World Health Organization

WHO R&D Blueprint

novel Coronavirus

Outline of trial designs for experimental therapeutics

WHO reference number WHO/HEO/R&D Blueprint (nCoV)/2020.4

January 27, 2020, Geneva, Switzerland

R&DBlueprint

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Objectives of the call

- To further the key elements of trial design for experimental therapeutics for a novel coronavirus
- To agree on critical next steps to provide guidance in this area of work.

Summary of the Working Group on Treatment prioritization

Among the different therapeutic options, Remdesivir was considered the most promising candidate based on the broad antiviral spectrum, the in vitro and in-vivo data available for coronaviruses and the extensive clinical safety database (in particular coming from the Ebola virus disease clinical trial and MEURI) in eastern Congo). Further, studies in mice using Remdesevir showed superior efficacy over Kaletra + IFNbeta. A clinical trial is being planned in China to evaluate the safety and efficacy of Remdesivir in association with optimized standard of care.

Among the repurposed drugs, the investigation of the antiretroviral medicine (HIV protease inhibitors), lopinavir/ritonavir, either alone or in combination with IFNbeta1b, which is a combination currently investigated in the Kingdom of Saudi Arabia for the treatment of MERS-CoV (MIRACLE trial), was considered a suitable second option for rapid implementation in clinical trials. Preclinical data available and limited clinical experience in the context of MERS, would suggest that it could provide some degree of clinical benefit and would be worth investigating particularly in severe cases. Based on the investigation conducted in Saudi Arabia (with mortality at day 90 as the endpoint), a protocol assessing lopinavir/ritonavir as monotherapy, is being implemented in China,

with clinical improvement by day 28 as the endpoint. Recruitment of this trial is close to completion. Interim analysis outcomes are anticipated shortly.

It was reflected that monoclonal and polyclonal antibodies that are currently in early development are mainly targeting MERS. Based on current knowledge on the viral composition and homology with other coronaviruses, it might be anticipated that the likelihood that the current investigational immune-therapeutics will retain sufficient activity against the new virus might be low. However, since immune-therapies could play a significant role in the treatment of the nCoV, it is warranted to continue exploring the possibility to further develop medicines based on this approach specifically targeting the nCoV. Further preclinical studies are required to asses and validate emerging monoclonal antibodies before advancing them into clinical evaluation. There is ongoing work to ascertain if there is cross protection between available monoclonal antibodies and nCoV. Monoclonal antibodies could be promising and kept in view, but the focus currently should be on candidates that could be evaluated immediately.

The use of convalescent sera could also be an option for consideration, but it remains to be defined if sufficient amounts of sera with high antibodies titres could be feasibly collected, using concentration and purification processes.

Other agents in Phase I clinical development such as a TMPRSS-2 inhibitor might merit further discussion.

Among the products that should not be prioritised, there was consensus that Ribavirin does not appear like a candidate worth further investigating, based on the available evidence. The experience with its evaluation in SARS in Canada in 2003 may have resulted in higher mortality than in other countries. It also reduced haemoglobin concentration- a side effect that is undesirable in patients with respiratory disorders.

Immunosuppressants and immunostimulators (e.g. corticosteroids/steroids) were also identified as products to be deprioritised as there is not enough information when the treatment should be given, and they may possibly be harmful in the context of mild illness, although there is evidence of efficacy in the setting of severe illness. This again underlines the importance of differentiating between mild and severe disease.

Chloroquine was also mentioned as product for which there is insufficient evidence to support its further investigation.

Finally, there are other products, not on the list provided, in early development and that would deserve to be discussed in a second stage. Information will be shared by and with the meeting participants.

Summary of the deliberations on Master Protocol synopsis

There is strong agreement that the study design of the Master Protocol should be
– randomized
- multi-center
- multi-arm to accommodate the drugs prioritized by the Working Group on Treatment Prioritization.

- should be initiated as soon as possible with a pilot phase designed to learn more on the natural history of the disease. After a certain number of people enrolled, the Data Monitoring Committee would provide recommendations on some of the key methodological elements to the Trial Steering Committee based on the preliminary data available. It is agreed that the patients enrolled during the pilot should not contribute to the primary analysis.

Key methodological elements that still need require clarifications and consensus

Primary endpoint – A composite endpoint of "mortality and clinical improvement" from the time of first dose in eligible and consented participants, where the I-type error would be split between the two. In that case, success would be declared for a drug show significant effect on mortality OR on the indicator for clinical improvement.

Clinical improvement should be based on a ordinal scale, based on composite scores used in influenza trials. Several scales were proposed with death at the