NOT FOR PUBLICATION

COMMISSION ON HUMAN MEDICINES

Minutes of the Videoconference Meeting held on Monday 1st June 2020 at 12:00 via zoom network communication due to the Covid-19 virus crisis currently affecting the UK

Commissioners Participated
Professor S Ralston (Chair)
Ms S Bradford
Professor J S Friedland
Dr R J C Gilson
Professor M R Macleod
Dr R Mann
Professor S Meredith
Dr S Misbah
Professor Sir M Pirmohamed
Dr M Wilson

Apologies
Professor J Coleman
Dr J Fraser
Professor S Price

Invited Experts
Professor K M G Taylor
Ms H Ward

Visiting Expert
Professor P Sandercock

[redacted]

[1] Participated in specific topics

Key
LD = Licensing Division
VRMM = Vigilance & Risk Management of Medicines

Stuart Ralston
03/03/2021

[redacted]

[redacted]

1.7 The commission noted the information sought included

1. A trial status update: how many patients have received and are receiving hydroxychloroquine; how many have completed treatment; how many have discontinued treatment early, and how many are in follow-up.

2. An urgent review of the current status of the trial by the Data Monitoring Committee (or equivalent review body) for the trial, and the meeting minutes of that review (rather than just the concluding decision).

3. An updated, detailed risk-benefit discussion for the trial based on published data and emerging data from the trial.

4. A robust rationale as to why the trial should be allowed to continue in its current format.

5. A discussion of the implications of the safety data relevant to the conduct of the trial, including management of patients who have received, or are receiving, hydroxychloroquine, additional safety mitigations to be added, dose modifications, or other measures.

1.8 The Commission noted that investigators from seven trials confirmed that recruitment would be paused while the information requested was prepared. Investigators from the RECOVERY trial made representations to MHRA over the weekend of 23/24 May, including preliminary answers to the questions and a review of data available to 21 May by the independent Data Monitoring Committee which was reconvened on 23 May. Based on this response, the MHRA agreed that recruitment to this trial could continue pending a final decision.

1.9 The Commission noted that Sanofi had formally submitted a temporary halt to their trial and so no further responses were expected at this time.

2. Responses to CHM questions on Clinical Trials involving hydroxychloroquine or chloroquine in COVID-19

2.1 The Commission reviewed the body of data that had been submitted in response to the MHRA request for each trial. Deliberations also included consideration of a 146-signatory open letter to the authors of the Mehra M *et al* paper to the editor of the Lancet expressing methodological concerns with the study (28th May 2020 Published on Zenodo.org). The commission heard that the authors (Mehra M et al) had published an erratum to the paper to address some of these concerns while also noting that investigations were ongoing with regard to issues such as data collations and reporting. The CHM considered that in light of all the available information, particularly previous reports of increased QT prolongation and CV events, the safety signal noted was still relevant in the context of the ongoing trials employing hydroxychloroquine as a potential treatment and in prophylaxis, for Covid19 in the UK.

2.2 RECOVERY Trial

2.2.1 The Commission heard from the Chair of the RECOVERY trial Data Monitoring Committee (DMC), who provided a summary of the reviews the DMC had conducted for this trial. He confirmed that the DMC was experienced in oversight of adaptive design trials and had conducted a review of the available evidence on hydroxychloroquine. He further explained that the DMC met every 14 days to monitor accumulating safety and efficacy data. It was noted that the investigators felt that enrolment of 2000 patients per treatment arm might be required to detect a modest treatment effect on the primary outcome which was all cause mortality at 28 days. The Commission noted that the DMC was not asked to conduct a futility analysis as this had not been specified in the design of the study. In response to questions, the DMC Chair confirmed that frequency of arrhythmias between the two treatment groups were being monitored, and there had been no concern. The Chair of the DMC confirmed before he left the meeting that a more complex assessment of cardiac physiology had not been conducted.

2.2.2 The Commission noted that the DMC letter to MHRA did not provide a precise estimate of the hazard ratio for mortality in participants randomised to the HCQ arm in the RECOVERY trial , except to note that the hazard ratio observed in the RECOVERY trial was stated to be lower than the hazard ratio of 1.3 for mortality in subjects treated with CQ and HCQ reported in the Mehra M *et al* paper. The Commission noted the absence of any consistent data suggesting benefit thus far from trials of HCQ or CQ in COVID-19. In view of the potentially avoidable adverse events such as prolonged QT interval and reports of cardiovascular adverse events, implementation of risk mitigation measures was recommended. The Commission agreed that additional information was required in the study before a final decision could be made.

2.2.3 In addition to requesting more data on safety of participants in the HCQ arm of RECOVERY, the Commission discussed the need for a futility analysis from the trial and agreed that further comments would be sought from expert in

medical statistics to advise upon whether such an analysis would provide useful information on benefit risk balance or otherwise impact on the integrity of the study.

2.3 REMAP-CAP Trial

2.3.1 The Commission noted that a full response to the questions of 22 May 2020 had not been provided and advised that recruitment to the hydroxychloroquine arm of the REMAP-CAP trial should remain paused until a full response had been received and reviewed.

2.4 PRINCIPLE Trial

2.4.1 The Commission agreed with the proposed mitigations for the PIONEER trial and that recruitment to the trial could recommence once the substantial amendment was submitted and approved.

2.5 PROTECT-Surg trial

2.5.1 CHM advised that recruitment to the hydroxychloroquine arm of the PROTECT-Surg trial should remain paused until further justification and rationale was provided.

2.6 PROLIFIC and COPCOV trials

2.6.1 The Commission noted that the PROLIFIC and COPCOV trials were intended for prevention of COVID-19 in healthcare workers. The Commission considered the population to be enrolled and the dose and duration of treatment. The risk mitigation measures proposed for this population were discussed including the need to mandate ECGs in this population. The Commission did not advise a mandated baseline ECG, but noted that the DMC or sponsor may wish to implement a baseline ECG as part of the design. The Commission noted that sponsors of COPCOV provided a comprehensive response including nine additional risk mitigations and considered these were acceptable. The Commission advised that both PROLIFIC and COPCOV trials could recommence recruitment once the proposed actions were implemented via a substantial amendment.

3. In conclusion, the Commission advised MHRA that recruitment to the hydroxychloroquine arm of the trials should be suspended and may be recommenced pending the formal implementation of proposed conditions, specific to each trial. The Commission further advised that based on the case-by-case review of the trial population and current trial status, mitigation measures to protect participant safety currently in place, and the balance of data to inform on the safety for clinical trial participants, a suspension notification letter should be issued to each of the trials outlining the additional measures required for recommencement of recruitment.

4. The Commission advised that MHRA should inform the Health Research Authority and the relevant ethics committees were to be made aware to aid review of any update to patient information documentation.

5. **Any Other Business**

5.1 None.

6. **Date and Time of Next Meeting**

The next meeting is scheduled to take place on Thursday 18th June at 10:00 and Friday 19th June 2020 at 10:00.