World Health Organization

WHO R&D Blueprint

novel Coronavirus

WHO Working Group –

Therapeutics Prioritization for COVID-19

WHO reference number

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R&DBlueprint

Powering research
to prevent epidemics

Table of Contents

TABLE OF CONTENTS **2**
TERMS OF REFERENCE **3**
COMPOSITION ..... ERROR! BOOKMARK NOT DEFINED.
EXPERTS ..... **ERROR! BOOKMARK NOT DEFINED.**
WHO SECRETARIAT 3
DECLARATION OF INTEREST FOR WHO EXPERTS **9**

Terms of Reference

The current global nCoV public health emergency underscores the need to accelerate the selection and development of therapeutics for treatment and prophylaxis for COVID-19. The Working Group for therapeutics prioritization aims to provide guidance to researches to select medicines and be included in clinical trials to evaluate their efficacy again the disease. The technical advice will also serve to select the medicines to be used in the master-core protocol promoting by WHO.

The objectives of this group are:

1. To review the current antivirals used during previous nCoV outbreaks, SARS and MERS

2. To review all the therapeutics that could help to attenuated the ARDS symptoms

3. To make preliminary recommendations on whether the therapeutics should be prioritized to be included in the clinical trials.

The consultation will be divided in repurposed drugs to be immediately included in phase III efficacy evaluation and new compounds than can potentially be tested in phase I/II.

The evaluation of potential therapies can be classified in:

a) Antivirals agents licensed (protease inhibitors and nucleotides analogues)
b) Antiviral agents in investigational phase but with safety data
c) Antiviral agents licensed for other respiratory disease like influenza
d) Immunomodulators (Cytokines inhibitors)
e) RBD blockers ACE-2 /TMPRSS-2
f) Steroids

Method

WHO secretariat will organized face to face or teleconference consultations to discuss the exiting evidence:

a) In vitro (vero cells, HAE cells)

b) In vivo (hamster, ferrets, NHP)

c) In humans against other diseases

WHO secretariat will share in advance the available information with the WGs members under confidentiality undertaking.

The WG members are expected to provide and share data that may not had been seen by WHO secretariat

The WG members are also expected to provide their experience, advice and share the best knowledge on the specific therapeutics to contribute to the discussion and the prioritization process

The WG members are also expected to review the notes of the consultations

Prioritization criteria

Parameters in product profile assessment

Attribute	Minimally acceptable profile
Mandatory criteria	
Preclinical efficacy data in non-human primates (NHP)	Pre-clinical efficacy in NHP under well-controlled and documented conditions • Evidence of efficacy should include improved survival of COVID-19 inoculated rhesus macaques (or other NHPs) following treatment with the drug versus controls.
Safety profile from non-clinical studies	In the absence of human data, safety results from animal studies, as well as relevant in vitro data should be assessed with respect to safety in humans.
Quality of manufacturing (cGMP)	It is expected that the product will be manufactured in compliance with GMP (Good Manufacturing Practice). • Information on the active pharmaceutical ingredient (API) and finished pharmaceutical product (FPP) preparation, FPP composition, controls (specifications), known and potential impurities, as well as stability data supporting a reasonable shelf-life should be provided. • A list of intended changes for scale up, if any, along with a discussion on impact of these changes on the safety/efficacy profile of the product should also be provided.
Prioritization criteria	
Safety in humans single/repeat dose escalation	Evidence of acceptable risk-benefit profile, i.e. acceptable incidence of SAE, SUSARs or severe AEs with sequelae observed as documented by the DSMB. • Phase 1 clinical data should available for the drug at the exposure level proposed for treatment of COVID-19 • If evidence on dose escalation is available that would be an advantage. • If human PK trials or studies in other indications at the exposure level proposed for treatment of COVID-19 have been conducted, assessment of safety using standard parameters (adverse events,

	clinical laboratory monitoring, etc.) will serve as the most meaningful assessment of safety. • Clinical data supplemented by customary non-clinical at different exposure levels.
Time-efficacy window after challenge in animal models	Pre-clinical efficacy in NHP under well-controlled and documented conditions. • Evidence of efficacy should include improved survival of COVID-19 virus inoculated rhesus macaques (or other NHPs) following treatment with the drug versus controls. Surrogate markers, validated or reasonably expected to predict efficacy, e.g. viral load decreases, would be supportive.
Dosing rationale	A rationale should be provided for the proposed dosing in humans, with reference to drug exposures shown to be effective in suitable animal models. • Ideally, human pharmacokinetic data would be available, demonstrating similar levels of the drug following administration at the proposed dose, compared to blood levels seen in NHPs successfully treated with the drug.
Route of administration and administration challenges	What is the route of administration. • Over how long must the drug be administered, and • How many administrations are required to complete one treatment course?
Efficacy data in humans	Where clinical efficacy data from randomized controlled trials (RCTs) are available, this is clearly preferable to efficacy in animals. • Administration through MEURI does not generate useful information to support clinical efficacy determination due to the very high risk of bias and confounding factors. Surrogate markers, validated or reasonably expected to predict efficacy, e.g. viral load decreases, would be supportive. Information on combination with other agents, documented or potential drug and/or vaccine interactions would be desirable.
Access in event of success (mandatory)	Evidence that at least 5000 treatment courses compliant with GMP will be available and labelled by the trial initiation date Evidence that sufficient numbers of GMP treatment courses doses (>5000) will be available for immediate trial implementation for confirmed cases

