PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The use of connected digital products in clinical research following the COVID-19 pandemic: a comprehensive analysis of clinical trials
AUTHORS	Marra, Caroline; Gordon, William; Stern, Ariel

VERSION 1 – REVIEW

REVIEWER	Silva, Cícera Federal University of Campina Grande Centre of Teacher Education
REVIEW RETURNED	27-Jan-2021

GENERAL COMMENTS	I consider the manuscript relevant to the current clinical research scenario in the challenging context of the COVID-19 pandemic and with important reflections on the use of Connected digital products (CDPs) today and in the future. The article was well designed and written, however I believe that a revision is important for its improvement. The following are recommendations for the manuscript: - In the introduction, I believe that it would be interesting to mention the tendency to approach studies that used CDPs before the pandemic, since there was a considerable increase in them. - The research question needs to be clearly present in the introduction. - In table 1, in the item “Fitbit, videoconferencing”, you must add in the “Trial Type” field if it is “COVID” or “non-COVID”, as you did with the others. - The main details about the search on ClinicalTrials.gov, which are detailed in the supplementary materials, could be briefly described in the Methods. - I suggest adding a clearer description of the statistics performed in the Methods. With these revisions made, I consider the manuscript acceptable for publication in this journal.

REVIEWER	Das, Payal ICMR, Epidemiology and Communicable Diseases
REVIEW RETURNED	05-Feb-2021

GENERAL COMMENTS	Medical infrastructures in afflicted countries are under intense pressures due to the current loads of critical COVID-19 patients. In addition to risks from exposure to COVID-19 patients, there are risks of infection for medical staff from hospital environments, from infectious co-workers, due to rationing of personal protective

	equipment and from extended times in ICUs. Thus, it is timely to consider adoption and expansion of virtualised medical treatment approaches such as telemedicine to reduce the burden on hospitals and allow safer working environment for healthcare providers. I appreciate the work done by the authors. However, the submitted manuscript has neither defined the objectives properly nor the outcomes. I don't think the manuscript has achieved the required priority. This is not the need of the hour. The paper should be completely revised and some more work/information on adoption of telemedicine/telehealth in country/countries should be included which is actually important during this time.

REVIEWER	Byravan, Swetha Leicester Royal Infirmary, Rheumatology
REVIEW RETURNED	06-Feb-2021

GENERAL COMMENTS	Overall an interesting and well written article that is relevant to the current pandemic. The methods and results are well described, and the figures provide good illustration of data. But I feel the discussion could do with more work to talk around the results and to understand why there was not a significant increase in CPD use overall. What might stop trial groups from using it? There is an opportunity in the discussion to provide more context to the article. Please see the comments below regarding this. Comments: 1. The trials that were started prior to the pandemic, is that included in the figure of 12,863? If so, it would be interesting to know the proportion of trials which started after the pandemic which I am presuming is 1405; how many of these used CPDs? Was this proportion higher than pre-pandemic? 2. The acronym FDA needs to be expanded when first using the term. 3. What information can and cannot be collected by CPD- can some examples be included in the introduction? 4. I feel the discussion could be expanded to explore why the use of CDPs did not increase significantly post-pandemic and incorporate more perspectives, what are the obstructions to this: - Does the type of data that needs collecting by various trials preclude the use of CDPs? Could their data have been collected via CDP for all incorporated trials? - Is it due to pre-conceived ideas/attitudes by trial groups towards CDPs? - FDA is applicable for US licensing of drugs only and therefore for trials that are not US based and conducted in other countries they will have their own drug regulatory body. E.g., MHRA in the UK. Therefore, the new FDA guidance may not be applicable to them. - What is the cost of CPD- does the expense of it discourage its use/does setting it up require more finance? 5. Figure captions can be shortened and more concise. Good luck with the paper.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1: Dr. Cícera Silva, Federal University of Campina Grande Centre of Teacher Education
Comments to the Author:

I consider the manuscript relevant to the current clinical research scenario in the challenging context of the COVID-19 pandemic and with important reflections on the use of Connected digital products (CDPs) today and in the future. The article was well designed and written, however I believe that a revision is important for its improvement. The following are recommendations for the manuscript:

Thank you for your enthusiasm for the topic and you helpful suggestions, which are addressed below.

