The risk profile of acquired arrhythmia syndromes during COVID-19/SARS-CoV-2 infection and therapy: A sub-study of the RECOVERY trial

Guide for local clinical centres

Background

The significance of life-threatening arrhythmias and their aetiology in COVID-19/SARS-CoV-2 infection is unknown. Furthermore, the genomic profile of risk for acquired arrhythmia syndromes during COVID-19/SARS-CoV-2 infection and as a result of anti-viral therapy is unknown. We wish to develop genomic and clinical profiling to identify risk in the hospitalised and critically ill patient.

The RECOVERY trial offers an opportunity to study arrhythmia outcomes together with drug therapies. Co-recruitment to either ISARIC 4C (Ethics ref: 13/SC/0149) or GenoMICC (Ethics ref: 19/WM/0247) studies will take advantage of available whole genome sequencing (WGS), enhance recruitment to these important projects and permit correlation to genomic factors. As observational studies these do not conflict with the RECOVERY trial.

The project has two cohorts, a prospective and a retrospective. The prospective cohort will investigate new patients enrolled into RECOVERY and ISARIC 4C or GenoMICC. The retrospective cohort will look at previously enrolled patients who have had an ECG collected at day 0 and day 2 of treatment.

Instructions for data collection are attached overleaf. No additional ethical approvals are required.

Prospective cohort:

This cohort will include patients newly randomised to RECOVERY if they are randomised to receive azithromycin or no additional treatment.

Inclusion

- Adult (age >18 years) RECOVERY participants.
- Randomised prospectively to receive azithromycin (AZM) **OR** no additional treatment.
    - **AND**
- Suitable ECG data: at least a baseline ECG and an ECG at 48 hours after randomisation (see below).
    - **AND**
- Prospective co-enrolment in ISARIC 4C or GenoMICC studies. Co-enrolment is not essential for inclusion but is strongly encouraged.

Data to be collected (additional to the current RECOVERY dataset - see Figure 1):

Standard 12-lead ECGs

- Day 0 (Baseline) ECG
    - Perform a 12-lead ECG on the day of enrolment immediately before the first dose of study medication.
    - **OR**
    - If a 12-lead ECG has already been taken since admission but before the first dose of study medication, this can be used as the day 0 ECG.
- Perform a follow-up ECG on day 2 of treatment with study medication immediately before the next dose.
- Redact any identifiers on ECGs and mark clearly the RECOVERY participant ID and time and date of ECG on them.
- Scan the ECGs and then upload to the OpenClinica platform (see instructions below).

Co-enrolment in ISARIC 4C or GenoMICC study (if applicable)

- Record the identifier from either study for each participant in the RECOVERY OpenClinica platform (see instructions below).

