

The COPCOV Trial's position statement on "A living WHO guideline on drugs to prevent COVID-19."

On the 2nd of March, 2021, the WHO released a guideline making a strong recommendation against the use of hydroxychloroquine for individuals who do not have COVID-19 due to "*high certainty evidence that has emerged regarding the lack of effect of hydroxychloroquine prophylaxis*". There is no new information and no high certainty evidence regarding the lack of effect. Nearly all the information used to make this judgement has been in the public domain for several months. The randomised controlled trial (RCT) results clearly show that there is *considerable uncertainty* whether or not hydroxychloroquine provides a moderate benefit in preventing COVID-19. They also confirm that significant toxicity is very unlikely.

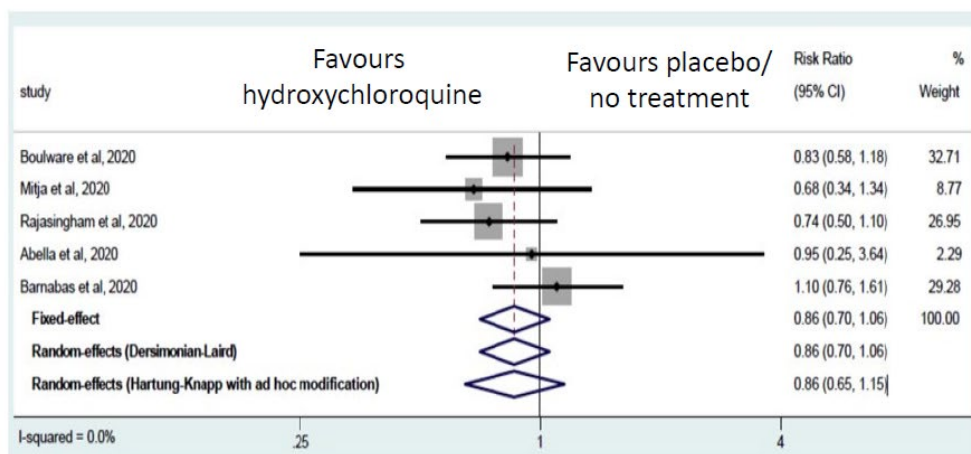
As recommended by the WHO guidelines, we have reconsidered whether or not to continue the COPCOV study. We have concluded that we should continue with the COPCOV study for the following reasons:

- There remains substantial uncertainty over the benefits of hydroxychloroquine in preventing COVID-19, while the tolerability profile is reassuring (the WHO assessment of adverse events leading to discontinuations contains an important numerical error- see below).
- New evidence will soon become available (HERO-HCQ study and Individual Patient Data analyses are ongoing). When these have been assessed we will reconsider again the continuation of the COPCOV study.
- The WHO panel judged that this drug is no longer a research priority. For COPCOV, investments have already been made so it is not a question of 'priority' for this study.
- There are no safety reasons to stop the study.
- Stopping the trial now could raise unnecessary concerns among existing participants and healthcare workers, and could undermine trust in the research teams and the clinical trial process.

Evidence:

No new evidence has emerged recently. The evidence used to justify this strong WHO recommendation comes from the 6 heterogeneous RCTs published between June and December 2020 which, in total, enrolled 6,059 participants. Three trials were of hydroxychloroquine Post-Exposure Prophylaxis (PEP: one of which was cluster randomised with no placebo), and three were of Pre-Exposure Prophylaxis (PrEP: by far the largest of these used a much lower dose of hydroxychloroquine than the other two). Details are provided in the appendices below.

A meta-analysis of the primary endpoints from five of these trials has been presented recently by the Harvard group (see below- the other trial is unpublished and included only one additional case of COVID-19). This evidence continues to suggest substantial uncertainty as to the benefit of hydroxychloroquine in preventing COVID-19, with an overall trend towards benefit, but with wide confidence intervals.