- In the introduction, I believe that it would be interesting to mention the tendency to approach studies that used CDPs before the pandemic, since there was a considerable increase in them. **The use of CDPs has indeed increased over time. This is documented in Marra et al., 2020, which is also cited in the Introduction, and we believe addresses your suggestion. Nevertheless, Figure 1 reveals that these shares were actually quite stable in the period leading up to the onset of the pandemic. We believe that the current draft of the manuscript acknowledges overall trends, while simultaneously showing how post-period increases were indeed quite modest.**
- The research question needs to be clearly present in the introduction. **In the 3rd paragraph of the Introduction, we have clarified the research question as suggested.**
- In table 1, in the item “Fitbit, videoconferencing”, you must add in the “Trial Type” field if it is “COVID” or “non-COVID”, as you did with the others.
  Thank you drawing attention to this. Though trials with start dates in the pre-period should be non-COVID related by definition (as the pre-period is defined as the 10 months prior to pandemic onset), we agree that the label should be included for consistency. We have made this update in Table 1.
- The main details about the search on ClinicalTrials.gov, which are detailed in the supplementary materials, could be briefly described in the Methods.
  We have moved some of the details regarding the ClinicalTrials.gov search into the Methods section as suggested.
- I suggest adding a clearer description of the statistics performed in the Methods.
  We have rephrased to clarify that statistical significance was calculated using two-sided z tests with means and standard deviations from the 10 month pre-period and 10 month post-period.

With these revisions made, I consider the manuscript acceptable for publication in this journal.

Thank you again for the suggestions.

Reviewer 2: Dr. Payal Das, ICMR
Comments to the Author:

Medical infrastructures in afflicted countries are under intense pressures due to the current loads of critical COVID-19 patients. In addition to risks from exposure to COVID-19 patients, there are risks of infection for medical staff from hospital environments, from infectious co-workers, due to rationing of personal protective equipment and from extended times in ICUs. Thus, it is timely to consider adoption and expansion of virtualised medical treatment approaches such as telemedicine to reduce the burden on hospitals and allow safer working environment for healthcare providers.

I appreciate the work done by the authors. However, the submitted manuscript has neither defined the objectives properly nor the outcomes. I don't think the manuscript has achieved the required priority. This is not the need of the hour.

The paper should be completely revised and some more work/information on adoption of telemedicine/telehealth in country/countries should be included which is actually important during this time.

We appreciate the reviewer's point that the most critical application of telehealth following the pandemic onset has been in ensuring continued delivery of essential medical care. However, this area has been well studied and the rapid switch to telehealth platforms in the care delivery setting has already been documented in several publications.

The purpose of this study is to understand whether the pandemic onset has increased the use of telehealth and remote monitoring technology in the clinical research setting. The onset of the pandemic caused several documented disruptions to clinical trials and as a result, regulatory agencies (such as the U.S. FDA) introduced guidance that encouraged trial sponsors to adopt remote monitoring technology in order to continue the pursuit of important medical research in an environment where in-person interaction was challenging.

Our objective is to quantify whether or not there has been a change in the use of connected digital products across clinical trials following the onset of the pandemic and the FDA's guidance for virtual trials. Measuring trends in adoption is both important and relevant as conversations about the potential for remote monitoring and telehealth in clinical research continue to appear with increasing frequency in the medical literature. That said, we have clarified differences between what we see in our study setting and overall trends in telehealth. These differences in and of themselves are likely to be surprising and interesting to readers who are more familiar with telehealth trends over the past year.

Reviewer 3: Dr. Swetha Byravan, Leicester Royal Infirmary
Comments to the Author:

Overall an interesting and well written article that is relevant to the current pandemic. The methods and results are well described, and the figures provide good illustration of data. But I feel the discussion could do with more work to talk around the results and to understand why there was not a significant increase in CPD use overall. What might stop trial groups from using it? There is an opportunity in the discussion to provide more context to the article. Please see the comments below regarding this.

Thank you for your comments, which are addressed below.

