PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	New prophylaxis regimen for SARS-CoV-2 infection in health professionals with low doses of Hydroxychloroquine and Bromhexine. A randomized, double-blind placebo clinical trial (ELEVATE Trial).
AUTHORS	GRANADOS-MONTIEL, JULIO; Hazan-Lasri, Eric; Franco-Cendejas, Rafael; Chavez-Heres, Tatiana; Silva-Bermudez, Phaedra; Aguilar-Gaytan, Rocio; Manzano-Leon, Natalia; Méndez-Maldonado, Karla; Alvarez-Arce, Alejandro; Martinez-Portilla, Raigam

VERSION 1 – REVIEW

REVIEWER	Dmitry Stepanov Marienkrankenhaus, Anaesthesiology, Intensive Care, Pain Management and Palliative Care
REVIEW RETURNED	07-Nov-2020

GENERAL COMMENTS	Dear authors of the research, Thank you for the submitting of the study protocol for the publication at the BMJ. I have studied it and have some concerns that are described below in details. A. The ABSTRACT of the study has several inaccuracies: 1. The SARS-CoV-2 virus binds to angiotensin-converting-enzyme 2 molecules on the surface of alveolar epithelial type 2 cells, not pneumocytes generally; 2. Hydroxychloroquine as well as bromhexine do not inhibit the binding of the virus to the ACE2 in the true sense; they just prevent the subsequent penetration of the virus into the cell – through increasing of the endosomal pH and inhibiting of the transmembrane serine protease that cleaves the S-protein, accordingly; 3. The objective of the study is to assess whether a prophylactic treatment of healthy persons exposed to a high infection risk with a combination of the both drugs is more effective than a prophylaxis with bromhexine alone. The design of the study does not enable to answer the question, whether such a prophylaxis is effective at all since there is no control group that would have only placebo of the both medications. Therefore, the study´s objective should be recast, for example as “to assess the efficacy and safety of the adding of hydroxychloroquine to the prophylaxis with bromhexine for SARS-CoV-2 infection in healthy health care workers…” B. The section “STRENGHTS AND LIMITATIONS” also shows some inaccuracies:

	1. The study is not able to provide an information about efficacy of the both medicines. It could only find out whether the prophylactic treatment with a combination of hydroxychloroquine and bromhexine is advantageous over bromhexine alone. The efficacy of the prophylaxis with bromhexine has obviously been already implied. Additionally, adverse reactions to bromhexine could also be revealed; however, those are generally extremely rare; 2. In spite of the name of the section, no limitations of the study are formulated by the authors in this section. This must be completed, among other things, taking into account the following remarks. C. INTRODUCTION 1. The genetic sequence of the virus SARS-CoV-2, not of the COVID-19 (this is a disease!) has been shared. Besides, this abbreviation “COVID” is also disclosed with a delay; 2. The data about the incidence and mortality should be actualized for every peer-review; 3. “Camostat mesylate” must be written without a comma; 4. The phrase “both drugs approved by the FDA but not available in Mexico and that produce side effects and contraindications” is grammatical incorrect. Besides, every drug has contraindications and side effects, even if they are very rare, thus, I would recommend not to include such an expression at all; 5. Bromhexine has only few contraindications, true, but still not “no” at all. For example, a history of Stevens-Johnson syndrome or toxic epidermal necrolysis could be considered as a relative contraindication, as well as cross-allergic reactions, for example, to ambroxol; 6. It might be mentioned that bromhexine is an over-the-counter drug; 7. I would suggest a recasting of the expression “In a letter to the editor in the NEJM”, for example, as “According to a letter to the editor of the NEJM”; 8. “This research regarding the use of hydroxychloroquine and bromhexine versus bromhexine in health personnel will allow us to determine und compare the effectiveness of both interventions, which is of vital importance to clarify whether these treatments are effective in preventing the appearance of infection in this population”. Again, we will not be able to determine the effectiveness of the prophylaxis on the basis of this trial since there is no fully placebo group receiving neither hydroxychloroquine nor bromhexine. Therefore, the question whether the prophylaxis is effective compared to the absence of any prophylaxis can´t be answered; we can only compare the both treatments and clear up whether hydroxychloroquine is of benefit, relying on the primary trial results and reported adverse effects. D. METHODS AND ANALYSIS 1. It´s not clear what means the expression “phase 3” in the Study design section; 2. The sentence “Likewise, health personnel working at … and falls within the inclusion criteria ...” seems to be grammatical incorrect; 3. It´s not clear what is represented by some operational definitions of variables used for the eligibility establishment, for example what mean such expressions as “individual risk of SARS, “individual risk of confusion”, “individual risk of hypothermia” etc. It remains also unclear why typical adverse effects of hydroxychloroquine such as

	"QT segment elongation" or "corneal opacity" are declared to be related to bromhexine; 4. It´s not clear described which variables are expected to be normal und which free distributed. On my opinion, the study requires an additional specialist statistical review; 5. The exclusion criteria seem to be very strong. Indeed, some criteria, for example, glomerular filtration rate < 20 ml/min or QT-lengthening drugs use are plausible. However, I can´t properly understand why persons having widely prevalent chronic diseases such as hypertension, diabetes and asthma are also excluded, whereas such persons make up a large portion of the healthcare staff. Moreover, those with chronic pulmonary and cardiovascular diseases are just the persons that must be protected against the coronavirus infection first of all. The results of the study, which includes only a sample of quite healthy persons, cannot be correct extrapolated to the whole population of the healthcare staff. Alas, this makes the results and their interpretation useful only to a certain extent. There is therefore a loud need to discuss this item properly in the section "Strengths and limitations"; 6. A relatively small sample size and the fact, that this is a single-center trial, require also a clear statement under "Strengths and limitations". Again, I guess, there could have been an opportunity to recruit much more participants and perform a subgroup analysis if the exclusion criteria would have not been such strong. Moreover, if this would have been the case, a third group with only placebo medications could also have been included; 7. There is no information whether and how often ECGs will be performed routinely since QT lengthening can´t be active reported by participants; 8. It´s not clear whether the participants who will get COVID-19 symptoms and will be tested out of the study will be excluded or considered to be infected? The latter stands probably to reason, nevertheless, should be mentioned distinctly; 9. The participants will be PCR-tested at days 30 and 60; these intervals are likely to be too long since it´s possible that some participants could become positive and later negative again between the appointments. In my humble opinion, this is an important disadvantage of the study that could affect the results, for example making them statistical non-significant or affecting their value doubtful. I find that this point must be disclosed under "Limitations" and worked out properly in the later article under "Discussion"; 10. There is another instant of time mentioned in the section "Primary endpoint": 7 days after the start of the treatment. Will the participants also be tested at this point? 11. It´s hard to understand why there are a primary endpoint considering the proportion of the staff infected within 60 days and a secondary endpoint taking account of the staff infected within the first 30 days of the treatment. Since the treatment scheme will not be changed during the study it´s not clear which value would this distinguishing represent for the interpretation of the study results. 12. Moreover, no other endpoints regarding clinic states of participants are included, whereas the treatment with hydroxychloroquine and bromhexine are expected to protect against the infection. There are conceivable situations when a treatment wouldn´t prevent a contamination with the novel coronavirus but could protect from the development of symptoms or further clinical deteriorating. This aspect is not mentioned in the study description at all, positive PCR results are equated to infection as such without distinguishing between clinical symptomatic and asymptomatic cases (see also p. 8 above).

	Assuming that the researchers have collected the information about the health state of the participants I would recommend the authors to analyse the data about the incidence of clinical symptomatic COVID-19 and to perform a correction of the outcome measures with a respective explanation. This wouldn´t represent a major change in the course of the study and provide the information to make up for the above-mentioned deficiencies, including the large time periods between the PCR-tests (see p. 9). With all this going on, the study protocol must not be rejected because of these flaws. Additionally, I would recommend, to present the text of the protocol to a native speaker of English. Although I have revealed some mistakes and misprints, I´m still not fully confident. I hope, these censorious remarks will help the authors to improve the design and the presentation of the study, as well as to understand the reasons for possible concerns and objections. I´m looking forward to further discussions.

