Thursday 18 June 2020

Chair of the Executive Group of the Solidarity Trial
to the National Principal Investigators of the Solidarity Trial

Subject: Cessation of Hydroxychloroquine and Strategic Decision to Modify the Treatment Arms of the Solidarity Trial to evaluate only Remdesivir and Interferon

Dear Solidarity Trial Principal Investigator,

The Executive Group met on the 10th and 12th of June to discuss i) a review of interim analyses of hydroxychloroquine vs standard of care data from the Solidarity/Discovery trials and a pooled analysis conducted including UK Recovery trial data and ii) subsequent decisions for continuation with the Solidarity trial and its associated add-on studies. After careful consideration, the Executive Group agreed on the following decisions.

i) The hydroxychloroquine arm of Solidarity will be stopped due to futility

The internal evidence from Solidarity/Discovery, the external evidence from Recovery, and the combined evidence, bring together fairly large scale randomized evidence on hydroxychloroquine vs standard of care for treatment of hospitalized COVID-19 patients in countries around the world. The results confirm with high a degree of confidence that hydroxychloroquine is not effective at reducing mortality in hospitalized COVID-19 patients. It is important to note that these results are not applicable to use of hydroxychloroquine for prophylaxis or non-hospitalized patients where some uncertainty still remains about the effectiveness or lack of effectiveness for COVID-19.

Based on the analyses above, and a review of the available published evidence from other sources, the Executive Group made the decision to cease the hydroxychloroquine arm of the Solidarity trial. The hydroxychloroquine arm will be removed from the online randomization software. Hence, investigators cannot randomize further patients to hydroxychloroquine in the Solidarity trial. Patients who have already started hydroxychloroquine but who have not yet finished their course in the trial may complete their course or stop at the discretion of the supervising physician. WHO has decided to go public on this specific clinical trial decision in the press conference on the 17th of June, but note that this is not a WHO policy or guidelines recommendation; separate processes at WHO develop guidelines. WHO's existing clinical management guidance does not recommend any specific antiviral as part of standard of care for hospitalized COVID-19 patients. A short research communication is being drafted to publish the evidence from the Solidarity trial on hydroxychloroquine.

ii) The Solidarity trial protocol will be amended strategically to address the remaining questions of public health importance

Solidarity is now randomising more than 500 COVID-19 patients a week, which is more than any other trial. It was conceived as an adaptive trial, so it has an opportunity and

responsibility to contribute to other key public health questions that have not yet been reliably answered. Hence, the best way to adjust the protocol to focus on the critical public health questions best addressed through the Solidarity trial was considered during the 10th and 12th June meetings of the Executive Group.

The Executive Group considered that Remdesivir and Interferon beta-1a are the two study drugs which Solidarity trial is best placed to evaluate definitively for possible effects on mortality, and therefore recommended the following modification of the randomization arms.

A) Remdesivir + SoC
B) Interferon-beta 1a + SoC
C) Remdesivir + Interferon-beta1a + SoC
D) SoC alone

This four-arm 2 x 2 factorial design will allow two main analyses to be carried out: Remdesivir vs 0 (stratified for Interferon), and Interferon vs 0 (stratified for Remdesivir).

The Lopinavir/ritonavir arms will therefore be discontinued, as it is expected that the UK Recovery trial, given its current size, will assess Lopinavir/ritonavir robustly without additional recruitment into Solidarity. This discontinuation is a strategic decision, taken without knowledge of the still-blinded data, so the scientific community should not draw any conclusions about benefit or lack of benefit from it. Evidence from Recovery will together with the data from Solidarity will provide good data on Lopinavir/ritonavir in due course.

The Executive Group has made these decisions and have communicated them to WHO as sponsor of the trial. WHO has asked for analyses of both the HCQ as well as the Lopinavir/ritonavir data before confirming these protocol changes. Such analyses are now being conducted and will be communicated as soon as possible. We trust this written communication will serve as confirmation of the decisions and the considerations that motivated them. An amended protocol will soon be circulated. Until then, collaborating investigators should not allocate patients to hydroxychloroquine and can choose not to allocate to Lopinavir/ritonavir by answering "no" when the program at the time of randomization asks whether these drugs are available. We encourage all study sites to at least have one study drug available with support from their national Principal Investigator and the Trial Secretariat.

Thank you for your continued collaboration,

John-Arne Røttingen

The Executive Group of the Steering Committee of the SOLIDARITY trial is John-Arne Røttingen (Chair), Quarraisha Abdool Karim, Marissa M. Alejandria, César Hernández García, Marie-Paule Kieny, Reza Malekzadeh, Srinivas Murthy, Srinath Reddy, Mirta Roses Periago, Richard Peto (observer, DSMC Statistician) and Soumya Swaminathan (on behalf of WHO)