The WHO guideline prioritised mortality in their assessment. This was a rare event in prophylaxis trials. Indeed, in five of the six trials there were no deaths, and in the other (the cluster randomised PEP trial) there were 5 deaths in hydroxychloroquine recipients and 8 in subjects who did not receive hydroxychloroquine; relative risk 0.77 (95% confidence interval 0.39 to 1.53). Somehow from these very small numbers the WHO guideline panel were able to conclude from this that there was “*high certainty evidence*” that hydroxychloroquine *did not* reduce mortality. There is clearly something wrong with this assessment. This is illustrated by the contrast with the WHO guideline assessment of dexamethasone in severe COVID-19 based on over 1,500 deaths, for which the relative risk of death was 0.80 (95% CI: 0.70 to 0.92). This transformative result was described as only “*moderate certainty evidence*”.

In truth no high certainty evidence has emerged regarding the lack of effect of hydroxychloroquine prophylaxis, and moderate benefits have not been excluded.

With regard to toxicity, in justifying their strong recommendation the WHO guidelines state that hydroxychloroquine “*probably increases the risk of adverse effects leading to discontinuation of the drug (moderate certainty).*” This appears to result from a numerical error. In fact, in the two PrEP studies reporting discontinuations there were more discontinuations in the placebo groups (N=8) than in the hydroxychloroquine groups (N=4). A corrected forest plot is shown in the appendix.

Judgement:

The following statement is made in the WHO guideline; “*almost all people would not consider this drug worthwhile,*” and that “*it is no-longer a research priority*” and also “*that funders and researchers should reconsider the initiation or continuation of these trials.*”

It is clear that this is not a conclusion backed by the limited evidence from these six heterogeneous trials (with very few endpoints in the three pre-exposure prophylaxis studies, and a miscalculation in the study adverse events (AEs) leading to discontinuations). It is a judgement, and we do not believe that it is justified. Moderate benefit cannot be excluded. Suggesting that ongoing studies of hydroxychloroquine should stop and switch to “*more promising drugs*” when there remains substantial uncertainty is worrying, and it is a concern for the integrity of the guidelines process.

Appeal:

No drug has excited more controversy during COVID-19 than hydroxychloroquine. There have been unjustified claims for and against the drug. Yet many countries still recommend it, and many practitioners prescribe it. There is no justification for this. It is essential to find the **truth**: Is this drug beneficial or not? This premature assessment and worrying claim of certainty by the WHO guidelines group will not resolve the issue. That needs evidence from randomised controlled trials, and that is what the COPCOV trial, a rigorous randomised, double-blind, placebo-controlled trial, is trying to provide.

There are no proven preventative drug therapies for COVID-19. Furthermore, many people, in particular in LMICs, will be without vaccines for years. A drug that has moderate protective benefit can still save thousands of lives, a result demonstrating moderate protection is well within the confidence intervals shown in the WHO's guideline. As such the study remains scientifically justified and important. Finding out whether hydroxychloroquine provides protective benefit is particularly important for those areas where vaccine deployment will be delayed, or if vaccine escape mutants appear.

Our recommendation

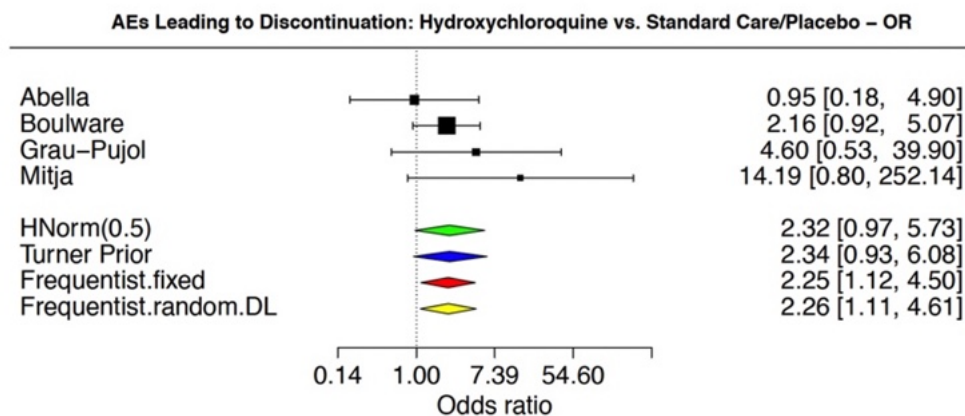
WHO recommendations should always be taken seriously and they are certainly influential. We have always supported the recommendation against the routine use of hydroxychloroquine in either treatment or prevention of COVID-19, but we disagree that currently available evidence provides 'high certainty' of lack of benefit in prevention. As shown there is *substantial uncertainty*. The WHO guideline's assessment of tolerability in chemoprophylaxis based on study withdrawals appears to be a calculation error. The WHO recommendations on hydroxychloroquine in prevention are, according to the authors, '*a living guideline*' and they state that given the number of ongoing studies '*further evidence will emerge to inform policy and practice*'. The COPCOV trial will contribute to this and should continue. A definitive answer is needed. More evidence is likely to emerge in the near future, which may affect our decision to continue with the study. We will continue to review this evidence as it appears.

