Dear all,

We understand there are huge challenges arising in relation to the COVID-19 pandemic, which will have a significant impact on the running of the health service and all clinical research, including the STOP-ACEi trial. We would like to provide some initial guidance.

STOP-ACEi follow-up and treatment was designed to mirror standard care as closely as possible. Recruitment into the trial is complete, and around 2 thirds of participants have already completed follow-up. The treatments used in the trial form part of standard care, and are prescribed and used as they would be under standard care. Therefore we are anticipating the impact on the trial overall to be minimal. However, we do understand there will be additional protocol deviations over this period as staff are stretched, or drafted into clinical care, and participants may be unable or unwilling to attend for follow-up as scheduled.

1. **SAE reporting:** please **DO NOT FAX** these. Due to access restrictions (see below) we may not be able to pick up a fax. Email all SAEs as soon as possible to the trial office mailbox (stopacei@trials.bham.ac.uk). We will always confirm receipt of an initial SAE report within 1 working day, so please e-mail if you think any have not been received. We understand there may be delays in the research team becoming aware of SAEs if participants are not being seen in outpatients as usual. As always, please be careful to thoroughly anonymise any clinical reports sent.
2. **SAE clinical review:** Clinical review of SAEs is considered a matter of patient safety. Please continue to arrange PI assessment of SAEs to determine whether or not the event is related to the allocated trial treatment. This should be done and reported to BCTU within 7 days of becoming aware of a new event. Any doctor with this responsibility delegated can perform this assessment. We strongly recommend that all centres consider whether more clinicians could be delegated this responsibility to ensure cover in case of staff absence.
3. **BCTU and communication**: As of 18th March 2020, access to the University of Birmingham, including the STOP-ACEi trials office, has been restricted. All staff will continue working normal hours, but will be working remotely. E-mail is the preferred means of communication, but we can arrange to call you if needed. Always use the trial mailbox rather than e-mailing individual members of staff so we can ensure cover should there be staff absences.
4. **Participant follow up and data collection**:
    - National and local policies are restricting travel and attendance to hospitals, and hospital systems are planning for a major increase in emergency medical admissions. Outpatient clinics are also moving to remote methods to follow-up patients. Trial participants may not want to attend clinics due to fear of infection, or in a desire to participate they may undertake ill-advised travel. In order help ensure participants' safety and minimize the impact of Covid-19 on the trial's integrity, we have updated our advice:
        1. Please follow your national and local policy with respect to infection control.
        2. There are a number of patients with 36 Month Follow Up visits approaching in the next two months who may not be able to attend depending on the current and planned restrictions affecting outpatient appointments. Depending on the phase of the Covid-19 pandemic in your region, and your current Trust policy, please consider whether it is possible and appropriate to bring forward an appointment (i.e. to the start of the ± 6 weeks visit window) to potentially allow a visit, or for the primary outcome measure (creatinine) to be obtained.
    - The majority of the data collected for STOP-ACEi, including the primary outcome measure, are recorded as part of routine monitoring and care. The trial Protocol already anticipates that data from routine care records will be used, and there is a generous visit window of ± 6 weeks so that a clinical visit of any date will fall into

one of the trial visit windows. The most important item of data is the creatinine reading, especially at the final visit at 36 months.

- Where possible, follow up data should be taken from patient medical records/hospital notes and the relevant CRF completed as fully as possible. We understand there may be a delay with data entry and this may need to be done retrospectively, e.g. if staff are drawn into clinical work or stretched due to staff absences.
- We understand that outpatient appointments will be missed or disrupted. We also appreciate it may not be possible to perform non-routine tests (e.g. the walk test), or that you may only be able to capture some data remotely (e.g. posting questionnaires or confirming information with a patient over the phone rather than in clinic). A comment in the 'Notes' section on the Remote Data Capture system to explain any missing data will help keep queries to a minimum.
- The reason for any missed visits, missing data due to tests not being performed, or data being collected remotely, should be documented in the source records as normal for a protocol deviation. We understand there may be delay in doing this as staff will be stretched. The regulatory authorities have emphasised that deviations to the protocol over this period will be viewed with understanding, but that there will still be an expectation that the reason for any deviations will be documented (see guidance on MHRA blog: https://mhrainspectorate.blog.gov.uk/2020/03/12/advice-for-management-of-clinical-trials-in-relation-to-coronavirus/).

5. **Participant withdrawal**: If a participant does not want to attend a clinic visit or have additional research assessments for any reason, please do not immediately withdraw them from the trial. Please firstly ask if they would be happy to continue to allow their routinely collected clinical data to be used for the trial. This will allow them to continue to contribute to the trial, but without attending additional clinics or having additional research assessments. If the patient still wants to fully withdraw from the trial, of course, they always have this choice. Please see the trial Protocol for full guidance regarding partial withdrawal.
6. **Ongoing data cleaning**: We are aiming to maintain business as usual for the Clinical Trials Unit as far as possible. Therefore, we will continue to review the trial data and raise queries as normal to avoid a backlog building up. However, we appreciate you are unlikely to be able to address these. We are suspending chasing for query responses to alleviate some pressure. The exception will be for clinical review of SAEs and for adequate detail on SAEs to permit central clinical review, as these have patient safety and regulatory implications.

Thank you very much for all of your assistance in this difficult time, and with your continued support of the STOP-ACEi trial. We wish you the best in dealing with this outbreak.

Best Wishes,
Alastair Maund
Trial Manager