REVIEWER	Michael White University of Connecticut
REVIEW RETURNED	19-Nov-2020

GENERAL COMMENTS	OVERALL ASSESSMENT: The concept may be a good one to try dual therapy to enhance the impact of hydroxychloroquine but this methods paper is not well written as I explain below. TITLE: Can you really say it is placebo controlled if you believe that both hydroxychloroquine and bromhexine are effective at blocking the ACE2 receptor? ABSTRACT: The intro section is unnecessarily too long. Start at the sentence - "In Mexico, COVID-19 has produced..." It should be laser focused on why prophylaxis is needed and why this trial might yield unique findings. What is it about bromhexine that the investigators believe make this regimen better than HCQ alone that second paragraph could be more specific. You need the extra words to bolster the abstract's methods section. Abstract: Line 25: The sentence is awkwardly written, it could be read as your saying that bromhexine is as effective (identical) as hydroxychloroquine + bromhexine rather than it looks identical. Abstract in General: The method is also a bit confusing, if you believe that bromhexine can enhance hydroxychloroquine efficacy, why use it as a "placebo". Also, an extra sentence should be added on why you believe a 16% difference in "infection" is clinically relevant and how that endpoint is defined. While the sample size calculation is given, it does not explicitly say how many people will be recruited. Are you going for 70 per group? It is unclear in the abstract. I am not sure why it is a "simple" RCT... Strengths and Limitations: Bullet 4 or 5 - I am not sure you can say that the data collected WILL play a role or crucial role in anything. It is not a commonly employed regimen at this time globally so only if the results are positive for the combination therapy can you say it will have impact on clinical practice. It can inform whether dual blockade of the ACE2 receptor is an effective approach to prevent COVID-19 infection but aside from that, you are limited.

	INTRODUCTION: I am not a fan of this introduction as it is written. I think it will take a full re-write to accomplish what the investigators need to do. Paragraph 1 - We do not need this history lesson. Cut the fat and get to the point in two sentences about why it is important you do this study. The entire intro meanders, is unfocused, and if it was concisely written could be much more impactful. THE biggest thing the investigators need to convince the readers at this point is - with the vaccines coming in 2021, why would anyone want to prophylactically take this every day? There are compelling reasons (delays in rolling out the vaccine to developing countries, possibilities that the vaccine might not work as well in select populations that were not represented in clinical trials, hospital workers will likely see more superspreaders and the transmission risk could be enhanced, etc, etc). The SECOND biggest thing is that the scientific underpinnings are sound. Why do you believe that hydroxychloroquine is going to be effective based on previous RCTs in this space, why do you believe that bromhexine is going to be effective, why do you believe the combination will be better than either drug alone, if they are both effective, why use this study design that will obscure the benefits by not supplying a true placebo group? If you believe that bromhexine is ineffective alone but will be effective at enhancing hydroxychloroquine, you need to show data that leads the reader to believe it. STUDY DESIGN, Lines 47 to 49: The investigators are back to saying it is placebo controlled and they dropped the term simple. They should refer to the trial in the same terms each time throughout the paper and not lose and add terminology. Table: SARS - SARS is the disease several years ago before MERS. Is that what you are really asking about? Inclusion Criteria: Normal ECG - So sinus tachycardia gets people excluded? I would remove this and then focus on ECG findings that exclude people below as you did. Exclusion Criteria: "Use of other drugs such as..." is not helpful. Are these drugs excluded because they are QTc interval prolongers, because they are cardiac medications, or another reason? It is impossible to know what drugs not on that list would lead to patient exclusions based on this description. Why eliminate people with comorbidities if they have the highest risk of negative outcomes should they be infected? If you show it works in people at the lowest risk of having a negative outcome should they be infected, does that mean it will translate into benefits for the highest risk people? We know that ACE2 expression is higher in cardiac patients for a variety of reasons. If you believe the mechanism that you do, why would you exclude these people? Sample Size Calculation: Now I see that you are referring to an absolute risk reduction of 16% (from 20% to 4%). This was not clear before and looked like it could have been a relative risk reduction. I am pretty sure based on other data that this will not be achievable but I do understand where you are coming from. If you do show this magnitude of benefit, that would be very impactful except you wouldn't know whether the combination regimen was not benefiting

	from a negative effect of bromhexine since there is no true placebo control. Investigational Product: This is not clearly written or the trial is not what is stated above. If one group is getting hydroxychloroquine tablets and the other is not, that is not blinded. Sure they are both getting syrup in the groups but one is also taking tablets and the other isn't. Based on other trials that has been conducted, I worry the the RT-PCR positivity for the primary endpoint will make the trial difficult to show a difference. It looks like other prophylactic regimens studied previously found better impact on the combined endpoint of RT-PCR positive or signs and symptoms of COVID-19 infection. I would ask the investigators to also look at this combined endpoint, it would be important to meta-analysts. I believe that the false positive and false negatives with the RT-PCR tests are covering up the potential effects of hydroxychloroquine therapy and the combined endpoint is therefore superior. This may not b true but based on the data I have reviewed, it is a possible hypothesis.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dear authors of the research,
Thank you for the submitting of the study protocol for the publication at the BMJ. I have studied it and have some concerns that are described below in details.

A. The ABSTRACT of the study has several inaccuracies:
   1. The SARS-CoV-2 virus binds to angiotensin-converting-enzyme 2 molecules on the surface of alveolar epithelial type 2 cells, not pneumocytes generally;
      Thank you for your observation, we have amended the Abstract as follows: “High infectivity of SARS-CoV-2 is related with cell entry mechanism, through the angiotensin-converting enzyme (ACE) receptor” (lines 28-29).
   2. Hydroxychloroquine as well as bromhexine do not inhibit the binding of the virus to the ACE2 in the true sense; they just prevent the subsequent penetration of the virus into the cell – through increasing of the endosomal pH and inhibiting of the transmembrane serine protease that cleaves the S-protein, accordingly;
      Thank you; we have changed the Abstract text due to extended word count and have removed this sentence: “We propose studying prophylactic treatment with hydroxychloroquine (HCQ) and bromhexine (BHH), which have been shown to be effective in preventing SARS-CoV-2 infection progression when administered in early stages” (lines 30-32).
   3. The objective of the study is to assess whether a prophylactic treatment of healthy persons exposed to a high infection risk with a combination of the both drugs is more effective than a prophylaxis with bromhexine alone. The design of the study does not enable to answer the question, whether such a prophylaxis is effective at all since there is no control group that would have only placebo of the both medications. Therefore, the study´s objective should be recast, for example as “to assess the efficacy and safety of the adding of hydroxychloroquine to the prophylaxis with bromhexine for SARS-CoV-2 infection in healthy health care workers…”
      We aim to assess the efficacy of both treatments and the Reviewer is correct. We originally had no plans to include a bromhexine placebo due to financing and the complexity of the design, however we were recently authorized to do so; thus, the study will include 4 groups with the respective placebos: “Study groups will be defined as follows: 1) HCQ 200mg/d + BHH placebo; 2) BHH 8mg/8h + HCQ placebo; 3) HCQ 200mg/d + BHH 8mg/8h; and 4) HCQ placebo + BHH placebo”; (lines 36-38).

B. The section “STRENGHTS AND LIMITATIONS” also shows some inaccuracies:

1. The study is not able to provide an information about efficacy of the both medicines. It could only find out whether the prophylactic treatment with a combination of hydroxychloroquine and bromhexine is advantageous over bromhexine alone. The efficacy of the prophylaxis with bromhexine has obviously been already implied. Additionally, adverse reactions to bromhexine could also be revealed; however, those are generally extremely rare;
   We have corrected study design in order to evaluate each drug independently.
2. In spite of the name of the section, no limitations of the study are formulated by the authors in this section. This must be completed, among other things, taking into account the following remarks.
   We have addressed this point as requested and have corrected this section adding limitations (lines 63-65)

C. INTRODUCTION

1. The genetic sequence of the virus SARS-CoV-2, not of the COVID-19 (this is a disease!) has been shared. Besides, this abbreviation “COVID” is also disclosed with a delay;
   Thank you for your observation. We have amended the text as SARS-CoV-2 (line 81).
2. The data about the incidence and mortality should be actualized for every peer-review;
   We have removed old references and updated our data from Mexico with the most recently reported.
3. “Camostat mesylate” must be written without a comma;
   Thank you for your observation, we have removed the section where it is mentioned.
4. The phrase “both drugs approved by the FDA but not available in Mexico and that produce side effects and contraindications” is grammatical incorrect. Besides, every drug has contraindications and side effects, even if they are very rare, thus, I would recommend not to include such an expression at all;
   We have removed the expression as requested.
5. Bromhexine has only few contraindications, true, but still not “no” at all. For example, a history of Stevens-Johnson syndrome or toxic epidermal necrolysis could be considered as a relative contraindication, as well as cross-allergic reactions, for example, to ambroxol;

6. It might be mentioned that bromhexine is an over-the-counter drug;
   We agree with the reviewer and have edited this section to mention that there are few contraindications to BHH, and that it is an over the counter medication (lines 120-123).
7. I would suggest a recasting of the expression “In a letter to the editor in the NEJM”, for example, as “According to a letter to the editor of the NEJM”;
   We have corrected this (line 124)
8. “This research regarding the use of hydroxychloroquine and bromhexine versus bromhexine in health personnel will allow us to determine und compare the effectiveness of both interventions, which is of vital importance to clarify whether these treatments are effective in preventing the appearance of infection in this population”. Again, we will not be able to determine the effectiveness of the prophylaxis on the basis of this trial since there is no fully placebo group receiving neither hydroxychloroquine nor bromhexine. Therefore, the question whether the prophylaxis is effective compared to the absence of any prophylaxis can´t be answered; we can only compare the both treatments and clear up whether hydroxychloroquine is of benefit, relying on the primary trial results and reported adverse effects.
   We have corrected the design due to the reviewer’s comments, since we fully agree, and will now include 4 groups.

