PEER REVIEW HISTORY

This paper was submitted to a another journal from BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

(This paper received four reviews from its previous journal but only three reviewers agreed to published their review.)

ARTICLE DETAILS

TITLE (PROVISIONAL)	CHARACTERISTICS OF REGISTERED CLINICAL TRIALS ASSESSING TREATMENTS FOR COVID-19
AUTHORS	Mehta, Hemalkumar; Ehrhardt, Stephan; Moore, Thomas; Segal, Jodi; Alexander, G Caleb

VERSION 1 – REVIEW

REVIEWER	Baiges, Juan-Carlos Patient
REVIEW RETURNED	15-Apr-2020

GENERAL COMMENTS	Review for Manuscript ID BMJ-2020-056804 REGISTERED CLINICAL TRIALS ASSESSING TREATMENTS FOR COVID-19 • Are the questions the paper addresses relevant and important to patients and/or carers? Yes, from the point of view of patients / carers, it is very relevant. At this point of global alarm and taking into account the lack of knowledge by the medical-scientific community of effective treatments and of the intrinsic mechanisms of action of the virus, a first review of all the efforts to find an effective therapy is very valuable. Although this review is adequate in the current circumstances, a subsequent review will be necessary since, as the authors state, in some cases the design of clinical trials is not the most appropriate. • Are there topics or issues that are missing, or need to be highlighted more? The approach is adequate and the topics studied are sufficient. Although the information obtained would probably be redundant, the EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/ctr-search/search?query=covid-19) should be included in the clinical trials information sources. • Is the treatment or intervention suggested or guidance given something which patients/carers can readily take up? or does it present challenges?

	I believe that the review and analysis of the information is appropriate, and shows the logical challenges facing the medical community in an emergency situation and in front of such a new threat. • Are the outcomes described/measured in the study important to patients/carers? Are there others that should have been considered? Yes, they are important, it shows the dynamism of the scientific community in the face of a global alert. • Do you have any suggestions that might help the author(s) strengthen their paper and make it more useful for doctors to share and discuss with patients/ carers? Although it is not the intention of this review it would be interesting to introduce some comments on ethical considerations. • Do you think the level of patient/carer involvement in the study could have been improved? If there was none do you have ideas on how they might have done so? N/A

REVIEWER	Laidlaw, Lynn Patient reviewer
REVIEW RETURNED	21-Apr-2020

GENERAL COMMENTS	I enjoyed reading this paper which I have reviewed purely from a patient and member of the public's perspective. It was well written, understandable, informative and exceptionally timely given the current pandemic situation. I appreciated the amount of work the authors undertook in a short period of time to provide this overview of registered clinical trials assessing treatment for COVID 19. The question addressed is very relevant to patents and carers, there has never been so much interest in participation in clinical trials or research. The conclusion that " many trials lack features to optimize their scientific value " needs to be disseminated, enabling people to make an informed decision about whether to participate. It was interesting that the authors decided to look at trial intervention, sponsorship, critical design elements and specified outcomes. I would have liked to have seen information about whether any of the trials assessed had any Patient and Public Involvement or Quality of Life as an outcome measure. It was concerning that 42.3% of the trials studied had surrogate endpoints or biomarkers, the question for me is how do these relate to a persons experience of COVID 19, are we measuring what is perceived as measurable rather than what is meaningful which as the authors point out is " improved chances of recovery from COVID 19 " The flaw in the paper for me is the statement " It was not appropriate or possible to involve patients or the public in the design, conduct, reporting or dissemination of our research ". The authors offer no rationale or explanation for this statement which is confusing given that they point out they " provide timely and globally important information for researchers, policy makers and the general public ". How can you provide timely and important information relevant to a group that you have chosen to

	exclude and therefore have limited understanding of what is important to them? Its perplexing especially with regard to dissemination, drugs such as hydroxychloroquine have been widely touted as " cures " for COVID 19 on very little evidence, people have come to harm as a result. How can patients and the public make informed decisions if reviews such as these don't address issues of relevance to them and disseminate their findings in appropriate language? This was a disappointing feature in an otherwise great paper, the conclusion that we require global coordination and increased funding of high quality research is sound.

REVIEWER	Marušić, Ana University of Split School of Medicine, Department of Research in Biomedicine and Health
REVIEW RETURNED	26-Apr-2020

GENERAL COMMENTS	This is an interesting and timely study of the characteristics of trials testing treatments for COVID-19. It is clearly written and methodologically very rigorously executed, including search of all publicly available trial registries. The results are important for better understanding of what the future holds for the treatment options in the midst of a pandemic. I do not have major comments but have two minor comments that need to be resolved: 1. The title and the abstract state that the objective of the study is to analyze trials assessing treatments for COVID-19 but then the results section in the Abstract and the Methods section in the body of the manuscript state that the authors looked at trials testing drugs and plasma and that they excluded all other treatments. It is not clear how many trials were excluded - this information is not provided in the manuscript. The rationale for excluding treatments must be better justified in the Methods section, and the title and abstract should be revised to make clear that drug and plasma trials were studied. 2. In Table 2, one of the trial registry sources has ICTRP listed (with 2 registered trial).ICRTP is not a registry, but a registry platform for trial registries. Did the authors perhaps mean IRCT (Iranian Registry of Clinical Trials) or ISRCTN (a registry c/o BioMed Central)?

VERSION 1 – AUTHOR RESPONSE

Reviewer #2

1. Are the questions the paper addresses relevant and important to patients and/or carers? Yes, from the point of view of patients / carers, it is very relevant. At this point of global alarm and taking into account the lack of knowledge by the medical-scientific community of effective treatments and of the intrinsic mechanisms of action of the virus, a first review of all the efforts to find an effective therapy is very valuable. Although this review is adequate in the current circumstances, a subsequent review will be necessary since, as the authors state, in some cases the design of clinical trials is not the most appropriate.

