Informal consultation on the role of therapeutics in COVID-19 prophylaxis and post-exposure prophylaxis - **Prophylactic studies (PrEP) subgroup**

Date, time and venue

Wednesday 15 April 2020 - 16:00 – 17:00 (CET) - Webex

Participants

Group1: PrEP in HCW	
Michael Avidan	Washington University, St Louis, USA
Hakim Dehbi	University College London, UK Statistician C-Coronation Trial
Tom Fleming	University of Washington, USA
Scott Miller	Bill & Melinda Gates Foundation, USA
Eric Pelfrene	European Medicines Agency, Netherlands
Dennis Shanks	Department of Defense Australia
Peter Smith	London School of Hygiene and Tropical Medicine, UK
Ross Upshur	University of Toronto, Canada
Nicholas White	Mahidol University, Thailand

Additional participants: Rupesh Agrawal (Tan Tock Seng Hospital, Singapore), Janice Culpepper (BMGF, USA), Julia de Amo (Ministry of Health, Spain), Adrian Hernandez (Duke University, USA), Megan Mclandes (University of Toronto, Canada), Romani Moonesinge (UCL, UK), Helen Rees (University of University of Witwatersrand, South Africa).

WHO Secretariat: Ira Longini, Marie-Pierre Preziosi, Kolawole Salami and Siya Temu.

Agenda items

- Discussion of the first draft of the core protocol
- Deliberation on a proposed way forward for a central DMC
- Next steps

Overview of deliberations

1. Brief overview and updates of ongoing/ soon-to-start PrEP studies:

- Scott Miller shared an excel sheet summary of ongoing and planned PrEP studies. It was noted that this list was by no means exhaustive as there has been a massive proliferation of such studies involving healthcare professionals within the last two weeks, with the majority of these evaluating prophylactic efficacy of Hydroxychloroquine and Chloroquine, and a few evaluating protease inhibitors. Although there are some differences in defined endpoints, most of the primary endpoints are fortunately quite similar.

- It was, however, noted that there were also differences in the frequency of sampling for each of the studies, especially as some studies have asymptomatic infection as an endpoint. It is essential to get more information on this. There appears to be a consensus on most studies to do pre and post-test serological tests. Still, again these needs to be further validated with the need for a target product profile for COVID-19 serology.

- Studies evaluating the validity of self-administered swabs versus the standard practice of physician-administered swabs are presently being planned. BMGF has funded similar research comparing patient-collected swabs for SARS-CoV-2sles, and the result showed no significant difference in accuracy with health care worker collected swabs.

2. Discussions on the first draft of the core protocol

- The WHO PrEP draft core protocol was shared with the participants to get agreement on critical components and features of the protocol. The protocol is hinged on equitable access to research participation and the evaluation of many candidate SARS-CoV-2 PrEP regimens available for testing now or in the future. To achieve this prompt, efficient, and reliable evaluation of their safety, tolerability, protective efficacy, and recommended schedule and dosing, the protocol follows an adaptive design that allows the simultaneous assessment of different therapeutics. The core primary endpoint will be virologically

confirmed COVID-19 disease, regardless of severity, while participating sites are free to decide on secondary endpoints.

- The experts' panel acknowledged the usefulness of the WHO adaptive template, especially as it allows rapid response adaptation and change, depending on which approach is successful. However, this protocol may be more applicable to the therapeutics study setting. For the prophylactic study, it takes a while to measure the endpoint. Hence, recruitment strategy needs to be aligned to this, such that all participants are not recruited at the start of the study. The latter would create a challenging scenario with inability to adapt the study for other participants, since all recruited participants would have reached their endpoint by the time interim analysis is conducted.

- It was asserted that it would be essential to incorporate the measurement of adherence, especially in subjects taking the placebo. Lessons learned from the HIV PrEP studies should be leveraged in the design and conduct of these planned clinical trials. Also, if partial protective efficacy of chloroquine (CQ) or hydroxychloroquine(HCQ) is established in ongoing clinical trials, then it implies that the experimental therapeutic would not be tested against a placebo but against CQ or HCQ or in combination therapy. This consideration must be included in the core protocol.

- From a statistical point of view, it is pertinent to pre-specify if we are testing for superiority first or whether there are non-inferiority questions nested in the study. For example, testing if lower doses are as effective as the highest dose (as planned in the CROWN CORONATION trial) is a non-inferiority question.

3. On a proposed way forward for a central DMC

- WHO proposes the development of a core data monitoring committee (DMC), which would have three purposes, to collectively assess safety data and primary endpoints on ongoing PrEP studies and PEP studies (working closely with the DMCs of other studies), and ultimately, this core DMC will be evolved for large core PEP and core PrEP studies.

Next steps

1. BMGF/Scott to update the spreadsheet with recent studies, including the Duke University study that would be shared by Adrian Hernandez.
2. Helen and Scott to share details of the studies comparing self/physician-administered swabs
3. PIs of individual ongoing clinical trials to contact their DMCs and share back their opinions on the 'mega DMC.'
4. WHO to finalize a draft proposal for the central DMC (Process & TORs)
5. Ira/WHO to revise first draft of the core protocol
6. All to send any additional suggestion on the draft core protocol to Ira/WHO

Next TC

- Friday 24 April 2020 16h00-17h30 (with PEP group)