D. METHODS AND ANALYSIS

1. It´s not clear what means the expression “phase 3” in the Study design section;
   We are sorry for this; we have added the explanation of the phases the Mexican government has used for the pandemic: “The Mexican government defined 3 phases to determine risk for SARS-CoV-2 infection: imported cases from outside Mexico; community infection and spread of the disease throughout the country (also known as Phase 3). In the latter, it is assumed that every person who enters a hospital is a potentially infected carrier; currently our centre is in Phase 3.” (lines 147-150).
2. The sentence “Likewise, health personnel working at … and falls within the inclusion criteria ...” seems to be grammatical incorrect;

We have asked a native English speaker to correct the manuscript's grammatical errors.

3. It´s not clear what is represented by some operational definitions of variables used for the eligibility establishment, for example what mean such expressions as "individual risk of SARS, "individual risk of confusion", "individual risk of hypothermia" etc. It remains also unclear why typical adverse effects of hydroxychloroquine such as "QT segment elongation" or "corneal opacity" are declared to be related to bromhexine;
   We have corrected the operational definitions of the variables and double checked the possible adverse effects of medication (Table 1).
4. It´s not clear described which variables are expected to be normal und which free distributed. On my opinion, the study requires an additional specialist statistical review;
   We have described in the Statistical Analysis section evaluation of normal distribution and subsequent analyses; while we may expect how some variables behave, we will determine from our results the type of variable distribution. We have consulted with our statistician and this is his recommendation.
5. The exclusion criteria seem to be very strong. Indeed, some criteria, for example, glomerular filtration rate < 20 ml/min or QT-lengthening drugs use are plausible. However, I can´t properly understand why persons having widely prevalent chronic diseases such as hypertension, diabetes and asthma are also excluded, whereas such persons make up a large portion of the healthcare staff. Moreover, those with chronic pulmonary and cardiovascular diseases are just the persons that must be protected against the coronavirus infection first of all. The results of the study, which includes only a sample of quite healthy persons, cannot be correct extrapolated to the whole population of the healthcare staff. Alas, this makes the results and their interpretation useful only to a certain extent. There is therefore a loud need to discuss this item properly in the section "Strengths and limitations";
   We understand the reviewer's concerns and completely agree. The main problem is that the use of hydroxychloroquine has become very controversial due to previous studies (which have now been retracted) regarding higher mortality and a high incidence of complications. Thus, we have been required to include only healthy people, at least in this initial study, in order to reduce possible complications due to medication.
6. A relatively small sample size and the fact, that this is a single-center trial, require also a clear statement under "Strengths and limitations". Again, I guess, there could have been an opportunity to recruit much more participants and perform a subgroup analysis if the exclusion criteria would have not been such strong. Moreover, if this would have been the case, a third group with only placebo medications could also have been included;
   We have changed study design to include all combinations possible of the medication evaluated, and we have verified that our sample size is correct and sufficient to conduct our study. The Strengths and Limitations section only allows for 5 bullet points, so we have tried to include your suggestions in this limited area.
7. There is no information whether and how often ECGs will be performed routinely since QT lengthening can´t be active reported by participants;
   ECG evaluation will be performed weekly at the assessment mentioned in the follow-up paragraph (line 381).
8. It´s not clear whether the participants who will get COVID-19 symptoms and will be tested out of the study will be excluded or considered to be infected? The latter stands probably to reason, nevertheless, should be mentioned distinctly;
   We have specified that if patients included in the study present with symptoms or infection within 7 days, they will be excluded from analysis. Patients from day 7 onward will be included as intention-to-treat analysis. This is mentioned in the "Outcome measures" section.
9. The participants will be PCR-tested at days 30 and 60; these intervals are likely to be too long since it´s possible that some participants could become positive and later negative again between the appointments. In my humble opinion, this is an important disadvantage of the study that could affect the results, for example making them statistical non-significant or affecting their value doubtful. I find that this point must be disclosed under "Limitations" and worked out properly in the later article under "Discussion";
   We agree with the Reviewer, and this would be material to discuss once the results have been obtained. However, at this point, while maybe weekly testing would be optimal, financially it is not possible to do so, thus we would have to acknowledge the possibility that is here mentioned.

10. There is another instant of time mentioned in the section “Primary endpoint”: 7 days after the start of the treatment. Will the participants also be tested at this point?
    No, we have only established 7 days as the initial window where a patient may present symptoms and subsequently be eliminated from the study. We have tried to clarify this.
11. It´s hard to understand why there are a primary endpoint considering the proportion of the staff infected within 60 days and a secondary endpoint taking account of the staff infected within the first 30 days of the treatment. Since the treatment scheme will not be changed during the study it´s not clear which value would this distinguishing represent for the interpretation of the study results.
    We consider the secondary endpoint as the interim analysis to evaluate whether there exist adverse or beneficial effects we should consider in order to continue the study.
12. Moreover, no other endpoints regarding clinic states of participants are included, whereas the treatment with hydroxychloroquine and bromhexine are expected to protect against the infection. There are conceivable situations when a treatment wouldn´t prevent a contamination with the novel coronavirus but could protect from the development of symptoms or further clinical deteriorating. This aspect is not mentioned in the study description at all, positive PCR results are equated to infection as such without distinguishing between clinical symptomatic and asymptomatic cases (see also p. 8 above).
    We completely agree, however we believe that a specific protocol in infected patients should be conducted to assess this, whether the incidence of progression to severity may be slowed with the use of either or both drugs.
13. Assuming that the researchers have collected the information about the health state of the participants I would recommend the authors to analyse the data about the incidence of clinical symptomatic COVID-19 and to perform a correction of the outcome measures with a respective explanation. This wouldn´t represent a major change in the course of the study and provide the information to make up for the above-mentioned deficiencies, including the large time periods between the PCR-tests (see p. 9). With all this going on, the study protocol must not be rejected because of these flaws.
    We are very grateful for your constructive comments and thorough review; we will consider these modifications or to further include the data as secondary outcomes and register it.

Additionally, I would recommend, to present the text of the protocol to a native speaker of English. Although I have revealed some mistakes and misprints, I´m still not fully confident. I hope, these censorious remarks will help the authors to improve the design and the presentation of the study, as well as to understand the reasons for possible concerns and objections. I´m looking forward to further discussions.
We have corrected English language with a native speaker and verified it is in United Kingdome English throughout the manuscript.

Reviewer: 2
Comments to the Author
OVERALL ASSESSMENT: The concept may be a good one to try dual therapy to enhance the impact of hydroxychloroquine but this methods paper is not well written as I explain below.

TITLE: Can you really say it is placebo controlled if you believe that both hydroxychloroquine and bromhexine are effective at blocking the ACE2 receptor?
We have corrected the design to include 4 groups and to be able to determine the individual effects of each drug studied.

ABSTRACT: The intro section is unnecessarily too long. Start at the sentence - "In Mexico, COVID-19 has produced..." It should be laser focused on why prophylaxis is needed and why this trial might yield unique findings. What is it about bromhexine that the investigators believe make this regimen better than HCQ alone that second paragraph could be more specific. You need the extra words to bolster the abstract's methods section.
Abstract: Line 25: The sentence is awkwardly written, it could be read as your saying that bromhexine is as effective (identical) as hydroxychloroquine + bromhexine rather than it looks identical.
Abstract in General: The method is also a bit confusing, if you believe that bromhexine can enhance

hydroxychloroquine efficacy, why use it as a "placebo". Also, an extra sentence should be added on why you believe a 16% difference in "infection" is clinically relevant and how that endpoint is defined. While the sample size calculation is given, it does not explicitly say how many people will be recruited. Are you going for 70 per group? It is unclear in the abstract. I am not sure why it is a "simple" RCT...
We have edited the Abstract accordingly, to match word requirements and with your suggestions: we have explained more thoroughly in the Methods section since the Abstract has a limit of 300 words.

