

19<sup>th</sup> November, 2020

Dear REMAP-CAP sites,

**RE: Tocilizumab and Lopinavir/ritonavir Platform Conclusions**

I am writing to inform you that on the 18<sup>th</sup> of November we received correspondence from the REMAP-CAP DSMB notifying us of two Platform Conclusions arising from an interim analysis.

Tocilizumab and the Immune Modulation Domain

An interim analysis of the first 303 patients randomised in the Immune Modulation Domain of REMAP-CAP revealed that the tocilizumab had reached a statistical trigger for efficacy when compared to the 'no immune modulation' intervention.

The trial data revealed an estimated odds ratio of 1.87 for improved primary outcome (a composite ordinal scale of hospital mortality and days free of organ support in ICU to Day 21) with tocilizumab when compared to no immune modulation. This result has a high degree of statistical certainty, with 99.75% probability that tocilizumab is superior to no immune modulation. Currently we are unable to say whether tocilizumab is superior to any of the other active interventions in this domain.

As a result of these findings, the 'no immune modulation' intervention within this domain will be closed for randomisation. We acknowledge that sites will consider whether tocilizumab should become standard care in critically ill patients with COVID-19 at that site. However, it should be emphasised that other interventions within the domain may also be effective, or even more effective, than tocilizumab. While it is ethically imperative to withdraw the standard-of-care control arm, the domain is designed to continue, with all patients receiving an immune modulator to determine relative effectiveness. This was strongly encouraged by the DSMB and their only recommendation was to withdraw the standard-of-care control intervention.

For sites with two or more active immune modulation interventions, the domain remains available. For sites evaluating only a single active intervention, the removal of the control intervention will result in closure of the domain, but we would encourage such sites to consider adding additional interventions to allow the domain to continue at their site. Your regional leads will follow this letter with instructions and further conversations. Changes to the trial eligibility system, that remove the 'no immune modulation' intervention will occur at the same time as distribution of this letter.

The data from all patients randomised in the domain up to today will be analysed for full release and publication. Due to the rapid recruitment to this domain since this interim, we expect the final analysis to include data from many more participants. We would appreciate your assistance in making sure that data entry is up to date in preparation for this analysis, **with a planned lock of the database on December 12, which is 3 weeks + 2 days after the last randomized patient**

Lopinavir/ritonavir

This interim analysis also found that treatment with lopinavir/ritonavir was found to be ineffective, with an estimated odds ratio of 0.67 (worse than 'no antiviral' control), with a 99.9% probability of an odds ratio of less than 1.20 (which was the pre-specified Statistical Trigger for futility).

As a result, the lopinavir/ritonavir intervention in the COVID-19 Antiviral Domain will be closed to recruitment. This will effectively mean that the COVID-19 Antiviral Domain will enter a dormant state, but may be reactivated if future interventions are added to this domain.

I would like to thank the investigators, research coordinators, participants and their families, who continue to support REMAP-CAP for their contribution to these important findings.

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

Sincerely,



Professor Steve Webb  
Chair,  
REMAP-CAP International Trial Steering Committee

Phone: +61 408 866 274

Email: [Steven.Webb@monash.edu](mailto:Steven.Webb@monash.edu)