NOT FOR PUBLICATION

COMMISSION ON HUMAN MEDICINES

Minutes of the videoconference Meeting held on Friday 5th June 2020 at 14:00 via zoom network communication due to the Covid-19 virus crisis currently affecting the UK

Commissioners Participated

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

Apologies

Professor J Coleman
Dr R Mann

Invited Experts

Professor K M G Taylor
Ms H Ward
Professor C Weir

Stuart Ralston
03/03/2021

1 Participated in specific topics

Dr J Raine - CEO
Mr C Schneider - NIBSC

[redacted]

[redacted]

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

2.1 The Commission heard an update on the status of the safety data regarding hydroxychloroquine (HCQ) in COVID-19.

2.2 The Commission heard the paper titled "Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19" a multinational registry analysis" by Mehra et al and published in the Lancet on the 22nd of May 2020, had been retracted by three of the study authors. The basis for retraction was due to the independent reviewers being unable to complete an independent audit of the data underpinning the analysis meaning that they could no longer vouch for the veracity of the data. The CHM agreed that the data and findings of the study could no longer be considered in the evaluation of the safety of HCQ.

2.3 The Commission heard that there is limited published clinical data on the safety or efficacy of hydroxychloroquine or chloroquine in the treatment of COVID-19. A recent randomised double-blind trial (Borba M et al JAMA April 24th 2020) was terminated early due to the occurrence of serious adverse events, the author's subsequent analysis of the preliminary results from 81 patients concluded that the higher chloroquine dose defined in the study, should not be recommended for critically ill patients with COVID-19 because of its potential safety hazards. The Commission heard that the high dose group had a higher rate of QTc interval prolongation > 500 milliseconds. The Commission heard that another small randomised, controlled open label trial, (Tang et al. 2020) analysed data from 150 patients and showed a similar a rate of severe acute respiratory syndrome in patients receiving HCQ and standard of care versus standard of care alone.

2.4 The Commission heard a summary of four observational retrospective (Geleris et al NEJM, 7th May 2020; Ip et al, medRxiv 21st May 2020; Rosenberg et al, JAMA 11th May 2020: Singh et al, medRxiv,12th May 2020) studies reporting from US medical centres. None of the four studies reported any significant association between the use of HCQ and increased mortality, however, one study (Rosenberg et al, JAMA,11th May 2020) reported that cardiac arrest was significantly more likely in patients receiving HCQ and azithromycin (AZM).

2.5 The Commission was made aware of a preprint manuscript (Lane et al, medRxiv, 8th Apr 2020) reporting a recent epidemiological study comparing use of HCQ or AZM alone and HCQ in combination with AZM, in a non-COVID-19 population. Two study designs were executed across

a multinational, distributed database network including primary and secondary care data from healthcare records and insurance claims databases in Germany, Japan, Netherlands, Spain, the UK (CPRD and IMRD), and the USA. First, new user cohort studies were used to estimate the safety of HCQ compared to sulfasalazine (SSZ), and to assess the risks associated with the addition of AZM compared to amoxicillin (AMX) amongst users of HCQ in patients with rheumatoid arthritis (RA).

2.6 The results regarding the risk of serious adverse events associated with short-term (<30 day) hydroxychloroquine treatment were reassuring, with no excess risk of any of the considered safety outcomes (including all-cause mortality and cardiovascular events) compared with SSZ. When considering longer term use (>30 days), there was an overall increased risk of cardiac mortality in the hydroxychloroquine group when the results from the available databases were meta-analysed.

2.7 The Commission heard that although analyses were adjusted for confounders the studies may still suffer from biases due to differences in underlying severity of disease in patients treated with HCQ compared to those not treated.

2.8 The Commission heard there is a body of data on the risks of QT interval prolongation with HCQ, with and without AZM, in COVID-19 patients mainly from small case series.

2.9 The Commission heard that there are some data suggesting an increase in mortality when HCQ is used in combination with AZM which is in keeping with data which shows that HCQ and AZM in combination may prolong the QT interval, and predispose to arrhythmias.

2.10 The Commission heard that data from a number of additional planned or on-going studies on the topic of HCQ safety and efficacy will be reviewed when available, and the findings shared with the Commission.

3. Review of new paper - A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19 (Boulware et al; NEJM June 3, 2020)

3.1 The Commission discussed the above pragmatic randomized, double-blind, placebo-controlled trial investigating whether HCQ given for 5 days reduces the presumed or confirmed incidence of COVID-19 in 821 subjects. The Commission heard that overall, 10.7% of the participants (46 in the hydroxychloroquine group and 42 in the placebo group) did not complete the day 14 survey. For participants with missing outcome data, authors conducted a sensitivity analysis with their outcomes excluded or included as an event. The Commission heard that the asymptomatic infections were unlikely to be identified, that study population was younger, and had less co-morbidities than COVID-19 in the general

population. A further limitation was that COVID-19 infection was only confirmed by PCR in a small percentage of participants.