Strengths and Limitations: Bullet 4 or 5 - I am not sure you can say that the data collected WILL play a role or crucial role in anything. It is not a commonly employed regimen at this time globally so only if the results are positive for the combination therapy can you say it will have impact on clinical practice. It can inform whether dual blockade of the ACE2 receptor is an effective approach to prevent COVID-19 infection but aside from that, you are limited.
We have corrected the Strengths and Limitations Section to match journal format and rewording as requested.

INTRODUCTION: I am not a fan of this introduction as it is written. I think it will take a full re-write to accomplish what the investigators need to do.
Paragraph 1 - We do not need this history lesson. Cut the fat and get to the point in two sentences about why it is important you do this study. The entire intro meanders, is unfocused, and if it was concisely written could be much more impactful.

We appreciate your correction, we have made the change to the text

THE biggest thing the investigators need to convince the readers at this point is - with the vaccines coming in 2021, why would anyone want to prophylactically take this every day? There are compelling reasons (delays in rolling out the vaccine to developing countries, possibilities that the vaccine might not work as well in select populations that were not represented in clinical trials, hospital workers will likely see more superspreaders and the transmission risk could be enhanced, etc, etc).
We appreciate your correction, we have made the change to the text (line 93-101)

The SECOND biggest thing is that the scientific underpinnings are sound. Why do you believe that hydroxychloroquine is going to be effective based on previous RCTs in this space, why do you believe that bromhexine is going to be effective, why do you believe the combination will be better than either drug alone, if they are both effective, why use this study design that will obscure the benefits by not supplying a true placebo group? If you believe that bromhexine is ineffective alone but will be effective at enhancing hydroxychloroquine, you need to show data that leads the reader to believe it.
We appreciate your correction, we have included a placebo group, which will help us evaluate the real effect of both drugs. We add this information in “Intervention section in Methods and Analysis” (line 204-207)

STUDY DESIGN, Lines 47 to 49: The investigators are back to saying it is placebo controlled and they dropped the term simple. They should refer to the trial in the same terms each time throughout the paper and not lose and add terminology.
We appreciate your correction, we have made the change to the text, now we refer to it only as placebo. (line 140).

Table: SARS - SARS is the disease several years ago before MERS. Is that what you are really asking about?
We appreciate your observation. We have made the change in the table.

Inclusion Criteria: Normal ECG - So sinus tachycardia gets people excluded? I would remove this and then focus on ECG findings that exclude people below as you did.

It has been removed as suggested

Exclusion Criteria: "Use of other drugs such as..." is not helpful. Are these drugs excluded because

they are QTc interval prolongers, because they are cardiac medications, or another reason? It is impossible to know what drugs not on that list would lead to patient exclusions based on this description. Why eliminate people with comorbidities if they have the highest risk of negative outcomes should they be infected? If you show it works in people at the lowest risk of having a negative outcome should they be infected, does that mean it will translate into benefits for the highest risk people? We know that ACE2 expression is higher in cardiac patients for a variety of reasons. If you believe the mechanism that you do, why would you exclude these people?

We have amended this section and eliminated people with comorbidities as an exclusion criterion

Sample Size Calculation: Now I see that you are referring to an absolute risk reduction of 16% (from 20% to 4%). This was not clear before and looked like it could have been a relative risk reduction. I am pretty sure based on other data that this will not be achievable but I do understand where you are coming from. If you do show this magnitude of benefit, that would be very impactful except you wouldn't know whether the combination regimen was not benefiting from a negative effect of bromhexine since there is no true placebo control.

Thank you very much for your observation. In order to verify that the prophylactic use of both drugs was efficient, we have included the necessary controls. We have considered having 4 groups, which have been added in the abstract and it is mentioned in Interventions in Methods and Analysis section.

Investigational Product: This is not clearly written or the trial is not what is stated above. If one group is getting hydroxychloroquine tablets and the other is not, that is not blinded. Sure they are both getting syrup in the groups but one is also taking tablets and the other isn't.

Thank you very much for your observation. Groups in studies received either the drug or the placebo in tablet form. Therefore, they will not know which medication it corresponds to. Therefore, we ensure that the study is blind.

Based on other trials that has been conducted, I worry the the RT-PCR positivity for the primary endpoint will make the trial difficult to show a difference. It looks like other prophylactic regimens studied previously found better impact on the combined endpoint of RT-PCR positive or signs and symptoms of COVID-19 infection. I would ask the investigators to also look at this combined endpoint, it would be important to meta-analysts. I believe that the false positive and false negatives with the RT-PCR tests are covering up the potential effects of hydroxychloroquine therapy and the combined endpoint is therefore superior. This may not b true but based on the data I have reviewed, it is a possible hypothesis.

Thank you very much for your observation and suggestions. We have made the change to the text. We will use the quantitative RT-PCR (qRT-PCR) test to define the positivity of a sample.

VERSION 2 – REVIEW

REVIEWER	Dmitry Stepanov Marienkrankenhaus, Anaesthesiology, Intensive Care, Pain Management and Palliative Care
REVIEW RETURNED	15-Jan-2021

GENERAL COMMENTS	Dear authors of the research, Thank you for the major correction of the study protocol for the publication at the BMJ. However, I still have some items to discuss with you. First of all, I would strongly recommend adding an important

	exclusion criterion. The persons who have already got a vaccine against SARS-CoV-2 or intend to get it must be generally excluded, and this aspect must be mentioned in the study description, the best directly in the title. I find the argumentation and concerns about the vaccines that you express in the “Introduction” are rather weak, particularly after the convincing phase 3 trials of several preparations have been recently published and a vaccination campaign is now about to start worldwide. Sure, there is always a part of the population that deliberate reject the vaccination or can´t get it because of contraindications or expected adverse effects, and the vaccines are still wide of the common availability. In this setting, your study will investigate a considerable alternative for non-vaccinated health workers confronting the infection threat. I greatly appreciate that you have changed the design of the study to ensure that all groups – taking hydroxychloroquine, bromhexine and two arts of placebo – are now under consideration. Since this requires doubling of the number of participants, this is a great work that will substantially enhance the value of the trial. I am also glad to find many useful corrections that improve the presentation of the study and make it more transparent to reviewer and readers. However, I still have some questions regarding particular points. 1. Why should patients with common chronic diseases such as hypertension, diabetes and asthma be excluded? whereas such persons make up a large portion of the healthcare staff. Those are the very persons that might get the most benefit from protecting against coronavirus infection by all available means. Do you with the ethics committee consider that such persons are not allowed to enter a placebo-controlled study by this reason? However, this should be a weak argument too, since at least a part of participants would get a potentially useful medication. Whatever the case, the exclusion of many persons with prevalent chronic diseases should be short mentioned in the section “Limitations”. Besides, some of these excluding conditions can be found in the table about “Study variables”: the reason remains unclear, when such patients are not going to be included 2. There is a notice in the “Strengths and limitations” that the both drugs have minimal side effects; I would comment it with a notice “in the doses used in this study” since hydroxychloroquine can cause serious heart toxicity at higher doses 3. Regarding randomization, it would be not unreasonable to avoid labeling of lab samples and medical history information with the date of birth since this could make an unwanted disclosure of the patients´ data, particularly at the single hospital with a relatively small sample size 4. I would hold my own, that the PCR-tests at days 30 and 60 are not able to exclude asymptomatic infections arising between these timepoints. Proceeding from the assumption that participants developing COVID-19 symptoms will be immediately PCR-tested, I assume that clinically relevant infections will still be recognized. However, I do not understand why the medication will be discontinued when participants become symptoms and positive PCR after the day 14 of the treatment (s. “Interventions”). What will occur when a person develop symptoms between day 7 (< 7 days is an exclusion criterion) and day 14? Will this person be considered infected despite of the medication? I strongly recommend describing

