



WHO R&D Blueprint novel Coronavirus

Outline of trial designs for experimental therapeutics

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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 Remdesivir 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 assess 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 extreme end of the scale.

Participants noted that there are too many uncertainties around severe clinical features, including mortality, in hospitalized patients as well as risk factors for severe disease and therefore the study design should consider multiple endpoints given the current knowledge. To address those uncertainties, participants recommended to initiate the trial with a pilot phase to learn more about the natural history of disease while granting access to the most promising molecules. Data on safety and efficacy during the pilot phase would not contribute to the study primary analysis but will be assessed by the Study Data Monitoring committee, while results remain confidential, who would in turn



provide recommendations to the Trial Steering Committee on the primary endpoint to be considered during the trial continuation and for the primary analysis.

It remains critical to define what should be measured in patients during the pilot phase to support the assessment of the primary endpoint and further adjustment on sample size and power calculations.

Finally, it was noted that choosing a composite endpoint would increase the trial power, particularly if mortality is low.

Inclusion criteria – All nCoV symptomatic confirmed cases hospitalized patients should be included (with an objective criteria to define symptomatic)

Participants noted that there is a subset of patients that may be hospitalized for infection control only but who would remain asymptomatic, like it is the case for MERS-CoV outbreak control. This practice varies considerably across hospitals. For those patients, there may be a need to restrict trial enrolment for particular drugs based on safety, practical and availability issues. Alternatively, it was suggested that another study could be specifically conducted in asymptomatic patients for drugs with reasonable safety profile and sufficient availability to assess their effect on clinical progression and virologic outcomes, such as viral shedding.

Some of the participants noted that restricting the enrolment process to symptomatic or to severe cases would reduce the amount of information collected in the trial, would provide operational hurdles for eligibility assessment, and would decrease trial power, particularly in the perspective of a composite endpoint with clinical improvement. More importantly, restricting the enrolment process to severe cases only would delay the initiation of treatment and would potentially reduce the therapeutic benefit of early treatment initiation (such as preventing progression to pneumonia).

Here, data collected during the pilot phase and summarized to the Data Monitoring Committee could be extremely helpful to help reconsider the inclusion criteria.

Finally, it was noted that randomization could be minimized on patient characteristics (e.g. severity) at enrolment. The primary analysis should be stratified by center.



A standard of care comparator arm –

The comparator arm should be based on a standard of care arm, particularly if the standard of care can be optimized and harmonized across sites.

Some of the participants noted that more merit should be given to a trial design of type A:B:A+B, assuming Drug A and Drug B with sufficiently different mechanisms of action. Such design may enhance trial acceptability and enrolment as well as obtain faster ethical approval by providing at least an investigational drug to all participants. The effect of Drug A would be obtained after comparison of A+B vs B and the effect of Drug B would be obtained after comparison of A+B vs A.

However, it is unclear whether the potential sociological advantages of such design noted above would outweigh the scientific disadvantages of such trial. In general, the interpretability of a trial that would not have an oSOC control regimen, such as trials with two experimental arms (i.e., A vs B) or three experimental arms (i.e., A vs B vs A+B) raises important concerns. The 3-arm trial readily could yield either false positive or false negative conclusions about the effects of arms A and B; to be specific, false negative evidence could arise if single agent regimens A and B would be very effective, yet (due to having mechanisms of action that are not additive), their combination A+B would yield a similar result to single agent A and to single agent B; false positive evidence could arise if A and B are, individually, ineffective, yet A+B is effective due to positive synergy. In that latter scenario, we would recognize A+B would be preferred, yet one might improperly interpret this to be evidence that A alone is effective (since when added to B the combination beats B alone), and similarly that B alone is effective. That could be problematic in real world settings, such as when one of these products would be in short supply and it were incorrectly argued that patients still would benefit by administration of the other product alone.

Proposed next steps

- WHO will organize a follow-up call to finalize the proposed study design
- WHO will establish a separate Working Group on Protocol Writing to translate agreed methodological elements into a Master Protocol.