World Health Organization

WHO R&D Blueprint

Informal consultation on prioritization of candidate therapeutic agents for use in novel coronavirus 2019 infection

Geneva, Switzerland, 24 January 2020

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Appropriate WHO Confidentiality Undertakings were signed and submitted to WHO by all participating experts

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INTRODUCTION

Currently there are no therapeutic agents licensed and available for novel coronavirus 2019. At the time of the deliberations, one clinical trial was currently ongoing in China including with Lopinavir and Ritonavir. Another RCT is being planned to evaluate the safety and efficacy of Remdesevir. Chinese experts are considering a flexible design that could include additional study arms if pertinent.

In order to rapidly inform the further design and conduct of clinical trials in regions affected by nCoV, there is an urgent need to progress with the prioritisation of the investigational candidates most suitable for clinical trials. A preliminary review of the current pipeline of candidates for treatment of the nCoV, at different stages of development, was conducted based on available information provided. There are major gaps in knowledge around the new virus, in particular the extent of its susceptibility to the different therapeutic options considered, as none of these were developed specifically for nCoV. Nevertheless, it is important that a high level prioritization is made based on the limited information available and updated as further pertinent data emerges.

During the Ebola Public Health Emergency of 2014-2016 WHO further developed its ethical guidance on use of investigational/repurposed therapeutics during outbreaks. This guidance placed a major emphasis on prompt initiation of well designed, ethical clinical trials using the most promising therapeutic candidates available. In the context of the current outbreak of nCov, individual patients may be offered investigational therapeutics on an emergency basis outside clinical trials, as part of protocols for compassionate use or as part of randomized clinical trial. WHO's guidance "Managing Ethical Issues in Infectious Disease Outbreaks" states that compassionate use of unlicensed therapeutics, or Monitored Emergency Use of Unregistered Interventions, is only justified when clinical trials cannot be initiated immediately and where a set of defined ethical criteria are met (MEURI, https://www.who.int/emergencies/ebola/MEURI-Ebola.pdf).

Also important is the need to consider the potential operational challenges with the implementation of various trial designs and, with the administration and monitoring of different investigational therapeutic agents. The anticipation of such potential challenges is critical, so appropriate mitigation measures are implemented in advance, if pertinent.

Although there is incomplete information about several aspects related to the clinical evolution and severity of the disease and with respect to the safety and potential efficacy of available candidate therapeutics (the majority of which were designed or

considered to treat MERS-Cov and SARS), it is imperative to prioritise candidate therapeutics that could potentially reduce mortality and improve clinical disease.

This meeting was called to deliberate on potential therapeutic candidate that could be further evaluated in the current nCoV outbreak. The intention is to assess the evidence available for these candidates with regards to safety and efficacy and recommend those that should be advanced for clinical care through a compassionate protocol and/or evaluated in a clinical trial.

This expert consultation convened clinical care partners and experts in the field of randomized controlled trials (RCTs) for evaluating investigational therapeutics (in particular clinical experts, trialists, and statisticians).

OBJECTIVES OF THE CONSULTATION

The objectives of this consultation were:

1. To outline criteria that could inform the evidence-based selection of therapeutic agents for clinical trials;
2. To review and critically appraise the existing evidence regarding different investigational therapeutics agents;
3. To decide on the more promising candidate therapeutics - based on currently available evidence - that can be evaluated in humans infected with nCoV to reduce mortality and disease progression.

This Consultation presents an initial step towards the evaluation of candidate therapeutics against this novel Coronavirus. There are ongoing efforts to identify additional candidate therapeutics and to expand the body of evidence available on each of the candidates.