	these arrangements clearly in the section “Participant timeline” and further discuss the item in the final manuscript 5. It is still unclear which value and reason has the distinction between the cumulative infection proportion at day 30 (secondary endpoint) and day 60 (primary endpoint) 6. There are still no endpoints regarding clinic states of infected participants are included. This might be a valuable secondary endpoint of the study which could made the results much more useful. I would repeat what has been already mentioned in my first review: There are conceivable situations when a treatment would not prevent a contamination with the novel coronavirus but could protect from the development of symptoms or further clinical deteriorating. Could you collect the data about the incidence of symptomatic COVID-19 in the particular groups and the extent of severity of the disease? 7. The information how often ECGs will be performed routinely should be provided in the section “Participant timeline and intervention”, alongside with a detailed description of health state monitoring of participants to reveal possible adverse effects. Actually, it is mentioned below (weekly), but can be easily overlooked Additionally, there are some grammatical and stylistic inaccuracies that I have to inform of: 1. “In Mexico, up to December 2020, have been produced more than 1 million confirmed cases and ~130,000 deaths, according to WHO data”: I would offer “more than 1 million confirmed cases and ~130,000 deaths have arisen” 2. “It is transmitted through respiratory droplets from infected humans through contact with contaminated fomites and aerosols; on the other hand, asymptomatic patients in close contact can transmit the disease”: I think, it´s reasonable to change this into “…from infected humans AND through contact with contaminated fomites and aerosols; MOREOVER, EVEN asymptomatic PERSONS in close contact…” 3. I would suggest to transfer the paragraph about statistics on health care workers after the description of the medications, so that an entire part about the situation together with the data from the NEJM arises 1. “the use of HCQ and BHH in healthy health personnel exposed IN patients” – it would be correct to say “exposed TO” 2. “with parallel allocation at a 1:1 ratio with placebo, OF low doses of HCQ and BHH, for 60 days…” – should the word “OR” be better instead of “OF”? 3. “Exposition or caring for patients” should be changed into simply “Contacting” or “Exposition to or caring for” 4. “Researcher A will recruit the participants and assess the inclusion criteria according to the serological, electrocardiographic, and biochemical results” – and clinical investigation, too 5. “Informed consent will be obtained only by researcher A. If researcher A is not available, the study administrator may obtain informed consent for participation” – this sentence repeats twice 6. “if possible, by the same staff within which are part of the study” – this seems to be grammatically weird. Probably, “if possible, by the staff involved into the study”? I would recommend you presenting the text of the protocol anew to a native speaker of English to ensure there are no more inaccuracies.

	I hope, these remarks will help the authors to polish up the design and improve the value of the study, as well as to understand possible concerns of readers and reviewers when the trial has been already performed. I am looking forward for further questions and a productive communication.

REVIEWER	Michael White University of Connecticut
REVIEW RETURNED	05-Jan-2021

GENERAL COMMENTS	INTRODUCTION The introduction is too long and not well structured. The first paragraph is an unneeded history lesson. The whole introduction could be reduced by 2/3rds of a page. The last paragraph is how healthcare workers are susceptible which is highly relevant but already described previously. That can be consolidated. The authors suggest that HCQ has been shown to be effective (Page 6) but this is really not the case when the totality of literature is reviewed. I would be concerned about cherry picking data such as is done here, especially since in the section on relevance (Page 4), you say that none of the drugs have been proven to be effective. A piece that may be missing is why you believe this combination would be better than something like HCQ + zinc or BHH + something else. The piece that is missing is whether or not a study like this will still be relevant now that the vaccine is available. I believe strongly the answer is yes because some countries are not receiving the vaccine a rapidly, there is a delay in starting it, some people are not candidates, and some will choose not to be vaccinated. This should be written in to ensure the reader believes the article is worth the time. STUDY DESIGN It looks like this is a study of HCQ alone, BHH alone, the combination, and placebo. On Page 8, the description of the study design does not convey this. There is not enough info to ensure patients would be truly randomly allocated. SAMPLE SIZE I would be surprised if they had sufficient power to show an effect with 280 people in a 4 group comparison if proper statistical analyses were used (see below). STATISTICAL ANALYSES For the four group comparison, they would likely need a statistical test that accounts for 4 groups, like ANOVA with special 2 group comparisons being conducted only if there is a significant difference with the screening test. Now if they said they were doing a 2X2 factorial design whereby people would be randomized to HCQ or placebo and then to BHH or placebo, they could then analyze the data in a different manner but that is not what it looks like they are proposing. This could be in the way it is written up and it could be reasonable but I am not sure based on how it is described presently. ETHICS, FUNDING: No issues.

	OVERALL ASSESSMENT There is a need to streamline some of the writing but to better underscore the value of the project in the contemporary prophylactic world with vaccines. I am not sure, with the way it is written, that the methods are appropriate but this may be an issue with the methods employed themselves or the way it is written. In a few places, it seems like the authors are suggesting that HCQ has been shown, in the totality of the literature, to be effective for the prevention or treatment of HCQ. That is simply not the case at this point and that should be clear in this write up.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2
Dr. Michael White, University of Connecticut
Comments to the Author:
INTRODUCTION
The introduction is too long and not well structured. The first paragraph is an unneeded history lesson. The whole introduction could be reduced by 2/3rds of a page.

Thanks for your recommendation. We did the change in the text

The last paragraph is how healthcare workers are susceptible which is highly relevant but already described previously. That can be consolidated. The authors suggest that HCQ has been shown to be effective (Page 6) but this is really not the case when the totality of literature is reviewed. I would be concerned about cherry picking data such as is done here, especially since in the section on relevance (Page 4), you say that none of the drugs have been proven to be effective.

Thanks for your recommendation. We did the change in the text

A piece that may be missing is why you believe this combination would be better than something like HCQ + zinc or BHH + something else. The piece that is missing is whether or not a study like this will still be relevant now that the vaccine is available. I believe strongly the answer is yes because some countries are not receiving the vaccine a rapidly, there is a delay in starting it, some people are not candidates, and some will choose not to be vaccinated. This should be written in to ensure the reader believes the article is worth the time.

Thank you very much for your suggestion, it would undoubtedly be of great interest to evaluate different combinations such as those mentioned, including evaluating the effect together with Vitamin D, however at this time, we are only interested in evaluatin the protection capacity of the joint administration of HCQ plus BHH versus SARS-CoV-2 based on its pharmacological function. Regarding the vaccine, you have reason, thank you for your recommendation. We did the change in the text

STUDY DESIGN
It looks like this is a study of HCQ alone, BHH alone, the combination, and placebo. On Page 8, the description of the study design does not convey this. There is not enough info to ensure patients would be truly randomly allocated.

We appreciated your observation. We made the changes in the text. On the other hand, the information about how we will ensure that the formation of the study groups is random, is described in "Randomization and treatment allocation" section.

SAMPLE SIZE
I would be surprised if they had sufficient power to show an effect with 280 people in a 4 group comparison if proper statistical analyses were used (see below).

Thank you very much for your comment and suggestion. We are very sorry, and I apologize, but we have decided to have two study groups, HCQ plus BHH vs placebo. This is because at this moment in the hospital we do not have the possibility of having so many arms and for us it is logistically impossible. Therefore, for the moment it is better for us to do a pure parallel study. On the other hand, the application of the vaccine will reduce the number of volunteers and it will be difficult for us to reach the sample that was proposed in the previous version. We have made changes to the text. (line 302-309)

STATISTICAL ANALYSES
For the four group comparison, they would likely need a statistical test that accounts for 4 groups, like ANOVA with special 2 group comparisons being conducted only if there is a significant difference with the screening test. Now if they said they were doing a 2X2 factorial design whereby people would be randomized to HCQ or placebo and then to BHH or placebo, they could then analyze the data in a different manner but that is not what it looks like they are proposing. This could be in the way it is written up and it could be reasonable but I am not sure based on how it is described presently.

Thank you very much for your comment and suggestion. We have changed the sample size as I mentioned in the previous question. We have made the changes to the text. (line 629-632)

ETHICS, FUNDING: No issues.

OVERALL ASSESSMENT
There is a need to streamline some of the writing but to better underscore the value of the project in the contemporary prophylactic world with vaccines. I am not sure, with the way it is written, that the methods are appropriate but this may be an issue with the methods employed themselves or the way it is written. In a few places, it seems like the authors are suggesting that HCQ has been shown, in the totality of the literature, to be effective for the prevention or treatment of HCQ. That is simply not the case at this point and that should be clear in this write up.

Thank you very much for your comment and suggestion. We have made the changes to the text. We add some references in the introduction section.

Reviewer: 1
Mr. Dmitry Stepanov, Marienkrankenhaus
Comments to the Author:
Dear authors of the research,

Thank you for the major correction of the study protocol for the publication at the BMJ.

However, I still have some items to discuss with you.

First of all, I would strongly recommend adding an important exclusion criterion. The persons who have already got a vaccine against SARS-CoV-2 or intend to get it must be generally excluded, and this aspect must be mentioned in the study description, the best directly in the title. I find the argumentation and concerns about the vaccines that you express in the “Introduction” are rather weak, particularly after the convincing phase 3 trials of several preparations have been recently published and a vaccination campaign is now about to start worldwide. Sure, there is always a part of the population that deliberate reject the vaccination or can´t get it because of contraindications or expected adverse effects, and the vaccines are still wide of the common availability. In this setting, your study will investigate a considerable alternative for non-vaccinated health workers confronting the infection threat.

Thank you very much for your observation. We made the change in the text. (line 160-165)

I greatly appreciate that you have changed the design of the study to ensure that all groups – taking hydroxychloroquine, bromhexine and two arts of placebo – are now under consideration. Since this requires doubling of the number of participants, this is a great work that will substantially enhance the value of the trial.

