World Health Organization

WHO R&D Blueprint

COVID-19

Informal consultation on the role of therapeutics in COVID-19 prophylaxis and post-exposure prophylaxis

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R&DBlueprint

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

WHO reference number

INTRODUCTION

Currently, there are no licensed vaccines for the prevention of COVID 19. While efforts continue to develop effective vaccines, it is pertinent to examine the possible role of therapeutic agents in protecting healthcare workers and the general population who are at significant risk of contracting the virus, either before exposure to the virus or to prevent the development of clinical disease after exposure. Many countries have established treatment and prophylaxis protocols based on evidence that is yet unclear or insufficient. Following the start of the SOLIDARITY 1 clinical trial, the WHO is spearheading the coordination of research activities to provide evidence-based recommendations for prophylaxis and post-exposure prophylaxis.

This expert consultation convened clinical care partners and experts in the field of randomized controlled trials (RCTs), biostatistics, regulatory affairs, preclinical studies, and pharmacology to evaluate current progress in the area of COVID-19 chemoprophylaxis.

This is the second consultation on this important subject.

OBJECTIVES OF THE CONSULTATION

The objectives of this consultation were:

1. To collectively chart a pathway towards the harmonized evaluation of chemoprophylaxis.
2. To discuss on the appropriate scenarios (risk level categories), design and endpoints for PEP and PrEP clinical trials; as well as on therapies to be considered.

Agenda items

- Introduction and roll-call.
- Update on current plan for prophylaxis clinical trials.
- Discussion on possible study endpoints.
- Conclusions and next steps.

Participants

Name	Position	Institutional Affiliation
Marco Cavaleri **(Chair)**	Head of Anti-infectives and Vaccines	European Medicines Agency, Netherlands
Michael Avidan	Professor of Anaesthesiology	Washington University, St Louis, USA
Ruanne Barnabas	Associate Professor in Global Health and Medicine	University of Washington, USA
John Beigel	Associate Director for Clinical Research	NIH, USA
David Boulware	Professor of Medicine, Division of Infectious Diseases and International Medicine	University of Minnesota, USA
Peter Dull	Deputy Director, Integrated Clinical Vaccine Development	Bill & Melinda Gates Foundation, USA
Ken Duncan	Discovery & Translational Sciences team Lead	Bill & Melinda Gates Foundation, USA
Karl Erlandson	Interdisciplinary Scientist	Biomedical Advanced Research and Development Authority, USA
John Farley	Director, Office of Infectious Diseases	FDA, USA
Tom Fleming	Professor of Biostatistics	University of Washington, USA
Frederick Hayden	Professor Emeritus, Medicine: Infectious Diseases and International Health	University of Virginia, USA
Elizabeth Higgs	Global health science advisor for the Division of Clinical Research (DCR)	NIH, USA
Philip Krause	Deputy Director, CBER/OVRR	FDA, USA
John Marshall	Co-Director	Critical Illness Research, St Michaels Hospital, Canada

Name	Position	Institutional Affiliation
Hilary Marston	Medical Officer and Policy Advisor for Global Health.	NIH, USA
Scott Miller	Deputy Director, medical interventions	Bill & Melinda Gates Foundation, USA
Oriol Mitjà	Associate Professor, Infectious Diseases	Universitari Germans Trias I Pujol, Barcelona, Spain
Eric Pelfrene	Office of Anti-infectives and Vaccines	European Medicines Agency, Netherlands
Dennis Shanks	Director, Army Malaria Institute	Department of Défense, Australia
Peter Smith	Professor of Tropical Epidemiology	London School of Hygiene and Tropical Medicine, UK
Barbara Styrt	Associate Director for Medical Countermeasures	FDA, USA
Darrell Tan	Director, Clinical Research Unit on HIV Prevention	University of Toronto, Canada
Julia Tree	Research Scientist, Microbiological Services	Public Health England, UK
Ross Upshur	Director, Primary Care Research Unit, Sunnybrook and Women's College Health Sciences Centre	University of Toronto, Canada
Nicholas White	Professor of Tropical Medicine	Mahidol University, Thailand

Other invited experts unable to participate: Yaseen Arabi (KSAU-HS, Saudi Arabia), Monalisa Chaterjji (BMGF, USA), Bin Du (Peking, China), Yi Guan (Hong Kong), Helen Rees (Wits, South Africa), and Liang Wannian (MoH, China).