Comments:

1. The trials that were started prior to the pandemic, is that included in the figure of 12,863? If so, it would be interesting to know the proportion of trials which started after the pandemic which I am presuming is 1405; how many of these used CPDs? Was this proportion higher than pre-pandemic?
   The 12,863 figure (now revised to 26,009 following the expansion of our dataset – and specifically, with the addition of 5 more months of data) only includes trials with start dates <u>after</u> the pandemic onset, which is defined as the post-period from May 2020-Feb 2021. 15.8% (4,121/26,009) of trials started after the pandemic onset used CPDs. This is slightly higher than the proportion of trials using CDPs with start dates before the pandemic and the result is statistically significant (p<0.01). We have rephrased the

Results section in effort to make these numbers even more clear as this is the primary finding from the analysis.

2. The acronym FDA needs to be expanded when first using the term.
   Thank you for noting this omission. The change has been made.
3. What information can and cannot be collected by CPD- can some examples be included in the introduction?
   We have updated the 2nd paragraph in the Introduction to describe the type of products that can be classified as CPDs and briefly give a sense for the type of data that they are able to collect.
4. I feel the discussion could be expanded to explore why the use of CDPs did not increase significantly post-pandemic and incorporate more perspectives, what are the obstructions to this:
   Thank you for all of the below suggestions. We have made modifications to the discussion section to briefly address many of these and have provided more detailed explanations below.
   - Does the type of data that needs collecting by various trials preclude the use of CDPs? Could their data have been collected via CDP for all incorporated trials?
     This is an interesting question for further research but we cannot draw any conclusions based on the analysis in this paper. With that said, we do not expect that the specific types of data collected by CDPs would change for trials started in the pre-period vs. the post-period (which included trials conducted just 1 year apart). The proportion of trials started that were observational vs. interventional and industry-funded vs. non-industry funded remained highly consistent across the pre- and post-periods. Therefore, we do not expect the answer to this question to change any of our findings documented here.
   - Is it due to pre-conceived ideas/attitudes by trial groups towards CDPs?
     Though we do not have a way to directly measure attitudes of trial sponsors, this paper's findings suggest that regulatory guidance did not meaningfully change trial sponsor's perceptions about the importance of using telehealth and remote monitoring options in trials—at least not in the first ten months following the release of such guidance. If it did, we would have excepted a greater increase in CDP usage following the pandemic onset.
   - FDA is applicable for US licensing of drugs only and therefore for trials that are not US based and conducted in other countries they will have their own drug regulatory body. E.g., MHRA in the UK. Therefore, the new FDA guidance may not be applicable to them.
     We agree that FDA guidance documents are likely to be most relevant for interventions seeking US approval. In ClinicalTrials.gov, we can see the site location but cannot observe specifically which trials will end up being relevant for US regulators. We have learned of several cases where trials were conducted at sites outside of the US and later submitted to the FDA for US approval (in fact, one of the manuscript's co-authors recently sat in on an FDA review meeting where this exact scenario occurred). Yet we agree that overall, to the extent that CDP use increased in response to FDA guidance, such an increase would be expected to be *most acutely observed in US trials*. Therefore, we have partially recreated Figure 1 to document the trend in CPD usage for trials with a US site and placed this figure in the Supplementary Materials file as Figure 3. While we do observe a higher rate of CDP usage for US trials in general, the increase from trials started in the pre-period to trials started in the post-period is the exact same as for all trials (+1.7 percentage points).
   - What is the cost of CPD- does the expense of it discourage its use/does setting it up require more finance?

Though we expect that the use of CPDs in clinical trials may add some cost to the study, the expected expense associated with CPDs is marginal in relation to the overall cost of a clinical trial. For example, recent estimates suggest that the costs of conducting a pivotal trial for a new therapeutic can range anywhere from $12M-33M (Moore et. al. 2018) whereas a branded activity tracker, such as a Fitbit costs ~$100. Therefore, we do not expect the cost of technology inclusion to be a primary driver in precluding its use for many trials.

5. Figure captions can be shortened and more concise.
   Thank you for this suggestion. We have shortened the captions as much as possible without losing the explanation of the analysis window or the key numbers.

Good luck with the paper.

Thanks again for your helpful comments.

VERSION 2 – REVIEW

REVIEWER	Das, Payal ICMR, Epidemiology and Communicable Diseases
REVIEW RETURNED	26-Apr-2021

GENERAL COMMENTS	The manuscript has been sufficiently modified. It can be accepted in the current form.