	Evidence that production plans are in place to meet the treatments supply demand (millions of doses) in large-scale implementation in at-risk countries. Evidence of willingness to ensure that therapeutics will be manufactured and made available to WHO and the public health sector of the COVID-19 countries in sufficient amount and at an affordable price.
Additional prioritization criteria	
Staff training	Information on the specific training that medical staff would need to have received in order to safely and reproducibly administer the agent.
Administration and monitoring equipment	Is specific equipment that would not normally be present for COVID-19 treatment units (ICUs) needed to administer the agent? Is specific equipment that would not normally be present at ICUs needed to monitor the agent including laboratory equipment for e.g. haematology, biochemistry (e.g. liver, renal function).
Storage & shelf-life	Temperature, stability at given temperature
Total	

Origin of data: Data and evidence necessary to score the attributes will be collected from published data and information provided by the respective manufacturers.

Weighting/scoring: Scoring: Score 0 to 3 per attribute (0 = no data available; 1= does not meet minimally acceptable profile; 2=meets minimally acceptable profile; 3 likely to exceed minimally acceptable profile). Descriptive attributes are not weighted.

Output: The process based on this framework will result in a report describing the outcome of the assessment of available COVID-19 investigational therapeutics for use by the committee to make the formal decision on recommendations for inclusion in clinical trials at a given point in time. Such decisions are to be revisited upon emergence of significant new information.

Working group members

Chair: Marco Cavaleri

Name	Position	Institutional Affiliation
Marco Cavaleri	Head of Anti-infectives and Vaccines	European Medicines Agency, Netherlands
Eric Pelfrene	Regulator: Office of Anti-infectives and Vaccines	European Medicines Agency, Netherlands
Sina Bavari	Independent Consultant	
Karl Erlandson	Interdisciplinary Scientist	Biomedical Advanced Research and Development Authority, US Department of Health and Human Services
Yaseen Arabi	Chairman, Intensive Care Department	King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia
John Marshall	Co-Director, Critical Illness and Injury Research Centre, St Michael Hospital, Canada	Co-Director, Critical Illness Research, St Michaels Hospital
Ross Upshur	Director, Primary Care Research Unit, Sunnybrook and Women's College Health Sciences Centre, Canada Research Chair in Primary Care Research	University of Toronto, Canada
John Beigel	Associate Director for Clinical Research	NIH, USA
Thomas Fleming	Professor of Biostatistics	University of Washington
John Farley	Director, Office of Infectious Diseases	FDA, USA

Name	Position	Institutional Affiliation
Philip Krause	Deputy Director CBER/OVRR	FDA, USA
Regine Lehnert	Regulator	Federal Institute for Drugs and Medical Devices, Germany
Monalisa Chatterji	Senior Program Officer, Discovery & Translational Science	Bill & Melinda Gates Foundation, USA
Michael Kaufmann	Manager- Advisory	Price Waterhouse Cooper, USA
David Vaughn	Senior Program Officer	Bill & Melinda Gates Foundation, USA
Ken Duncan	Discovery & Translational Sciences team Lead	Bill & Melinda Gates Foundation, USA
Nicholas White	Professor of Tropical Medicine	Mahidol University, Thailand
Robert Walker	Chief Medical Officer and Director, Division of Clinical Development	Biomedical Advanced Research and Development Authority, US Department of Health and Human Services
Julia Tree	Microbiological Services	Public Health England
Scott Miller	Deputy Director, medical interventions	Bill & Melinda Gates Foundation, USA
Frederick Hayden	Professor Emeritus, Medicine: Infectious Diseases and International Health	University of Virginia

Name	Position	Institutional Affiliation
Jacqueline Kirchner	Senior Program Officer	Bill & Melinda Gates Foundation, USA
Elizabeth Higgs	Global health science advisor for the Division of Clinical Research (DCR)	NIH. USA
Helen Rees	Professor, Wits Reproductive Health and HIV Institute	University of Witwatersrand, South Africa
Matthew Frieman	Associate Professor, Microbiology and Immunology	University of Maryland School of Medicine

WHO Secretariat: Alejandro Costa, Ana Maria Henao-Restrepo, Kolawole Salami, Emer Cooke, Deusdedit Mubangizi, Matthias Mario Stahl, Raymond Corrin, Philip Coyne, Emma Collins and Severine Danmadji Nadlaou

Declaration of interest for WHO Experts

All working group members completed a declaration of interest.