot Cc CI and Trial Manager: Stop-covid19@dundee.ac.uk
- The pregnancy will be followed up until the end of the pregnancy. If the trial participant is a male, informed consent for follow up will be sought from his female partner.
- Pregnancy is not considered an AE unless a negative or consequential outcome is recorded for the mother or child/foetus. If the outcome meets the serious criteria, this would be considered an SAE.

11.11 Overdose

Whilst in hospital the trial medication will be held and given to participants as per drug record by the clinical team.
On discharge from hospital participants will take home enough medication to complete 28 days of treatment.

- An overdose will be defined as taking more than 50mg of trial medication in a 24-hour period.
- An overdose itself is not an AE. However, if the overdose results in clinical signs and symptoms, it requires an expedited reporting as if it is an SAE.
- In the case of an overdose, the Investigator should use clinical judgment in treating the overdose
- Once the Investigator becomes aware that an overdose (SAE) has occurred in a trial participant, they must report the information to the CI and TASC Pharmacovigilance Section within 24 hours of becoming aware of the event as per TASC SOP11. See Section 11.7

11.12 Emergency unblinding

- Unblinding will only be carried out where a physician considers that it is necessary for clinical safety.
- Participants should be evaluated as though they are taking active drug.
- When emergency unblinding is appropriate see Section 9.2

11.13 Urgent Safety Measures

- The CI or other trial physician will take appropriate immediate urgent safety measures in order to protect the participants against any immediate hazard to their health or safety.

- If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures.

11.14 Data entry

- AEs/SAEs will be recorded on the eCRF AE Log.
- A delegated research team member, at site, is responsible for data entry.
- Access the trial eCRF via https://stop-covid19.org.uk/

11.15 Pharmacovigilance associated documents

- TASC SOP11 Identifying, Recording and Reporting Adverse Events for Clinical Research.
- SAE Form.
- Pregnancy Reporting Form.
- Delegation Log.

12 Protocol & GCP Breaches

- This trial will be conducted in compliance with protocol, GCP and UK Clinical Trial regulations.
- This information is supplementary to SOP TA059: Reporting Breaches in Clinical Research.

12.1 Definitions

12.1.1 Breach

- A breach is a non-compliance with protocol, GCP or UK Clinical Trial regulations.

12.1.2 Serious Breach

- A serious breach is a breach which is likely to effect to a significant degree:
  - the **safety or physical or mental integrity** of the participants of the trial; or
  - the **scientific value** of the trial.

12.2 Recording and Reporting

- Without delay all breaches must be notified to the Trial Manager and CI:
  - stop-covid19@dundee.ac.uk;
- Suspected data breaches, involving Participant Identifiable Data, must be notified to data protection / information governance within the relevant institution.
- The TASC Breach Reporting and CAPA Form will be completed by the Trial Manager and detail:
  - the nature of and reasons for the breach.
  - Corrective and Preventative Actions.

12.2.1 Serious Breaches

- The sponsor will be notified immediately of any case where the Serious Protocol Breach definition applies during the trial conduct phase: TASCpotentialbreach@dundee.ac.uk
- Suspected serious breach of the protocol or GCP will be reported to the Sponsor immediately using the TASC Breach Reporting & CAPA Form and will be recorded in the eCRF and documented in the trial TASC Breach Report Log.
- The sponsor of a clinical trial will notify the MHRA in writing of any serious breach of:
  - the conditions and principles of GCP in connection with that trial; or
  - the protocol (including amendments) relating to that trial.

12.3 Sponsor Classification of Breaches

- Sponsor will categorise breaches as either:
  - Potential Serious Breach
  - Breach of GDPR
  - Non-serious Breach
  - Not a Breach.

12.4 Breach associated documents

- TASC SOP59: Reporting Breaches in Clinical Research.
- Breach Report Log.
- Breach and CAPA Reporting Form.

13 Trial monitoring

13.1 Monitoring plan summary

- Trial monitoring will be carried out by the Sponsor: University of Dundee/NHS Tayside.
- The Monitoring Plan will be developed by the Sponsor monitoring team based on the trial risk assessment which may include on site monitoring. The Monitoring Plan will detail the procedures and anticipated frequency of monitoring, processes reviewed.
- It is anticipated that due to the COVID-19 pandemic that monitoring will be completed **remotely**.

13.2 Monitoring activity

- Remote monitoring will be scheduled at intervals to maintain oversight of sites. Higher recruiting sites may be asked to undertake remote monitoring visits more frequently.
- The Sponsor monitor will contact the sites in order to complete Remote Monitoring.
- Planned Monitoring Activity:
    - Site initiation – prior to first participant first visit at each site.
    - First participant first visit (FPFV) monitoring will be arranged within one month of the first participant recruited at site.
    - Close out – after the last participant last visit at each site.
    - A further site or remote monitoring visit will take place between 4 to 6 months following the FPFV. Further visits will be determined based on the occurrence of factors including, but not limited to:
        - SAE reporting
        - Breaches
        - Number of participants consented at site
        - Frequency of staff changes
        - High number of actions at FPFV.
    - Close out – after the last participant last visit at each site.
- An escalation of monitoring may be required based upon the following trigger points:
    - Breaches of Protocol
    - Breaches of GCP
    - Breaches of GDPR
    - Extended times to query resolutions.
- Following each monitoring visit the Monitoring Visit Report will be produced with any detailing any actions to be addressed. This will be issued to the PI, CI, STOP-COVID19 site contact, Senior Clinical Trial Manager, Clinical Trial Manager, Senior Clinical Trial Monitor and Senior Research Governance Manager.
- If any issues are raised during the TCTU remote monitoring review, discussions with the site and the Clinical Trial Manager will take place to resolve these issues.
- Any major issues resulting from this process may trigger a site monitoring visit following discussions with Sponsor and Senior Clinical Trial Monitor.
- Additional areas of concern raised with the Monitoring team may also prompt a change to monitoring provision at a site.

