WHO R&D Blueprint

novel Coronavirus

Outline of designs for experimental therapeutics

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Table of Contents

TABLE OF CONTENTS ........................................................................................................ 2

PARTICIPANTS .................................................................................................................. 3

MEMBERS OF THE R&D BLUEPRINT CLINICAL TRIALS EXPERT GROUP .................................................. 3
WHO SECRETARIAT ............................................................................................................. 3

OBJECTIVES OF THE CALL .................................................................................................. 3

OVERVIEW OF THE EPIDEMIOLOGICAL SITUATION ........................................................................ 3

CONSIDERATIONS FOR TREATMENT TRIALS .................................................................................. 4

Target population .............................................................................................................. 4
Endpoints ............................................................................................................................. 4

PROPOSED NEXT STEPS .................................................................................................... 6
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Objectives of the call

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

Overview of the epidemiological situation

As of 20 January 2020, 278 confirmed cases were reported in China, including 51 severe cases, 12 in critical condition and 6 deaths. Among the 278 confirmed cases, 15 are reported to be healthcare workers. During the call, 4 additional cases were reported to have occurred in Shanghai and that have been hospitalized.

In addition, 2 separated exported cases were reported in Thailand, 1 in Japan and 1 in South Korea.

An observational study is ongoing in Wuhan to better understand the clinical features of the patients admitted in hospitals.

In parallel, an RCT to determine whether lopinavir/ritonavir is safe and effective in treating patients infected with nCoV has been recruiting patients in Wuhan and is close to complete enrolment. The patients covered a wide range of disease severity. The primary endpoint is a measure of time to clinical improvement.

Disease characterization

Some preliminary discussion on definitions being used/considered took place. Definitions of critical illness includes admission to an Intensive Care Unit (ICU) and presence of respiratory failure OR septic shock OR multi-organ failure.
Severe illness definitions include dyspnea OR respiratory rate more than 30bpm OR hypoxemia OR pulmonary infiltration progressed more than 50% within 24-48hrs.

Considerations for treatment trials

Following earlier deliberations on clinical trial designs that took place on 15 January, 2020, the experts were invited to consider potential end points for clinical trials under the assumptions that this was a nCoV, which transmits human to human via the respiratory route.

It was reiterated that the optimal approach will be the use of a master protocol, as part of a multicentric trial, in order to increase chances to yield robust and conclusive results. It was also underlined that it is important that selection to candidate therapeutics transparently select candidate treatment for evaluation under an evidence-based framework.

Target population

Participants reaffirmed that all symptomatic hospitalized nCoV confirmed patients should be part of target populations.

In the perspective of a multicentric trial, confirmatory diagnosis procedures should be harmonized across trial sites and case definition as well as the implementation of optimized supportive care.

On symptoms, participants noted that hospitalized but asymptomatic MERS-CoV patients – i.e. for containment purpose - are not eligible to the MIRACLE trial. Patient must exhibit some clinical features such as low blood pressure or requiring oxygen therapy to be eligible to the trial. Based on the MIRACLE trial, it was noted that recruiting ICU-admitted patients only is not appropriate mainly because of the associated delay in recruitment and treatment initiation. Instead, participants noted that, the analysis should be stratified to assess the effect of the drug in various subgroups, such as ICU-admitted patients.

Endpoints

Participants reaffirmed that a mortality primary endpoint alone is not appropriate given the current number of deaths to appropriately power a trial,
Coronavirus - Outline of designs for experimental vaccines and therapeutics
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noting that the current estimated CFR is between influenza and MERS-CoV. However, participants agreed that the number of deaths was of sufficient clinical concern and should be included in the definition of the primary endpoint.

Therefore, participants recommended that a composite primary endpoint based on a mortality endpoint + a measure of clinical improvement OR disease severity (to be defined) should be used.

On mortality, participants noted that among the deaths being reported, time from disease onset to death was as long as 40 days.

On the measure of clinical improvement or disease severity, various suggestions were made but no preferred component could be precisely defined, as we need to better understand the natural history of the disease. Overall, this component should be of clinical relevance and a reasonable predictor of disease severity.

Participants noted that a time-to-event endpoint, such as time-to-ICU admission, time-to-discharge, or time-to-some clinical feature predictive of disease severity should be further explored, recognizing the potential variability of those definition across hospitals. It was however reflected that an endpoint of hospital discharge, if not well defined upfront, would suffer from lacking objective criteria and considering a multicentric study, it cannot be excluded that biases would be introduced based on standard local practice and discharge criteria.

Other suggestions, based on influenza treatment trial, include the NEWS2 score, or any composite score that could be fit-for-purpose and could describe the clinical improvement and/or disease severity. Finally, viral shedding over time was also suggested, although it remains unclear on which specimen viral load would be measured.

**Randomization**

Participants reaffirmed the need for individual randomization within hospitals and reaffirmed the need for double-blinding as the number of enrolled patients is expected to be low and as the primary endpoint contains a “soft” endpoint that may be sensitive to clinical judgment in various populations and sites.
In the light of the unknowns with the nCOV, an exploratory lead-in randomised phase could be started with the aim of better defining clinical endpoint of value to be introduced in the study in a second stage that would be considered for primary analysis and while allowing to grant access to the most promising molecules. This approach was used in an influenza trial where the primary endpoint was determined by a pilot study of the first 50 subjects randomized in which the reproducibility of virologic samples, comparison between culture and PCR, and the impact of missing data were evaluated.

Proposed next steps

- WHO is preparing a landscape analysis of the vaccine and therapeutic investigational candidates that could be used against nCoV and will work on a evidence-based framework to transparently select most promising/advanced therapeutics and vaccines candidates to move forward for clinical evaluation.

- WHO will convene a meeting asap to discuss all critical steps that are required (e.g. proof-of-concept, preliminary safety data, regulatory expectations) ahead of planning for efficacy trials as well as key epidemiological and clinical aspects that we must learn and that will help enlighten vaccine and treatment development.

- WHO will share updates on the epidemiological situation and the outcomes of the vaccines and therapeutics landscape analysis with the group.

- WHO will convene the next TC of the Blueprint WG on clinical trials on January 23.