We believe the right thing to do is to continue to conduct the COPCOV study while we can. As ever, we appreciate your ongoing support, in what has been the difficult pursuit of truth.

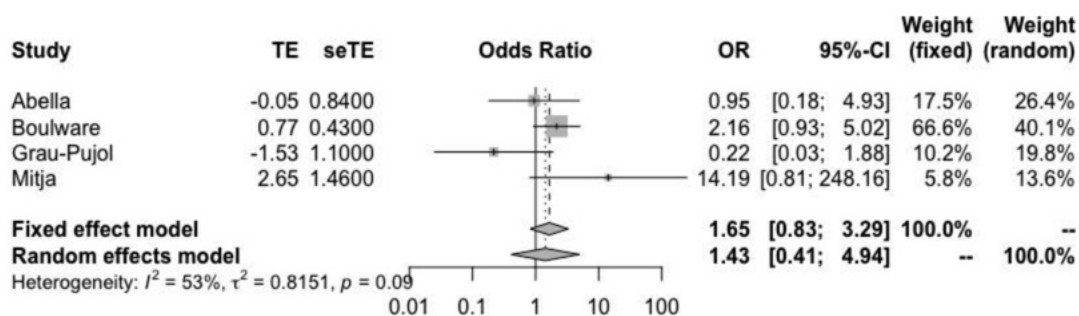
Appendix 2: Adverse Events (AEs) leading to discontinuation

We have carefully reviewed the analysis of 'AEs leading to discontinuation'¹ and found that in the Grau-Pujol *et al.* paper, it is both stated that there were **more** (in the text) and **less** (in the table) AEs leading to discontinuation in the hydroxychloroquine group. We contacted the authors to clarify and have confirmed there were **less** discontinuations in the hydroxychloroquine group, which is the opposite of the reported effect in the systematic review and which forms the evidence base for the WHO guideline.

The incorrect meta-analysis shown in the systematic review is based on 5 participants in the hydroxychloroquine arm and 1 in the placebo arm discontinuing, which is the wrong way round:



The correct meta-analysis, with 1 participant in the hydroxychloroquine arm and 5 in the placebo arm having adverse effects leading to discontinuation, which is reported in the Grau-Pujol *et al.* publication and confirmed by the author, is shown below:



The confidence interval now crosses the midline and undermines the guidelines statement that there is "probably increased adverse events leading to discontinuation (moderate evidence)".

¹ Although the premise of discontinuation after AEs can be challenged as the main concern of participants (as opposed to the severity of the particular AE), and introduces uncertainty as a surrogate of safety, as AEs are objectively graded, and the reasons to discontinue *may* also relate to severity but also other factors. Based on the decision to include AEs leading to discontinuation, the Barnabas *et al.* study which reported AEs grade 2 and above, a more objective marker of severity, and which did not show any difference between hydroxychloroquine and placebo, was not included. In addition, the results of Mitjà *et al.* study were included,

even though it was not placebo-controlled, and demonstrates a much larger proportion of AEs leading to discontinuation than the placebo-controlled trials.