3.2 The Commission heard full adherence to the trial intervention by participants differed, 75.4% HCQ group and 82.6% placebo group, the most common reason for discontinuation was due to side effects. Among the participants who took HCQ, 40.1% reported a side effect, as compared with 16.8% receiving placebo (P<0.001). Nausea, loose stools, and abdominal discomfort were the most common side effects. There were no serious intervention-related adverse reactions or cardiac arrhythmias. The authors' concluded that after high-risk or moderate-risk exposure to Covid-19, hydroxychloroquine when used as postexposure prophylaxis given for 5 days within 4 days after exposure, did not prevent illness compatible with Covid-19 or confirmed infection in this study.

3.3 The Commission noted that the reason behind the attrition from ~7000 to 821 participants was not specified.

4. The status of on-going trials which include HCQ treatment

4.1 The Commission discussed once again, the responses to the notification letters issued on 22 May indicating that the MHRA may be minded to suspend recruitment to trials involving HCQ for COVID-19 under Regulation 31 of the legislation. These letters of notification were considered once again at the extraordinary meeting of Commission on June 1st 2020. At that time CHM had advised MHRA that recruitment to the hydroxychloroquine arm of the trials should be suspended pending the formal implementation of risk minimisation measures specific to each trial. The Commission had further advised that based on a case-by-case review of the individual trials, a suspension notification letter should be issued to each of the trials outlining the additional measures required before the HCQ arms could be recommenced.

4.2 The CHM was made aware of the fact that before the letters had been issued to the trialists following the meeting on 1st June, further information had come to light including the "Expression of Concern" notifications published by the Lancet and New England Journal of Medicine (NEJM) on 2nd and 3rd June and the subsequent retraction of the studies from both journals by the authors (Mehra et al), on 4th June.
All of these developments were considered to have a material impact on the advice CHM provided on 1st June for each trial, prompting the Commission to reconvene on 5th June to review these new developments and additional data published on safety and efficacy of hydroxychloroquine.

4.3 The Commission heard the global Sanofi treatment trial had halted recruitment and had submitted a formal temporary halt notification to MHRA CTU. The RECOVERY trial was on-going (at time of discussion), following justifications provided in recent discussions with MHRA CTU.

Moreover, a total of 6 other trials halted recruitment to the HCQ arms; these included 3 treatment trials and 3 prophylaxis trials. Some trials had proposed additional mitigation steps following the letter from the MHRA on 22 May notifying sponsors that the regulator was minded to suspend their trial according to Regulation 31 of the legislation and asking for further information. The Commission was asked to consider if trials of HCQ in COVID-19 should continue based on the overall body evidence.

4.4 The Commission noted that the retraction of the Mehra et al paper contributed to the lack of clarity around adverse risks of HCQ in COVID-19. The Commission noted there were well known effects of HCQ such as inhibition of the human Ether-a-go-go-Related Gene (hERG) channel resulting in QT prolongation which is a surrogate marker for drug-induced Torsade de Pointes. The Lane et al study alluded to an increase in this risk with HCQ particularly when combined with other arrhythmogenic drugs including azithromycin.

4.5 The Commission noted that although the Borba M et al.,(JAMA, 24th Apr 2020) trial was small, it did suggest that higher dose of chloroquine may induce cardiac adverse effects, while also recognising that there is an incomplete understanding of the HCQ/CQ dose response relationship to these adverse effects within COVID-19 patients. The Commission also noted that due to cardiovascular involvement in the pathophysiology of COVID-19, a drug-disease interaction with HCQ or CQ could exacerbate the risk of cardiac adverse effects. The Commission noted that the risk mitigation measures previously proposed should continue to be implemented.

4.6 The Commission also noted that in addition to the possible safety concerns, there was also a lack of robust evidence for efficacy of HCQ in the treatment of COVID-19.

4.7 The Commission noted that the dose of HCQ was considerably higher in the RECOVERY trial as compared with other on-going treatment trials globally. The Commission also noted that in the context of prophylaxis, HCQ was being used at a lower dose, but noted that the potential risks associated with a longer duration of use would also need to be considered. The CHM also noted that numbers of participants required to demonstrate an effect are substantially larger in prophylaxis trials and the study populations are in better health. In view of this CHM felt the threshold of risk that would be acceptable in this population may be lower in this population as compared with patients with acute Covid-19 where the potential benefit might be greater.

4.8 The Commission noted that combined use of HCQ with other drugs that prolong the QTc interval, apart from macrolide antibiotics, have not been studied well in COVID-19 patients. The Commission noted that for treatment trials a useful risk mitigation would be to make known QTc interval prolonging drugs an exclusion criterion. The Commission heard

that for RECOVERY, a known prolonged QTc interval is an exclusion criterion, but for the other trials, there is scope to move co-administration of QTc prolonging drugs from a caution to an exclusion criterion.

4.9 The Commission noted that the list of contraindicated QTc prolonging drugs in Boulware et al study in NEJM omits a number of other drugs, such as ondansetron, but could otherwise be used as a reference list for proposed studies with HCQ.

4.10 The Commission noted the proposal to consider a futility analyses for the RECOVERY trial was currently unnecessary given the retraction of the Lancet paper. The Commission noted that the DMC charter provides it with the freedom to seek additional information during the trial as and when required.

