22\textsuperscript{th} January, 2021

Dear REMAP-CAP sites,

**RE: Therapeutic Anticoagulation Domain in Moderate State**

We are writing to inform you of decisions that have been made by the REMAP-CAP international trial steering committee (ITSC) in response to communication from the Data and Safety Monitoring Board (DSMB).

After reviewing the results of 1398 patients included in the combined multi-platform interim analyses and safety reports from REMAP-CAP and our collaborating trials ATTACC and ACTIV-4, the REMAP-CAP DSMB have notified the ITSC that the therapeutic anticoagulation intervention has reached the pre-specified threshold for **superiority** for patients in the Moderate State (patients not receiving qualifying organ support in ICU) of >99% posterior probability of benefit. This statistical threshold for the superiority of therapeutic anticoagulation over usual care thromboprophylaxis was met in both the low and high baseline d-dimer subgroups. The safety profile also supports the benefit of therapeutic anticoagulation in this patient population.

The unanimous recommendation of the DSMB was that this domain be closed for randomisation to patients in the Moderate State. This recommendation has been accepted by the ITSC. This will be implemented within the REMAP-CAP eligibility system at all sites.

Note that this decision complements the earlier advice from the DSMB and ITSC decision to pause enrolment in the Severe State (patients receiving qualifying organ support in ICU) for futility and concerns regarding safety.

All randomized patients, regardless of treatment assignment, should be followed up for 90 days as per the Core Protocol.

Patients currently receiving allocated treatment assignments in this domain may continue to do so at the discretion of the treating clinician. If it is decided that a patient randomized to the usual care arm should receive therapeutic dose heparin in the absence of a specific clinical indication for therapeutic anticoagulation (that is, they receive the REMAP-Therapeutic Anticoagulation treatment arm protocol), this may be administered but should be recorded in the CRF as a protocol deviation.

We will work to analyse and report these findings as soon as possible and request that sites make this information available only to relevant clinical staff.

On behalf of the REMAP-CAP ITSC we would like to thank the DSMB and the Statistical Advisory Committee for their vital work in ensuring the safety of patients enrolled in REMAP-CAP. We would
also like to sincerely thank all investigators, research coordinators, participants and their families who continue to support REMAP-CAP and the generation of evidence for the treatment of COVID-19.

If you have any questions about any of the above, please don't hesitate to contact us.

Sincerely,


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