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

Date, time and venue

Thursday 16 April 2020 - 17:00 – 18:00 (CET) - Webex

Group Members

Group2: PEP Household / Contacts	
Rupesh Agrawal	Tan Tock Seng Hospital, Singapore
(Ruanne Barnabas, unable to attend) Meighan Krows	University of Washington, USA
David R Boulware	University of Minnesota, USA
Peter Dull	Bill & Melinda Gates Foundation, USA
Tom Fleming	University of Washington, USA
Frederick Hayden	University of Virginia
Dennis Shanks	Department of Defense Australia
Oriol Mitjà	Universitari Germans Trias I Pujol, Barcelona
Darrell Tan	University of Toronto, Canada

Unable to attend: Jon Gilles (Columbia University, USA), Phil Krause (FDA, USA), Hilary Marston (NIH, USA)

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 PEP studies:

- The Singapore study is the latest to be added to the list of previously acknowledged PEP studies. The study is yet to start pending ethics and regulatory approvals. Recruitment is expected to start next week and to be completed within two months. Close contacts of index cases will be recruited, with a cluster randomized trial design and a primary endpoint of 30% reduction in virologically diagnosed cases among contacts. The PI is Prof David Lyle.

- The Minnesota study is progressing well. A total of 826 participants have been enrolled, including healthcare workers (HCW) and household contacts. An interim analysis is planned for next week Wednesday (22/04/2020). Some gastrointestinal disturbances have been documented as side effects, but 70% of study subjects have reported no side effects through day 5.

- The Barcelona study has now enrolled 2 800 participants (30% of the target population), including HCW, Household contacts and nursing care home residents. An interim analysis is currently taking place (first 600 participants) whose results will be available in 24 hours. The DSMB meeting is scheduled for Monday 20th of April. The threshold for efficacy was based on a 20% positivity rate among contacts that would be reduced by 10% with the intervention. Hence, the DSMB would consider halting the study if the reduction in positivity is < 2% (futility) or > 8% (efficacy). Only minor side effects were noticed from day 0-3 with highest dosing concentrations.

- The University of Washington study has started enrolling in 5 out of the 7 sites. More than 100 enrolled out of the targeted 2 000, including 97 households and 6 healthcare workers.

- The University of Toronto study would commence enrolment today, 16th April.

2. Discussion of the first draft of the core protocol:

- The WHO core protocol concise draft was developed with the aim to allow for the evaluation of different agents simultaneously and premised on a universally agreed primary endpoint, which is virologically confirmed disease. Potential secondary outcomes would be protection against infection or confirmed disease, viral shedding, death, etc. The main advantage of this approach being that it enables the

evaluation of multiple candidate PEP regimens in a single clinical trial. Randomization would be within households and between households to answer different research questions.

- All experts agree to the structure and content of the draft protocol. It was, however, advised that the issue of individuals who develop asymptomatic infection be revisited as this could be a 'beneficial' outcome and might be inappropriate to make this an endpoint. Symptomatic infection seems to be a more feasible option. The protocol should account for a possibly substantial pre-symptomatic transmission (e.g. recent report of 44% secondary cases infected by a-/pre-symptomatic index case - Gabriel Yeung et al.).

- Participants would also like to see a component of data sharing in the protocol.

- Other key issue raised were:
    - the flexibility of the protocol to consider alternate randomisation schemes (e.g. 2:1 or higher ration of agents vs. placebo) and to replace the placebo arm in case ongoing studies identify an efficacious therapeutic agent
    - the need to consider serology
    - the different levels of randomization
    - the challenges of different size of households, different units of randomisation

3. On a proposed way forward for a central DMC

The establishment of a central DMC was generally agreed to be important and WHO will be promoting this. For the main time, the core DMC will be liaising with DMCs of individual studies to facilitate collective evaluation of emerging information to support the development of consolidated global recommendations that would be very beneficial for all member states.

Action points

1. WHO to finalize a draft proposal for the central DMC (Process & TORs)
2. Ira/WHO to revise first draft of the core protocol
3. All to send any additional suggestion on the draft core protocol to Ira/WHO

Next TC

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