WHO Secretariat: Alejandro Costa, Pierre Gsell, Ana Maria Henao-Restrepo, Ira Longini, Marie-Pierre Preziosi, Kolawole Salami, Soumya Swaminathan and Siya Temu.

OVERVIEW OF THE DELIBERATIONS

Overall considerations

- There are several long-term care facilities such as nursing homes and chronic care facilities with COVID-19 cases, housing elderly patients at risk of infection and mortality. Such settings should be prioritized in the prophylactic studies (PrEP). The planned post-exposure prophylaxis studies (PEP) could be split into households and nursing homes, where rings are defined according to the type of contacts.

- The Mahidol University study is a randomized placebo-controlled trial of 40,000 healthcare workers (HCW) in Southeast Asia, also being extended to South Africa, Malawi, Uganda, Kenya, Niger, Cameroon and DR Congo. The study is scheduled to start recruiting participants in two weeks. This protocol is robust and could be considered as the basis for a core healthcare worker protocol.

- A vital issue was raised about the dose of hydroxychloroquine proposed in the Mahidol study. Modelling analysis done by the Gates foundation predicts that there would be a major challenge ensuring the global supply of hydroxychloroquine for use in healthcare workers at the dose used in the Mahidol study (daily dosing). Indeed, previous PK modelling suggests that a third of the dose used in the Mahidol study could be equally effective. However, it is recognised that these models are based on assumptions of active free drug penetration and accumulation in the lungs in sufficient amounts with no confirmation from human studies. It is pertinent that this is further discussed within WHO expert group.

- The CROWN CORONATION (Chloroquine Repurposing for Healthcare Workers for Novel Coronavirus Mitigation) Trial is an international multicentre trial with a primary focus on Africa, but also New Zealand and the United Kingdom. The study is based on pre-exposure prophylaxis rather than PEP. The African focus is intended to correct the skewed distribution of research relevant to COVID-19. There are > 200 African sites represented in the study. The study also aims to determine the optimal dose of chloroquine; hence, three different doses (high, medium, and low) would be tested compared to placebo. Overall, 55,000 healthcare workers are expected to be randomized.

- While plans are being finalized for the harmonized global clinical evaluation of chemotherapeutics for prophylaxis, it is also important to systematically collect data from countries (e.g., India) that have chosen to use unproven drugs to protect their healthcare workers, based on no evidence. This could be collected in registries which could be harmonized into a global repository.

- A Canadian Institute of Health Research funded PEP study testing Lopinavir/Ritonavir will launch next week in Toronto and Vancouver.

- There is currently variation in the endpoints of planned prophylactic clinical trials. Having a harmonized endpoint and a common DSMB is critical. The studies assessing prophylaxis are looking at both the prevention and mitigation of disease as main objectives. Both are relevant and important factors to be captured. The NIH team experience with the ordinal scale in the clinical evaluation of flu disease intervention, which was initially considered in the pilot phase of the assessment of Remdesivir for COVID-19, resulted in a decision to move now to a more simplified primary endpoint. It cannot be excluded that different primary endpoints might need to be considered for diverse study populations. However, a common approach to primary and secondary evaluations might be still preferable.

- It might be worthwhile to consider adopting some core measurements and endpoints with space made for secondary endpoints based on the peculiarities of the study population and location. As the protocol is a core, simple endpoints that could be collected across the sites is desirable. PCR