Agenda items

- Introduction and roll-call
- Assessment of potential conflicts of interest by the panel experts
- Update on current nCoV outbreak
- Update on therapeutics landscape
- Discussion on priorities
- Conclusions and next steps

EXPERT PANEL

Chairperson: Marco Cavaleri

Name	Position	Institutional Affiliation
Marco Cavaleri	Head of Anti-infectives and Vaccines.	European Medicines Agency, Amsterdam
Eric Pelfrene	Office of Anti-infectives and Vaccines, Human Medicines Evaluation Division	European Medicines Agency, Amsterdam
Sina Bavari	Independent Consultant	
John Marshall	Co-Director, Critical Illness and Injury Research Centre	St. Michael's Hospital, Toronto, Canada
Karl Erlandson	Interdisciplinary Scientist	Biomedical Advanced Research and Development Authority (BARDA)
Hilary Marston	Medical Officer and Policy Advisor	National Institute of Allergy and Infectious Diseases (NIAID)
Philip Coyne	Assistant Professor of Tropical Public Health	F. Edward Herbert School of Medicine, Uniformed Services University of the Health Sciences.
Josie Golding (standing in for Jeremy Farrar)	Epidemic Preparedness and Response Programme Officer	Wellcome, UK
Raymond Corrin	Special Access Program Advisor at Health Canada	University of Ottawa, Canada

Full list of invited experts but only those listed in the table above participated:
Raymond Corrin (Health Canada), Karl Erlandson (US HHS), Hilary Marston(US NIH), Philip Coyne(US PHS), Sina Bavari (Independent consultant), John Marshall (SMH Canada), Marco Cavaleri (EMA), Jeremy Farrar (Wellcome Trust), Markus Mueller(University of

Wien), Bin Du (Peking), Regine Lehnert (BfArM), Yaseen Arabi (Saudi Arabia); Yi Guan (Hong Kong); Wannian Liang (MOH China); Ross Upshur (University of Toronto)

WHO Secretariat: Alejandro Costa, Janet Diaz, Ana Maria Henao-Restrepo, Vasee Moorthy, Marie-Pierre Preziosi, Ximena Riveros Balta, Kolawole Salami, Siya Temu.

Assessment of conflicts of interest

WHO Declaration of Interest forms were completed and provided to WHO by all participating experts. Such DOIs were reviewed by the WHO Secretariat as par applicable WHO guidance. The following interests, if any, were declared: :

Name	Confidentiality Undertakings; Assessments of Conflicts of Interest
Marco Cavaleri	No conflict of interest declared
Eric Pelfrene	No conflict of interest declared
Sina Bavari	No conflict of interest declared
John Marshall	No conflict of interest declared
Karl Erlandson	No conflict of interest declared
Hilary Marston	No conflict of interest declared
Philip Coyne	No conflict of interest declared
Josie Golding (standing in for Jeremy Farrar)	No conflict of interest declared
Raymond Corrin	No conflict of interest declared

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UPDATE ON CURRENT nCoV OUTBREAK

As of 24 January 2020, a total of 846 confirmed cases of a novel coronavirus (2019-nCov, hereafter referred to as nCoV) have been reported, of which 830 cases were reported from China. Other confirmed cases were reported outside of China in six countries (see https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200124-sitrep-4-2019-ncov.pdf?sfvrsn=9272d086_2). Of the 830 cases, 177 cases have been reported as severely ill and 25 deaths have been reported to date.

UPDATE ON CANDIDATE THERAPEUTICS

An overview of the types/classes of candidate therapeutics included in the deliberations and their stages of development is presented in the attached high-level summary table. The table includes monoclonal and polyclonal antibodies, as well as repurposed drugs including nucleoside analogues and protease inhibitors.

OVERVIEW OF THE DELIBERATIONS

Overall considerations

- A preliminary review of the current pipeline of candidates for treatment of the nCoV, at different stages of development, was conducted based on available information and notwithstanding the current gaps in knowledge around the new virus, in particular the extent of its susceptibility to the different therapeutic options considered, which were mainly investigated and/or developed for MERS-CoV.

- It was agreed that candidate therapeutics that are still in preclinical phase of evaluation should not be prioritized over more advanced candidates with available clinical safety and efficacy data, as the purpose would be to identify products that