Thank you very much for your comment and you right, we need doubling of the number of participants. For this reason, we are very sorry and apologetic, but we have decided to have only two study groups, HCQ plus BHH vs placebo. This is because at this moment in the hospital we do not have the possibility of having so many arms and for us it is logistically impossible. Therefore, for the moment it is better for us to do a pure parallel study. On the other hand, the application of the vaccine will reduce the number of volunteers and it will be difficult for us to reach the sample that was proposed in the previous version. We have made changes to the text

I am also glad to find many useful corrections that improve the presentation of the study and make it more transparent to reviewer and readers.

However, I still have some questions regarding particular points.

1. Why should patients with common chronic diseases such as hypertension, diabetes and asthma be excluded? whereas such persons make up a large portion of the healthcare staff. Those are the very persons that might get the most benefit from protecting against coronavirus infection by all available means. Do you with the ethics committee consider that such persons are not allowed to enter a placebo-controlled study by this reason? However, this should be a weak argument too, since at least a part of participants would get a potentially useful medication. Whatever the case, the exclusion of many persons with prevalent chronic diseases should be short mentioned in the section “Limitations”. Besides, some of these excluding conditions can be found in the table about “Study variables”: the reason remains unclear, when such patients are not going to be included.

We appreciated your observation. In this case the known adverse effects of hydroxychloroquine prevent us from including the entire population, first we have to determine if low-dose HCQ has the

prophylactic effect and then we will evaluate to include people who are not candidates to receive the vaccine, due to some chronic diseases

2. There is a notice in the “Strengths and limitations” that the both drugs have minimal side effects; I would comment it with a notice “in the doses used in this study” since hydroxychloroquine can cause serious heart toxicity at higher doses

Thanks for your observation and yes, you are all right. We know that the HCQ can cause toxicity at higher doses, so in this case we will used low doses 200 mg per day. We have made changes to the text. (line 169-173)

3. Regarding randomization, it would be not unreasonable to avoid labeling of lab samples and medical history information with the date of birth since this could make an unwanted disclosure of the patients´ data, particularly at the single hospital with a relatively small sample size

We appreciated your observation. We made the change in the text. We will only identify the samples with the participant number and participant's initials. (line 393-394)

4. I would hold my own, that the PCR-tests at days 30 and 60 are not able to exclude asymptomatic infections arising between these timepoints. Proceeding from the assumption that participants developing COVID-19 symptoms will be immediately PCR-tested, I assume that clinically relevant infections will still be recognized. However, I do not understand why the medication will be discontinued when participants become symptoms and positive PCR after the day 14 of the treatment (s. “Interventions”). What will occur when a person develop symptoms between day 7 (< 7 days is an exclusion criterion) and day 14? Will this person be considered infected despite of the medication? I strongly recommend describing these arrangements clearly in the section “Participant timeline” and further discuss the item in the final manuscript.

Thanks for your observation. You have reason, the person who develop symptoms between day 7 and day 14 will be included in the analysis. We have made changes to the text in participant timeline section. (line 442-445)

5. It is still unclear which value and reason has the distinction between the cumulative infection proportion at day 30 (secondary endpoint) and day 60 (primary endpoint)

Thanks for your observation. You have reason, we have decided as the primary endpoint at day 60 after the start of treatment and we decided to follow-up 30 days more and the day 90 will be

secondary endpoint. We have made changes to the text in participant timeline section and in outcomes measure section.

6. There are still no endpoints regarding clinic states of infected participants are included. This might be a valuable secondary endpoint of the study which could made the results much more useful. I would repeat what has been already mentioned in my first review: There are conceivable situations when a treatment would not prevent a contamination with the novel coronavirus but could protect from the development of symptoms or further clinical deteriorating. Could you collect the data about the incidence of symptomatic COVID-19 in the particular groups and the extent of severity of the disease?

Thanks for your observation. Yes, you are a right. We will be analyses the incidence of symptomatic COVID-19, we are going to evaluate different parameters as oxygen use, admission to the ICU, presence of pneumonia, death and time from hospitalization to recovery in days. (line 497-500)

7. The information how often ECGs will be performed routinely should be provided in the section "Participant timeline and intervention", alongside with a detailed description of health state monitoring of participants to reveal possible adverse effects. Actually, it is mentioned below (weekly), but can be easily overlooked

Thanks for your observation. We have made changes to the text. (line 414)

Additionally, there are some grammatical and stylistic inaccuracies that I have to inform of:
1. "In Mexico, up to December 2020, have been produced more than 1 million confirmed cases and ~130,000 deaths, according to WHO data": I would offer "more than 1 million confirmed cases and ~130,000 deaths have arisen"

Thank you very much for your observation. We made the change in the text.

2. "It is transmitted through respiratory droplets from infected humans through contact with contaminated fomites and aerosols; on the other hand, asymptomatic patients in close contact can transmit the disease": I think, it´s reasonable to change this into "…from infected humans AND through contact with contaminated fomites and aerosols; MOREOVER, EVEN asymptomatic PERSONS in close contact…"

Thank you very much for your observation. We made the change in the text.

3. I would suggest to transfer the paragraph about statistics on health care workers after the description of the medications, so that an entire part about the situation together with the data from the NEJM arises

Thank you very much for your observation. We made the change in the text.

1. “the use of HCQ and BHH in healthy health personnel exposed IN patients” – it would be correct to say “exposed TO”

Thank you very much for your correction. We made the change in the text.

2. “with parallel allocation at a 1:1 ratio with placebo, OF low doses of HCQ and BHH, for 60 days…” – should the word “OR” be better instead of “OF”?

Thank you very much for your correction. We made the change in the text.

3. “Exposition or caring for patients” should be changed into simply “Contacting” or “Exposition to or caring for”

Thank you for your correction. We made the change in the text.

4. “Researcher A will recruit the participants and assess the inclusion criteria according to the serological, electrocardiographic, and biochemical results” – and clinical investigation, too

Thank you for your correction. We made the change in the text.

5. “Informed consent will be obtained only by researcher A. If researcher A is not available, the study administrator may obtain informed consent for participation” – this sentence repeats twice

Thank you for your correction. We review this, and we didn´t find it

6. “if possible, by the same staff within which are part of the study” – this seems to be grammatically weird. Probably, “if possible, by the staff involved into the study”?

Thank you for your correction. We made the change in the text.

I would recommend you presenting the text of the protocol anew to a native speaker of English to ensure there are no more inaccuracies.

Thank you for your suggestion. We review and we made the change in the text.

I hope, these remarks will help the authors to polish up the design and improve the value of the study, as well as to understand possible concerns of readers and reviewers when the trial has been already performed.

I am looking forward for further questions and a productive communication.

VERSION 3 – REVIEW

REVIEWER	Dmitry Stepanov Marienkrankenhaus, Anaesthesiology, Intensive Care, Pain Management and Palliative Care
REVIEW RETURNED	05-Mar-2021

GENERAL COMMENTS	Dear authors of the research, Thank you for a major correction of the study protocol for the publication at the BMJ. I would let the fact pass, that the four groups with hydroxychloroquine and bromhexine are disappeared, and there is a new study in that way, but you may have had reasons for it. However, I have still to discuss some points. 1. The sample size calculation in the abstract does not agree with the size in the main article (140 vs. 214 participants) 2. The fact that hydroxychloroquine can cause heart arrhythmias is, strictly speaking, not a limitation of your study, but just a fact which must be discussed further, concerning adverse effects and measurements for the monitoring the participants 3. I can´t support the assertion, that “early trials have shown minimal immune protection” through vaccination. Alas, there are no references confirming this statement. However, there is currently an evidence controverting it. The sentence “Therefore, it is not known if the vaccines that are now in the phase end of the clinical study and those that are administered will work with the same efficacy for the SARS-CoV-2 virus that gave rise to Covid-19” is not clear at all. I recommend performing a correction 4. When the results about the experimentally measured maximal concentrations of hydroxychloroquine are discussed, there is no explanation how you would interpret these results, especially bearing on the SARS-CoV-2. The sentence seems to have been included just as an additional information load providing no substantiation of the item. There is also no communication with a further these that hydroxychloroquine provides its antiviral effect in infected patients only in high doses. An attempt to use low doses could also be justified through the combination with bromhexine since both drugs could potentiate each other; however, the basis should be clearly settled in definite terms 5. The exclusion of many persons with prevalent chronic diseases must be mentioned in the section “Limitations” 6. The exclusion of vaccinated persons is an essential item, and I´m glad to find that you have taken account of it 7. There are two sentences in the section “Intervention” that probably contain mistakes: do you really mean that treatment will not be discontinued when a participant develops severe or intolerable adverse effects related to the drugs? And a poor adherence of a participant should also become a reason to eliminate the patent from the study.