See Monitoring Plan, a copy can be found in the ISF.

13.3 Documents to be monitored

- Investigator Site File.
- Informed Consent Forms – 100%.
- Source document verification of critical data (endpoint data, dose adjustments, concomitant medications).
- Source document verification of adverse event reporting (AE, SAE, SUSAR) – 100%.
- Source document verification of eligibility.
- Trial medication management.

13.4 Monitoring associated documents

- Monitoring Plan.

14 Standard Operating Procedures

- As a condition of co-sponsorship by University of Dundee and NHS Tayside all trial sites will use TASC mandatory SOPs.
- All trial sites will implement the SOPs as detailed below.
- Once the PI and site personnel have reviewed the SOPs please sign/date the Training Log (to be filed in the Investigator Site File).
- SOPs should not be downloaded and filed. All current versions will be available via a link on the https://stop-covid19.org.uk/ for reference.

14.1 Sponsor SOPs

SOP Number	Title	Link to Website
TASC SOP11	Identifying, Recording and Reporting Adverse Events for Clinical Research	https://www.ahspartnership.org.uk/tasc/for-researchers/sops/safety-and-pharmacovigilance
TASC SOP59	Reporting Breaches in Clinical Research	https://www.ahspartnership.org.uk/tasc/for-researchers/sops/research-governance

15 Appendices

Schedule of Procedures

	Screening[d]	Randomization[d]			Follow-up Assessments	Follow-up assessments	Follow-up Assessments	Unscheduled Assessments
Timeline	Day 0 or 1	Day 1 Up to 24 hours after screening	Daily whilst hospitalised	Days 3, 5 &11 [c] (telephone call if at home)	Day 8[c] (telephone call if at home)	Day 15 [c] (telephone call if at home)	Day 29 [c] (telephone call if at home[b])	As Required in the event of AE
Informed Consent	X							
Inclusion/Exclusion Criteria Check	X	X						
Medical History	X							
Record Concomitant Medications	X	X			X	X	X	X
Check Vital Signs*^	X	X			X∞	X∞	X∞	X
ECG*	X							
Full blood count*+	X			X∞	X∞	X∞	X∞	
Urea and electrolytes*+	X			X∞	X∞	X∞	X∞	
Liver function tests*+	X			X∞	X∞	X∞	X∞	
SARS CoV-2 PCR*	X							
Record SARS CoV-2 PCR results, only if done for clinical reasons				X	X	X	X	
Nasal swab for SARS CoV-2 PCR* (Tayside only)						X∞	X	
Research Blood Sample * (Tayside and Sheffield only)		X			X∞	X∞	X	X
Sputum sample for storage if available*+ (Tayside only)		X			X∞	X∞	X	
Endotracheal aspirate sample for storage if available*+a (Tayside only)					X∞	X∞	X∞	

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Clinical status on 7 point scale	X	X	X	X	X	X	X	X
NEWS recording*	X	X	X	X∞	X∞	X∞	X∞	
EQ-5D questionnaire							X	
Record supplemental oxygen*	X	X			X∞	X∞	X∞	X
Record CT scan results, only if done for clinical reasons	X	X	X	X∞	X∞	X∞	X∞	X∞
Pregnancy Testing (urine or blood) If Applicable	X							
Record Adverse Events		X	X	X	X	X	X	X
Randomisation		X						
Dispense Trial Drugs		X						
Drug Return And Compliance Check							X	

CODE:
^ Vital Signs: Blood Pressure, pulse, temperature, oxygen saturation
*indicates procedures that will be performed by the clinical team as part of routine care, but results will be recorded and included in the eCRF. If not performed by the clinical team, but clinically indicated, the research team may assist in this being performed but all processes will avoid duplication and exposure to potentially infected participants.
[+]Excess biological samples that are being taken for clinical reasons may be stored for future use if no longer required for clinical purposes (Tayside only).
[a]For those participants who are intubated.
[b]For the Tayside and Sheffield site only, the day 29 assessments will be carried out face-to-face either at a NHS facility or at the participant's home. Home visits will only be carried out if no one in the household has symptoms of COVID-19.
[c]Research blood samples (Tayside and Sheffield only) and, once discharged, assessments may be completed within +/- 1 day
[d]Screening and randomisation may occur on the same day if all eligibility criteria are met. Day of first dose of IMP will be considered as day 1 for the calculation of follow up assessments

∞ These assessments will not be completed if the participant has been discharged from hospital except at the Tayside/Sheffield site where discharged participants will attend a Day 29 visit.