   We appreciate these thoughtful comments.

2. Are there topics or issues that are missing, or need to be highlighted more? The approach is adequate and the topics studied are sufficient. Although the information obtained would probably be redundant, the EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/ctr-search/search?query=covid-19) should be included in the clinical trials information sources.

   We appreciate this point and clarify that in fact we included the EU Clinical Trials Register as one of our sources (line 130, eFigure 1).

3. Is the treatment or intervention suggested or guidance given something which patients/carers can readily take up? or does it present challenges? I believe that the review and analysis of the information is appropriate, and shows the logical challenges facing the medical community in an emergency situation and in front of such a new threat.

   Thank you

4. Are the outcomes described/measured in the study important to patients/carers? Are there others that should have been considered? Yes, they are important, it shows the dynamism of the scientific community in the face of a global alert.

   Thank you

5. Do you have any suggestions that might help the author(s) strengthen their paper and make it more useful for doctors to share and discuss with patients/ carers? Although it is not the intention of this review it would be interesting to introduce some comments on ethical considerations.

   We appreciate this point though we agree as well that such considerations are beyond the scope of our report.

6. Do you think the level of patient/carer involvement in the study could have been improved? If there was none do you have ideas on how they might have done so?

   Not applicable

Reviewer #3

1. I enjoyed reading this paper which I have reviewed purely from a patient and member of the public's perspective. It was well written, understandable, informative and exceptionally timely given the current pandemic situation. I appreciated the amount of work the authors undertook in a short period of time to provide this overview of registered clinical trials assessing treatment for COVID 19.
   The question addressed is very relevant to patents and carers, there has never been so much interest in participation in clinical trials or research. The conclusion that " many trials lack features to optimize their scientific value " needs to be disseminated, enabling people to make an informed decision about whether to participate.

   Thank you for these supportive words. We agree!

2. It was interesting that the authors decided to look at trial intervention, sponsorship, critical design elements and specified outcomes. I would have liked to have seen information about whether any of the trials assessed had any Patient and Public Involvement or Quality of Life as an outcome measure. It was concerning that 42.3% of the trials studied had surrogate endpoints or biomarkers, the question for me is how do these relate to a persons experience of COVID 19, are we measuring what is perceived as measurable rather than what is meaningful which as the authors point out is " improved chances of recovery from COVID 19 "

Interestingly, we did not identify any trials that assessed "Patient and Public Involvement" or "Quality of Life." We have expanded our Results (lines 246) and Discussion (line 292) to note this important point.

3. The flaw in the paper for me is the statement " It was not appropriate or possible to involve patients or the public in the design, conduct, reporting or dissemination of our research ". The authors offer no rationale or explanation for this statement which is confusing given that they point out they " provide timely and globally important information for researchers, policy makers and the general public ". How can you provide timely and important information relevant to a group that you have chosen to exclude and therefore have limited understanding of what is important to them? Its perplexing especially with regard to dissemination, drugs such as hydroxychloroquine have been widely touted as " cures " for COVID 19 on very little evidence, people have come to harm as a result. How can patients and the public make informed decisions if reviews such as these don't address issues of relevance to them and disseminate their findings in appropriate language? This was a disappointing feature in an otherwise great paper, the conclusion that we require global coordination and increased funding of high quality research is sound.

   We appreciate this perspective and did not mean to understate the importance of patient-focused drug development, including for therapeutics to address COVID-19. However, we did not directly involve patients, whether recovering from COVID-19 or otherwise, in the conduct of our study. We have modified our section on "Patient and Public Involvement" to read:

   > *"While we did not directly involve patients in the design or conduct of our investigation, our analyses were motivated by a belief that it is important for patients, and the general public, to have accessible, high-quality information regarding the structure and outcomes of clinical trials assessing therapeutics targeting COVID-19." (lines 218-222)*

Reviewer #4

1. This is an interesting and timely study of the characteristics of trials testing treatments for COVID-19. It is clearly written and methodologically very rigorously executed, including search of all publicly available trial registries. The results are important for better understanding of what the future holds for the treatment options in the midst of a pandemic.

   Thank you for these kind words.

2. I do not have major comments but have two minor comments that need to be resolved. The title and the abstract state that the objective of the study is to analyze trials assessing treatments for COVID-19 but then the results section in the Abstract and the Methods section in the body of the manuscript state that the authors looked at trials testing drugs and plasma and that they excluded all other treatments. It is not clear how many trials were excluded - this information is not provided in the manuscript. The rationale for excluding treatments must be better justified in the Methods section, and the title and abstract should be revised to make clear that drug and plasma trials were studied.

   We now clarify in the abstract objective (line 67) and methods (line 70) that we studies trials on drugs or plasma. It reads as: "trials assessing drugs or plasma treatments for COVID-19" and "Relevant trial entries of drugs or plasma were downloaded."

   We now provide rationale in methods (line 157), It reads as: "Because study focus was on evaluating pharmacological or plasma treatments, we excluded trials of stem cell transplants, devices, diagnostic tests, traditional Chinese medicines/herbal medicine, rehabilitation, dietary supplements and psychological interventions."

3. In Table 2, one of the trial registry sources has ICTRP listed (with 2 registered trial).ICRTP is not a registry, but a registry platform for trial registries. Did the authors perhaps mean IRCT (Iranian

Registry of Clinical Trials) or ISRCTN (a registry c/o BioMed Central)?

We appreciate this close read and have corrected this to read ISRCTN (Table 2).