	8. It´s not clear which test for IgG/IgM antibodies detection you will use: in the section “Primary endpoint” an Elecsys test system from Roche is mentioned, whereas further in the text a FDA-approved Cellex Rapid Test is described. An information about the sensitivity and specificity of the test should be also provided and supplied with a reference to a reliable source 9. I welcome the decision to record and further evaluate the information about the health state of the infected personnel and not to exclude them from the study. 10. Regarding arrhythmias as a possible life-threatening adverse effect of hydroxychloroquine, I would suggest considering whether each participant should get an ECG not only at days 30, 60 and 90, but every week. This must not necessarily include a thoroughly physical examination, but at the same time would provide an additional safety for all participants. A “weekly assessment of adverse events” is anyway mentioned below, but this doesn´t agree with the part “Participant timeline and interventions” 11. “The statistical analysis will be carried out by evaluation the difference between the DIFFERENT groups of HCQ plus BHH versus placebos”; but there are only one intervention group and one placebo group now 12. I would kindly ask for a better formulating of the statistical analysis. For example, the sentence “To adjust the primary objective to possible confounders such as age, gender, service in which the participant works, body mass index etc.” seems to be either incomplete or commit double meaning in conjunction with the adjacent clauses. 13. I would generally call you to be careful and logical formulating many particulars since this would be always a reason for misunderstanding at reviewers and readers and hence a reason to decline the text again and again. You should also better argue some assertions with actual references. I´m looking forward for further questions and a productive discussion.

REVIEWER	Michael White University of Connecticut
REVIEW RETURNED	16-Feb-2021

GENERAL COMMENTS	There have been many enhancements in this paper since the first time I have seen it. I like that the groups are now clear and that there is a rationale for using it even with the onset of vaccinations. That paragraph can be made more specific talking about new variants that may render the vaccines less effective and updating the vaccine and rolling it out throughout the globe will have a lag time. So it is approaching a version that is clearer as to what is going to occur and why and is more defensible in that regard. I would like to see in the limitations area more focus on the lack of demonstrated efficacy with HCQ for prophylaxis to date in the available studies but that you believe that bromhexine is the secret ingredient that will unleash HCQ's efficacy. I see in line 70 that you are now hoping to study 140 people but in line 270 you still calculate that you need 214 people to have adequate power. Which one is it and why the discrepancy? If you need 214 but will only anticipate enrolling 140, that would be an issue.

	From an ethical perspective, you are excluding people who HAVE been vaccinated but does this mean they are also excluded from being vaccinated over the days they are actually in the trial? This is ok if that is what it is (and the healthcare workers agree) but it should be specified. With case counts dropping and the number of people being vaccinated growing, will you have a sufficient sample size to finish this trial (even at 140 people)? There have been a number of trials that have been stopped when the large case wave of COVID passed them by and it became impossible to recruit. If recruitment is slower than anticipated, is there a plan to expand the eligible pool? Finally, it seemed in version 1 that the trial was underway, not just being planned, and the changes since that time have been extensive. I wonder what is happening with those already enrolled when things have changed?

VERSION 3 – AUTHOR RESPONSE

Reviewer: 2
Dr. Michael White, University of Connecticut
Comments to the Author:
There have been many enhancements in this paper since the first time I have seen it. I like that the groups are now clear and that there is a rationale for using it even with the onset of vaccinations. That paragraph can be made more specific talking about new variants that may render the vaccines less effective and updating the vaccine and rolling it out throughout the globe will have a lag time. So it is approaching a version that is clearer as to what is going to occur and why and is more defensible in that regard.

Thanks for your comment, we did the change in the text… (123-125)

I would like to see in the limitations area more focus on the lack of demonstrated efficacy with HCQ for prophylaxis to date in the available studies but that you believe that bromhexine is the secret ingredient that will unleash HCQ's efficacy.

Thanks for your comment, we did the change in the text… (98-100)

I see in line 70 that you are now hoping to study 140 people but in line 270 you still calculate that you need 214 people to have adequate power. Which one is it and why the discrepancy? If you need 214 but will only anticipate enrolling 140, that would be an issue.

Thanks for your observation. We have corrected the error in the text. We need 214 volunteers, this number of volunteers will allow us to find a difference of 16% between groups with a power of 90% and an attrition of 20%.

From an ethical perspective, you are excluding people who HAVE been vaccinated but does this mean they are also excluded from being vaccinated over the days they are actually in the trial? This is ok if that is what it is (and the healthcare workers agree) but it should be specified.

Thank you very much for your observation. The volunteer staff will sign an informed consent in which it is clarified that they will not be able to be vaccinated during the 90 days that the study will last.

With case counts dropping and the number of people being vaccinated growing, will you have a sufficient sample size to finish this trial (even at 140 people)? There have been a number of trials that have been stopped when the large case wave of COVID passed them by and it became impossible to recruit. If recruitment is slower than anticipated, is there a plan to expand the eligible pool?

Thanks for your observation. Without a doubt, it is a great challenge to have the number of volunteers with the characteristics that we are including in the study, however, we consider that it is feasible to have this sample size. If there is an alternative plan, which is to include the general population that meets the inclusion criteria. This is feasible because the population that we are including in the study has not yet been vaccinated due to the lack of vaccines. To date, the most vulnerable population has been vaccinated, the population over 60 years of age (population that is not included in our study).

Finally, it seemed in version 1 that the trial was underway, not just being planned, and the changes since that time have been extensive. I wonder what is happening with those already enrolled when things have changed?

Thanks for your observation. However, the changes made to this protocol do not affect recruitment. On the other hand, the volunteer personnel have not yet been assigned to the study group.

Reviewer: 1
Mr. Dmitry Stepanov, Marienkrankenhaus
Comments to the Author:
Dear authors of the research,

Thank you for a major correction of the study protocol for the publication at the BMJ.

I would let the fact pass, that the four groups with hydroxychloroquine and bromhexine are disappeared, and there is a new study in that way, but you may have had reasons for it.

However, I have still to discuss some points.

1. The sample size calculation in the abstract does not agree with the size in the main article (140 vs. 214 participants)

Thanks for your observation. We have corrected the error in the text. We need 214 volunteers, this number of volunteers will allow us to find a difference of 16% between groups with a power of 90% and an attrition of 20%.

2. The fact that hydroxychloroquine can cause heart arrhythmias is, strictly speaking, not a limitation of your study, but just a fact which must be discussed further, concerning adverse effects and measurements for the monitoring the participants

Thanks for your comment. The volunteers will be monitored by electrocardiogram weekly. Which can tell us if there is a problem with the drug administered. We have made the clarification in the text in the section of Participant timeline and intervention (line 368)

3. I can´t support the assertion, that “early trials have shown minimal immune protection” through vaccination. Alas, there are no references confirming this statement. However, there is currently an evidence controverting it. The sentence “Therefore, it is not known if the vaccines that are now in the phase end of the clinical study and those that are administered will work with the same efficacy for the SARS-CoV-2 virus that gave rise to Covid-19” is not clear at all. I recommend performing a correction

Thanks for your comment, we did the change in the text… (123-125)

4. When the results about the experimentally measured maximal concentrations of hydroxychloroquine are discussed, there is no explanation how you would interpret these results, especially bearing on the SARS-CoV-2. The sentence seems to have been included just as an additional information load providing no substantiation of the item. There is also no communication with a further these that hydroxychloroquine provides its antiviral effect in infected patients only in high doses. An attempt to use low doses could also be justified through the combination with bromhexine since both drugs could potentiate each other; however, the basis should be clearly settled in definite terms

Thanks for your comment, we did the change in the text… (144-152)

5. The exclusion of many persons with prevalent chronic diseases must be mentioned in the section “Limitations”

Thanks for your comment, however, the population with chronic disease was already included in the limitations section

6. The exclusion of vaccinated persons is an essential item, and I´m glad to find that you have taken account of it

Thank you for your comment

7. There are two sentences in the section “Intervention” that probably contain mistakes: do you really mean that treatment will not be discontinued when a participant develops severe or intolerable adverse effects related to the drugs? And a poor adherence of a participant should also become a reason to eliminate the patent from the study.

Thanks for your observation. We did the changes in the text. (line 298)

8. It´s not clear which test for IgG/IgM antibodies detection you will use: in the section “Primary endpoint” an Elecsys test system from Roche is mentioned, whereas further in the text a FDA-approved Cellex Rapid Test is described. An information about the sensitivity and specificity of the test should be also provided and supplied with a reference to a reliable source

Thanks for your observation, this was a mistake. We have been correct it and we did the change in the text. (428-430)

9. I welcome the decision to record and further evaluate the information about the health state of the infected personnel and not to exclude them from the study.