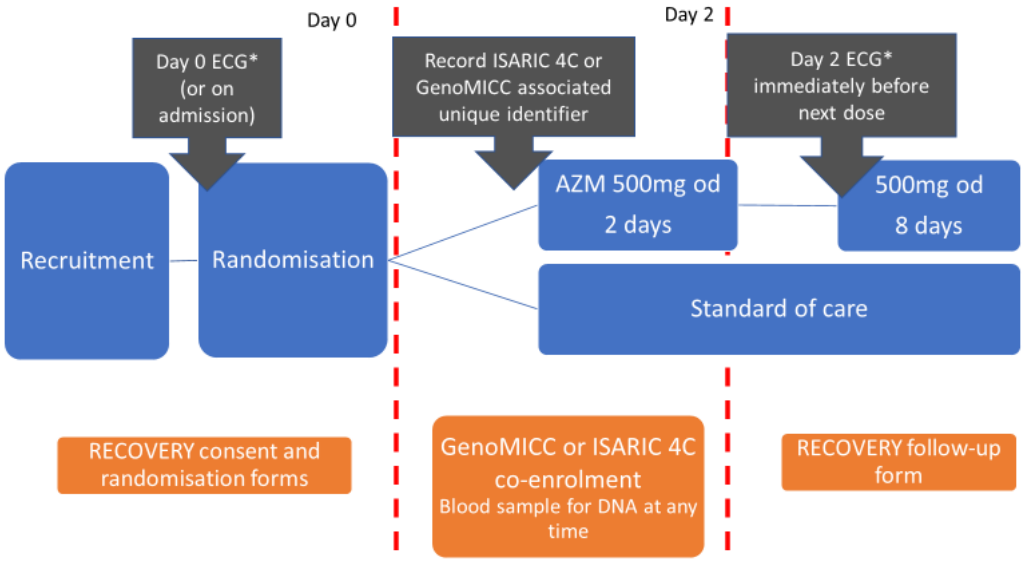


Figure 1: Prospective cohort: Algorithm for recruitment, timing of ECGs and data to be collected additional to the RECOVERY dataset (grey boxes). The orange boxes indicate usual study activity that would already be in progress. * ECGs will have any identifiers removed and the RECOVERY participant ID, time and date of ECG clearly marked before they are scanned and uploaded to the OpenClinica platform.

Retrospective replication cohort:

This cohort will look at participants who have previously been randomised in RECOVERY to receive one of azithromycin, hydroxychloroquine or lopinavir-ritonavir. Patients will also need to have been recruited to ISARIC 4C and/or GenoMICC, and will need to have had an ECG taken before initiating study treatment and on day 2 of treatment.

Inclusion

- Adult participants (age >18 years) previously recruited to RECOVERY trial
- Received AZM, hydroxychloroquine (HCQ) or lopinavir-ritonavir (L-R).
    - **AND**
- Prior recruitment to ISARIC 4C and/or GenoMICC.
    - **AND**
- Previously collected suitable ECG data: at least a baseline ECG and an ECG at 48 hours after randomisation (see below).

Data to be collected (additional to the current RECOVERY dataset - see Figure 2):

Identify participants previously recruited to AZM, HCQ and L-R arms

Confirm enrolment in ISARIC 4C or GenoMICC study

- Record the identifier from either study for each participant in the RECOVERY OpenClinica platform.

Identify if required 12-lead ECGs are available

- ECG on day 0 of enrolment immediately prior to initiation of therapy **OR** if an ECG has been done after admission but before the first dose of study treatment then this can also be used.
- Follow-up ECG taken at day 2 of therapy.
- Redact any identifiers on ECGs and mark clearly the RECOVERY participant ID and time and date of ECG on them.
- Scan the ECGs and then upload to the OpenClinica platform (see instructions below).

