Informal consultation on the role of therapeutics in COVID-19 prophylaxis and post-exposure prophylaxis - **Working Group on Protocols for Therapeutics in COVID-19 PrEP and PEP.**

Date, time and venue

Friday 1st May 2020 - 16:00 – 17:30 (CET) - Webex

Participants

Name	Position	Institutional Affiliation
Marco Cavaleri **(Chair)**	Head of Anti-infectives and Vaccines	European Medicines Agency, Netherlands
Rupesh Agrawal	Adjunct Associate Professor	Tan Tock Seng Hospital, Singapore
Michael Avidan	Professor of Anaesthesiology	Washington University, St Louis, USA
Ruanne Barnabas	Associate Professor in Global Health and Medicine	University of Washington, USA
David Boulware	Professor of Medicine, Division of Infectious Diseases and International Medicine	University of Minnesota, USA
Julia Del Amo	Professor of Research in Biomedical Sciences, National Center for Epidemiology	Institute of Health Carlos III, Spain
Hakim Dehbi	Head of Statistics at Comprehensive Clinical Trials Unit	University College London, UK
Peter Dull	Deputy Director, Integrated Clinical Vaccine Development	Bill & Melinda Gates Foundation, USA

Name	Position	Institutional Affiliation
John Farley	Director, Office of Infectious Diseases	FDA, USA
Tom Fleming	Professor of Biostatistics	University of Washington, USA
Jon Giles	Associate Professor of Medicine	Columbia University, USA
Frederick Hayden	Professor Emeritus, Medicine: Infectious Diseases and International Health	University of Virginia, USA
Philip Krause	Deputy Director, CBER/OVRR	FDA, USA
John Marshall	Co-Director	Critical Illness Research, St Michaels Hospital, Canada
Hilary Marston	Medical Officer and Policy Advisor for Global Health	NIH, USA
Megan McLandes	Associate Professor, Emergency Medicine Division	University of Toronto, Canada
Scott Miller	Deputy Director, medical interventions	Bill & Melinda Gates Foundation, USA
Oriol Mitjà	Associate Professor, Infectious Diseases	Universitari Germans Trias I Pujol, Barcelona, Spain
Robin Mogg	Clinical Biostatistics Leader, Medical Research Institute	Bill & Melinda Gates Foundation, USA
Ramani Moonsinghe	Consultant in Anaesthetics and Critical Care Medicine	University College London, UK
Eric Pelfrene	Office of Anti-infectives and Vaccines	European Medicines Agency, Netherlands

Name	Position	Institutional Affiliation
Helen Rees	Executive Director of the Wits Reproductive Health and HIV Institute	University of University of Witwatersrand, South Africa
Dennis Shanks	Director, Army Malaria Institute	Department of Défense, Australia
Peter Smith	Professor of Tropical Epidemiology	London School of Hygiene and Tropical Medicine, UK
Darrell Tan	Director, Clinical Research Unit on HIV Prevention	University of Toronto, Canada
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

Additional participants: Elizabeth Halloran (University of Washington, USA)

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

Agenda items

- Meeting agenda and Goal (Chair)
- Proposed way forward for generating evidence and scope of the core Data Monitoring committee (WHO, Tom Fleming)
- MRI data and statistical platform (BMGF)
- Current landscape and progress update for PrEP studies (BMGF, Principal Investigators)
- Current landscape and progress update for PEP studies (BMGF, Principal Investigators)

- Progress update for Core PrEP and PEP protocols (WHO, Ira Longini)
- AOB and action points

Overview of deliberations

1. Proposed way forward for generating evidence and scope of the core Data Monitoring committee

- Separate meetings of investigators from the PrEP and PEP teams have been held in the past weeks to chart a way forward for coordinated monitoring of the safety and efficacy data emerging from prophylaxis studies. A charter has been drafted for the core DSMC that could help make the most of the evidence.

- WHO presented the possible scenarios of the DSMC's data exchange and governance mechanisms for two types of study contexts, i.e., "soon to start" studies and ongoing studies. The soon-to-start studies are encouraged to join the core DSMC if they wish. Consequently, the data from these studies would be centralized in a harmonized fashion with the oversight of the core DSMC. On the other hand, ongoing studies already have their respective DSMCs, and it is imperative to preserve the independence of such DSMCs as well as to provide better clarity on the possible interactions between the DSMCs of individual studies and the core DSMC.

- Several options for harmonization were explored, but questions arose concerning the role of the core DSMC and that of the individual DSMCs. WHO has proposed an arrangement (subject to the agreement of individual study PIs, statisticians, and DSMC chairs) in which sharing of confidential data and reports occurs across committees as well as between committees and the core DSMC, so that all DMSCs would benefit from the overall evidence generated in these studies.