Thanks for your observation.

10. Regarding arrhythmias as a possible life-threatening adverse effect of hydroxychloroquine, I would suggest considering whether each participant should get an ECG not only at days 30, 60 and 90, but every week. This must not necessarily include a thoroughly physical examination, but at the same time would provide an additional safety for all participants. A “weekly assessment of adverse events” is anyway mentioned below, but this doesn´t agree with the part “Participant timeline and interventions”

Thanks for your observation, we did the change in the text

11. “The statistical analysis will be carried out by evaluation the difference between the DIFFERENT groups of HCQ plus BHH versus placebos”; but there are only one intervention group and one placebo group now

Thanks for your observation. The answer is yes, the statistical analysis will be done by comparing the group that received both drugs and the group that received the placebo. The objective is to know if the administration of both drugs reduces the SARS-CoV-2 infection. In case there is infection during the study, either in the control group or in the intervention group, the follow-up of the volunteers will give us information on the severity of the infection in the intervention group compared to the placebo group.

12. I would kindly ask for a better formulating of the statistical analysis. For example, the sentence “To adjust the primary objective to possible confounders such as age, gender, service in which the participant works, body mass index etc.” seems to be either incomplete or commit double meaning in conjunction with the adjacent clauses.

Thanks for your observation, we did the change in the text (line 595-596)

13. I would generally call you to be careful and logical formulating many particulars since this would be always a reason for misunderstanding at reviewers and readers and hence a reason to decline the text again and again. You should also better argue some assertions with actual references.

We greatly appreciate your comment and suggestion.

I´m looking forward for further questions and a productive discussion.

VERSION 4 – REVIEW

REVIEWER	Dmitry Stepanov Marienkrankenhaus, Anaesthesiology, Intensive Care, Pain Management and Palliative Care
REVIEW RETURNED	25-Apr-2021

GENERAL COMMENTS	Dear authors of the research, Thank you for a new correction of the study protocol for the publication at the BMJ. I appreciate that the most censorious remarks have been taken into account and the trial looks much better now. I would still recommend more explanation of exclusion criteria like “persons who are not candidates to receive a vaccine due to chronic diseases”; the exclusion of all persons with wide prevalent chronic diseases remains a loss of the trial that inspires my regret. Since these remarks had been expressed in every review and no changes have been made from then on, it seems to be a strong decision of the researchers. The study limitations are still not well structured and should be

	elaborated further in detail. However, this can be made in the final version of the manuscript, after obtaining and processing of the results. Besides, every time I performed the review, I found several passages that consisted grammatical errors or unfortunate misprints. A typical example could be found in the last revision: “HCQ has been reported to lock the infection … through inhibition of ACE glycosylation receptor”. Obviously, it was meant “glycosylation of ACE receptor”. Alas, such errors are spread over the text. I appeal to you anew to be careful before you send your texts to the reviewer. The best of all would be to let somebody with a good expertise in English read the text thoroughly and make corrections. However, I see no reasons more to decline the publication of your study protocol in the present form. I wish you every success in the performing of the research and am looking forward to the results.

REVIEWER	Michael White University of Connecticut
REVIEW RETURNED	06-Apr-2021

GENERAL COMMENTS	After several iterations, this version is much improved. Line 88-91 - This sentence, as written, is confusing. I would suggest "Bromhexine has minimal side effects and is commercially available worldwide so, if positive findings are found, could be applied in a timely fashion in different regions of the world." Line 92, 94, 98 - What are these extra lines for? Lines 99-102 - This last bullet is presumptuous as written. Say "hydroxychloroquine has not been shown to be effective in monotherapy or with azithromycin but the adjunctive impact of BHH could be an effective combination. Line 124 - Replace "...and the protection is only temporary" for "...and the protection may wane over time so periodic vaccination or booster shots for new variants may be needed." Line 128 - Add space after mRNA. Line 147 - The fact that lower doses does not cause retinopathy does NOT mean it may be effective or that it is SAFE. You need to be more exacting with your language given the nature of the literature as it exists, not as you want it to be. Line 237 - Change to "positive" Line 358 - Summoned is not the right word. "scheduled" is better. Line 361 - Patients will come in to get an ECG every week? It is ok, just makes me less confident in patients ability to go in and have all of these things done. Line 420, 421 - When the test was changed, the sentence retained extra words ot no longer needed. Please re-write. Line 446 - The 's' you added was added in the wrong place. Line 473 - Diet per week does make sense - someone will just tell you daily if they ate 3, 4, or 5 meals or if they avoided shellfish? Line 454-457 - What are these open spaces for? Line 493 - Muscle enzymes - What are these, is it CK? CK-mm?

VERSION 4 – AUTHOR RESPONSE

Reviewer: 2

Dr. Michael White, University of Connecticut

Comments to the Author:

After several iterations, this version is much improved.

Line 88-91 - This sentence, as written, is confusing. I would suggest "Bromhexine has minimal side effects and is commercially available worldwide so, if positive findings are found, could be applied in a timely fashion in different regions of the world."

Thank you for your observation; we have changed the sentence “Bromhexine has minimal side effects and is commercially available worldwide so positive results could be applied in a timely fashion in different regions”.

Line 92, 94, 98 - What are these extra lines for?

Thank you for your observation; we corrected this.

Lines 99-102 - This last bullet is presumptuous as written. Say "hydroxychloroquine has not been shown to be effective in monotherapy or with azithromycin but the adjunctive impact of BHH could be an effective combination.

Thank you for your observation; we have changed the sentence to “Hydroxychloroquine has not been shown to be effective in monotherapy or with azithromycin, but adjunctive BHH could be an effective combination to inhibit SARS-Cov-2 infection”.

Line 124 - Replace "...and the protection is only temporary" for "...and the protection may wane over time so periodic vaccination or booster shots for new variants may be needed."

Thank you for your observation; we have changed the sentence as suggested.

Line 128 - Add space after mRNA.

Thank you for your observation; we corrected this.

Line 147 - The fact that lower doses does not cause retinopathy does NOT mean it may be effective or that it is SAFE. You need to be more exacting with your language given the nature of the literature as it exists, not as you want it to be.

Thank you for your observation; we have changed the sentence “The above indicates that the use of HCQ at low doses to avoid SARS-CoV-2 infection, has a low possibility of being toxic and could be used as a prophylactic treatment”.

Line 237 - Change to "positive"

Thank you for your observation; we corrected this.

Line 358 - Summoned is not the right word. "scheduled" is better.

Thank you for your observation; we corrected this.

Line 361 - Patients will come in to get an ECG every week? It is ok, just makes me less confident in patients ability to go in and have all of these things done.

Thank you for your observation; ECG will be the only study performed weekly, with blood work performed at 7, 30, 60 and 90 days of treatment.

Line 420, 421 - When the test was changed, the sentence retained extra words ot no longer needed. Please re-write.

Thank you for your observation; we corrected this.

Line 446 - The 's' you added was added in the wrong place.

Thank you for your observation; we corrected this.

Line 473 - Diet per week does make sense - someone will just tell you daily if they ate 3, 4, or 5 meals or if they avoided shellfish?

Thanks for your observation. It will only be an interrogation for the clinical history, to know approximately how many meals a day the health personnel eat.

Line 454-457 - What are these open spaces for?

Thank you for your observation; we corrected this.

Line 493 - Muscle enzymes - What are these, is it CK? CK-mm?

Thanks for your observation. We did change in the text.

Reviewer: 1

Mr. Dmitry Stepanov, Marienkrankenhaus

Comments to the Author:

Dear authors of the research,

Thank you for a new correction of the study protocol for the publication at the BMJ.

I appreciate that the most censorious remarks have been taken into account and the trial looks much better now.

I would still recommend more explanation of exclusion criteria like “persons who are not candidates to receive a vaccine due to chronic diseases”; the exclusion of all persons with wide prevalent chronic diseases remains a loss of the trial that inspires my regret. Since these remarks had been expressed in every review and no changes have been made from then on, it seems to be a strong decision of the researchers.

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Besides, every time I performed the review, I found several passages that consisted grammatical errors or unfortunate misprints. A typical example could be found in the last revision: “HCQ has been reported to lock the infection … through inhibition of ACE glycosylation receptor”. Obviously, it was meant “glycosylation of ACE receptor”. Alas, such errors are spread over the text. I appeal to you anew to be careful before you send your texts to the reviewer. The best of all would be to let somebody with a good expertise in English read the text thoroughly and make corrections.

Thank you for your observation; we corrected this.

However, I see no reasons more to decline the publication of your study protocol in the present form. I wish you every success in the performing of the research and am looking forward to the results.