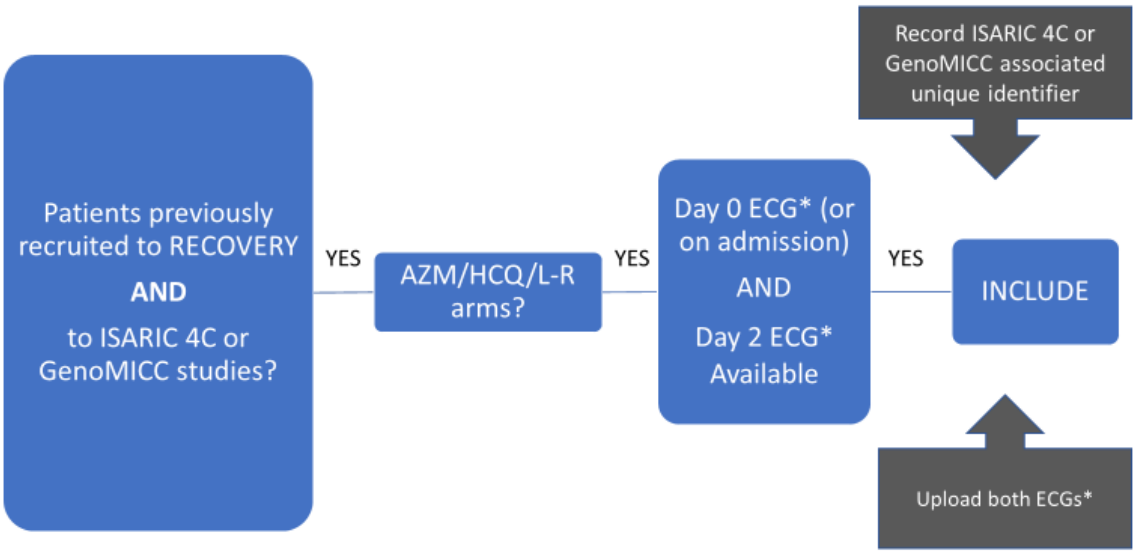
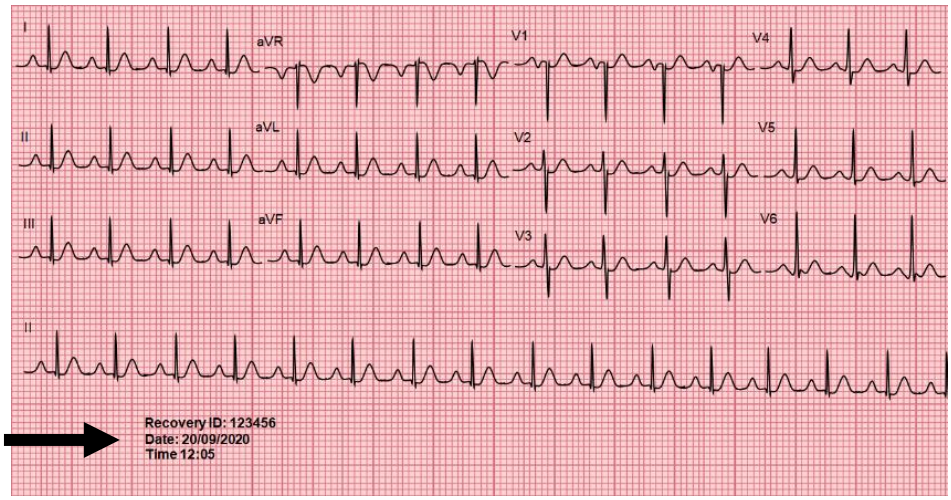


Figure 2: Retrospective replication cohort: Algorithm for inclusion of cases and data to be collected to the RECOVERY platform (grey boxes). *ECGs will have any identifiers removed and the RECOVERY participant ID and time and date of ECG clearly marked on them, before they are scanned and uploaded to the OpenClinica platform.

Instructions for uploading ECGs to the OpenClinica platform

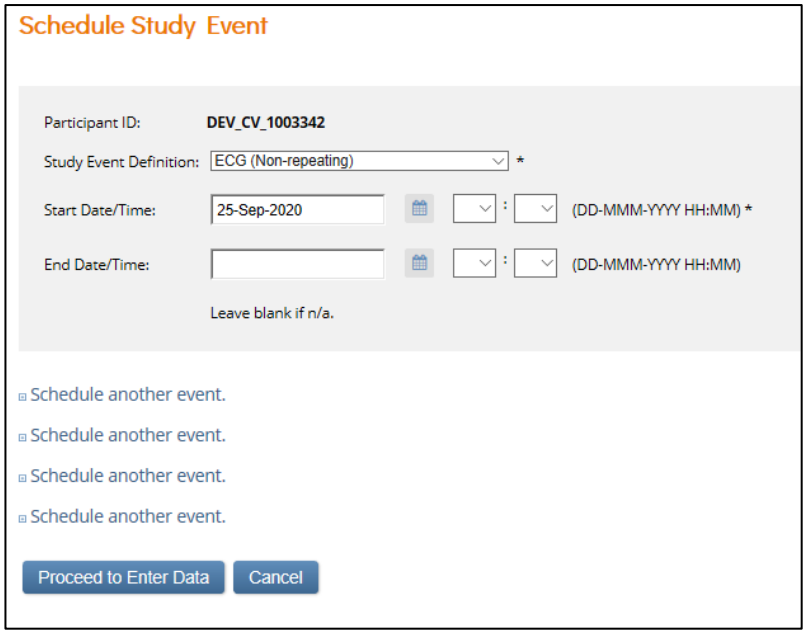
Before uploading:

1. Ensure any patient-identifiable information has been redacted
2. Clearly mark the following information on the ECG:
    - RECOVERY participant ID
    - Date that the ECG was taken
    - Time that the ECG was taken

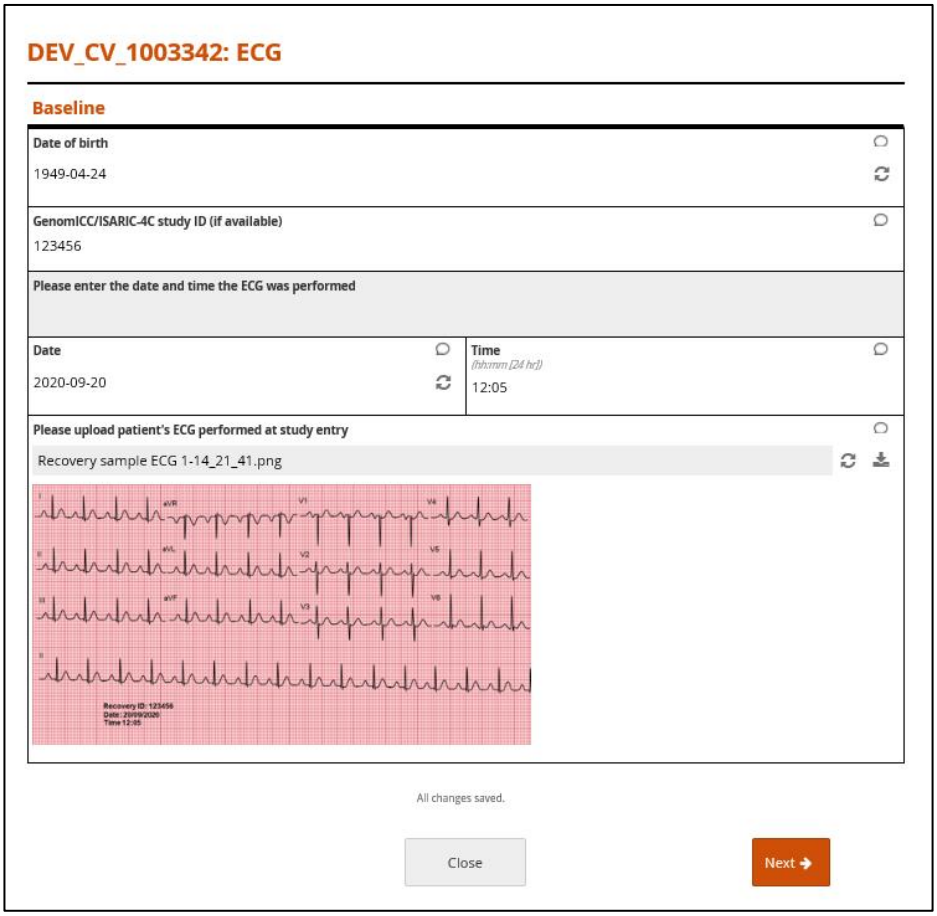


To upload ECGs:

1. Scan the Day 0 and Day 2 ECGs
2. Log into OpenClinica and search for the participant using the RECOVERY participant ID
3. Click on the schedule event button in the ECG event column. Click Schedule in the pop-up box
4. Click Proceed to Enter Data



5. Click the data entry  button
6. Enter participant's date of birth, the GenomICC/ISARIC-4C study ID (if available), along with the time and date the ECG was taken
7. Click in the box to upload the baseline (day 0) ECG (maximum file size of 95 MB)
8. Click next



9. Upload the day 2 follow-up ECG and enter date and time of day it was taken
10. When you have checked to ensure the entered data are correct, click ‘Complete’ to complete the process and save the form.