- In addition, the possibility of post-trials data aggregation and analysis was suggested. This would ensure that a joint review is carried out and the outcomes presented to the WHO Scientific Advisory Group (SAG) of the WHO. The WHO showed a flow chart of what the proposed arrangements might look like.

- Tom Fleming discussed the purpose of the proposed data sharing and the potential benefits. He cited his experience from a previous clinical trial of

HIV/AIDS combination therapy and how the sharing of information between his study DSMC and a similar study DSMC helped his trial DSMC to conclude to continue the trial. Participants also reiterated the benefits of the soon to start trial working with the core DSMB rather than constituting individual DSMBs.

- The Singapore study PI praised the proposal of a core DSMB, citing the fact that the research in Singapore has been temporarily put on hold by the authorities on the basis of the dose of hydroxychloroquine proposed in the protocol - considered to be high. Rupesh Agrawal said that information from other similar trials could help allay the safety concerns of the Singaporean authorities.

- To further highlight the role of the core DSMC, it was also explained that differences in endpoints between studies should not affect the oversight functions of the core DSMC. For example, while a trial with the duration of hospital stay as an endpoint may be advised by the core DSMC to halt a trial based on the information shared, a similar clinical trial with all-cause mortality as the endpoint should be allowed to continue. However, it was stressed that this approach does not interfere with the independence of individual DSMCs to make recommendations on trial modification, continuation, or discontinuation. The shared reports and information are not expected to affect the schedule of the individual DMCs.

- The University of Washington study group expressed satisfaction with the proposal but raised a concern about DMC's ability to cope with the demands of overseeing multiple studies at once within the rapidly evolving epidemic. PI Michael Avidan also wants to know if the DMC can quickly assess the safety data and ensure that the public's concern about a therapeutic agent's side effects is allayed. Concerns about workload were, however, allayed by Tom Fleming, who served on the DMC board in more than 200 such studies. Also, regarding safety, it was reiterated that although the confidentiality clause would be adhered to, the DMC would ensure information about safety is flagged appropriately.

- The core DMC members would be appointed to reflect diversity in gender, geography, and professional specialty.

- With regards to post-trials data aggregation and analysis, it was suggested that mechanisms be put in place on how these data are pulled together for analysis- preferably early after study end.

- Participants shared opinions on how best to facilitate the sharing of information of closed reports across DMCs, bearing in mind the need for efficiency and security. Rupesh Agrawal introduced participants to an integrated platform for data collection and data analysis, which could be adapted quickly to serve this purpose. The platform is a dashboard with an overview of what's happening with different studies globally, and selected data points from each centre can be highlighted on this dashboard in real-time. It could be a potentially useful tool for the core DMC, and deep data analysis and graphs/plots/charts could be built into the platform.

- Robin Mogg, volunteered the support of the Gates MRI to achieve real-time coordination of information for the core DMC. This could also extend, subject to the approval of PIs, to the aggregation of data from the different studies and advising on analysis plans, etc. with guidance from the working group.

- All PIs on the call have expressed satisfaction with the proposal and are willing to support the core DSMC initiative after a few clarifications, given the benefits of taking advantage of a core DMC.

2. Progress update for Core PrEP and PEP protocols

- WHO is working on the core protocols and an advanced draft will be ready for further review by the working group within a month. Ira Longini will present an update at the next meeting.

3. Current landscape and progress update for PrEP and PEP studies

- Comprehensive and collated updates were shared as part of the meeting reference documents for the PrEP (Scott Miller) and PEP (Peter Dull) studies.

- Darrell Tan, PI of the University of Toronto PEP study gave an update. The study evaluating Lopinavir/Ritonavir was launched a week ago at one of the four sites. Recruitment has been a bit slower than anticipated, perhaps due to the decline in case count. There is already have a DSMB in place, but they are happy to participate in a core DMC.

- Meghan Mclandes gave an update on the PrEP study among healthcare workers evaluating the prophylactic efficacy of hydroxychloroquine. The research team is also experiencing slow recruitment, due partly to a plateauing of cases, but also to the new perceived safety concerns around hydroxychloroquine. The team would benefit from rapid safety analysis of ongoing studies involving hydroxychloroquine and publication of the outcome to allay fears.

Next steps

- WHO will work on clarifications with each PI to ensure that all investigators can shape the process and fully understand what the expectation is.

- Based on the above, WHO will collaboratively constitute the core DMC and develop the operational framework of information sharing in the two scenarios presented.

- WHO will now finalize the terms of reference for the working group accordingly and will ensure that all members of this group sign a dedicated declaration of interest form and confidentiality undertaking before the next meeting.

Next TC

- Thursday 14 May 2020 16h00-17h00 (TBC)