4.11 The Commission noted there still exists an imminent need for definitive evidence from well controlled randomised trials to establish the safety and efficacy of HCQ/CQ in COVID-19.

4.12 While the commission was in session, they were made aware of the press release from the RECOVERY trial investigators indicating that there was "no clinical benefit from use of hydroxychloroquine in hospitalised patients with COVID-19" and that enrolment of participants to the hydroxychloroquine arm of the RECOVERY Trial had been stopped by the trialists with immediate effect.

4.13 The Commission heard the high level results of the HCQ arm in the RECOVERY trial; a total of 1542 patients were randomised to hydroxychloroquine and compared with 3132 patients randomised to usual care alone. There was no significant difference in the primary endpoint of 28-day mortality (25.7% hydroxychloroquine vs. 23.5% usual care; hazard ratio 1.11 [95% confidence interval 0.98-1.26]; p=0.10). There was also no evidence of beneficial effects on hospital stay duration or other outcomes.

4.14 The Commission noted that this outcome from the HCQ arm of RECOVERY had potential implications for all other treatment trials investigating the use of HCQ in COVID-19. The Commission considered that these implications need to be carefully considered from both the regulatory and clinical equipoise perspective.

4.15 The Commission reviewed the on-going trials registered in the UK that are investigating HCQ in the context of COVID-19 and concluded, that for all such trials, investigators should review the data collected hitherto and provide a justification to proceed with the use of HCQ accounting for the recent lack of efficacy finding from the HCQ arm of RECOVERY. Sponsors of prophylaxis trial were additionally asked to consider the findings of the **Boulware et al** paper and the status of the disease in the community in their justifications. The Commission concluded that all trials

should be suspended until the justifications and specific questions from the Commission are answered.

4.16 The Commission noted no action was required for the RECOVERY trial as confirmation has been received that enrolment to the HCQ arm has stopped and is also reported publicly.

4.17 The Commission confirmed the advice provided on the 1st of June for REMAP-CAP was still applicable; namely, that the HCQ arm of the trial should not restart until full response including a robust justification of the basis to proceed had been submitted.

4.18 The Commission confirmed that points for clarification relating to the PRINCIPLE trial as previously detailed remained relevant. The Commission reasoned that if HCQ is not effective in established disease, prophylactic use following exposure would require stronger justification. The Commission noted that the population targeted in the PRINCIPLE study were older than 70, or older than 50 with risk factors and these individuals might be expected to have a higher risk of cardiac co-morbidity.

4.19 The Commission noted that the Sanofi treatment trial required no update as the HCQ arm is presently halted, and decisions can be made once the substantial amendment to restart has been received and is under CTU review.

4.20 The Commission noted that the PIONEER trialists had voluntarily paused recruitment to the HCQ arm but agreed that MHRA should formally suspend the trial until the request for a renewed and nuanced justification is provided that includes a more in-depth justification of for the combined use of HCQ, azithromycin and Zinc. The Commission felt that the Favipiravir antiviral arm can currently proceed as planned.

4.21 The Commission heard that PROTECT-Surg is a prophylaxis trial primarily targeting patients scheduled for surgery, noting patients can test positive for SARS-CoV-2 but must be asymptomatic. The Commission heard a prior justification to proceed has been provided, however, the rationale relied almost exclusively on precedent that the recruitment to the HCQ arm of the RECOVERY trial was continuing. The Commission confirmed that the same advice as provided on the 1st June should be issued; and the trial suspended until a more robust justification can be provided.

4.22 The Commission heard COP-COV is an international pre-exposure prophylaxis trial which envisaged recruiting approximately 10,000 participants in the UK. The Commission noted that the investigators had proposed 9 additional risk mitigation measures. The Commission noted same approach should be taken as with the other trials, in terms of discussing the scientific rationale and justification in the context of the

finding from the **Boulware et al.,** paper. The Commission also suggested inclusion of an interim analysis and stopping rules in the protocol.

4.23 The Commission discussed PROLIFIC, a prophylaxis trial in a population primarily defined as health care professionals is similar to COP-COV but with fewer participants (~1000). The Commission noted that the trial's data collection includes ECGs for some participants and PK studies of all participants. The Commission sought justification for continuation of the trial in light of, RECOVERY trial findings; a discussion of the relevance of the study in the context of **Boulware et al** paper including consideration of the impacts of changing epidemiological landscape / disease status in the community on the study's power/sample size.

4.24 The Commission noted that the MHRA has a statutory obligation to inform the ethics committee when a suspension notice is issued, and any changes to patient facing information would be reviewed by the ethics committee.

4.25 The Commission noted with concern that confirmation of the provenance of the data, as expected for a reputable journal such as the Lancet had not been obtained. This subsequently led to retraction of the Mehra et al study which had been considered during the CHM meeting of June 1st 2020. The Commission discussed options to mitigate against similar occurrences, such as the potential for published data to be inaccurate, retracted, or fraudulent in the future. While noting that the group considers data in a hierarchal manner, the Commission debated the need for a formal framework and guidance with in-built flexibilities.

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 2020 at 10:00 & Friday 19th June 2020 (TBC).