Peer Review File

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First External Peer Review

Reviewer A

Comment 1: I understand English may not be your first language but I would suggest hiring an English proofreader to give the article a final look as there are numerous grammatical mistakes that need to be addressed. It gets to a point where it is hard to focus on reading without stopping at colloquial words.

Discussion

As is can be seen from our study, -> Our Study shows that...

Reply 1: Thanks for your comments. To improve the language quality of our manuscript, we hired a professional English proofreader to check and polish it thoroughly. All the grammar mistakes we found, as well as overused words or phrases, and vague or ambiguous wording were revised in the updated manuscript. We wish it meets the criteria now.

In particular, the phrase that you pointed it out was changed from "As is can be seen from our study," to "Our Study showed that..." (see Page 16, Line 240). Other revisions were detailed in the updated version of the manuscript.

Reviewer B

Comment 1： English MAJOR review; maybe ask for the support of an English native reviewer; unclear sentences; verb tenses in disagreement with what is reported in the past, etc. Examples: line 59: “but the conduct of clinical research IS never the same as before.” Correct -> “but the conduct of clinical research WAS never the same as before.” / line 78: “and all the other roles in clinical trials ARE also welcomed to feed back their opinions.” Correct -> and all the other roles in clinical trials WERE also welcomed to feedback their opinions

Reply 1: We appreciate your comments and hired an English proofreader for the help of language checking and polishing throughout the manuscript. All grammar mistakes, especially the inappropriate verb tenses, were changed as follows for examples:

“the conduct of clinical research **is** never the same as before” was changed to “the conduct of clinical research has not resumed to where it used to be” (see Page 3, Line 61); and “all the other roles in clinical trials **are** also welcomed to feed back their opinions” was changed to “all the other roles in clinical trials **were** also welcomed to feed back their opinions” (see Page 4, Line 89).

Please refer to the revised manuscript for all detailed correction.

Comment 2: Not discriminated in the abstract a sentence with the statistical methodology.

Reply 2: Thanks for your advice. A description of the statistical method has been added to the Methods section in abstract as below:

A nationwide cross-sectional questionnaire was distributed to respondents in the 272 study sites throughout mainland China between September and October 2021. The participants assessed the impact of COVID-19 pandemic on clinical trials based on a 5-point Likert-type scale, and exploratory factor analysis (EFA) was used to confirm the factor structure. Statistical analyses were performed to discover the differences between different groups. (see Page 2, Line 29)

Comment 3: “It was designed a self-administered questionnaire to understand researchers’ perceptions and attitudes about the impact of COVID-19 pandemic on clinical trials in China.” However, the CRCs were invited in particular as the main participants for our survey”.

How could it be? They are not the investigators/co-investigators of the clinical trials that can precisely address the real impact of COVID-19 in this scenario. CRS have a very important role in the clinical trials process, but their activity is restricted to the bureaucratic part and not to the process of referring patients to trials and in the clinical decision. How can we draw definitive conclusions when the target audience of this survey is so heterogeneous...!?

Reply 3: Thank you for the comments, and we understand why you feel puzzled by our design and results. Please allow us to explain as follows:

1) Firstly, it's our fault that we didn't write it clear enough. It is indeed that we "designed a self-administered questionnaire to understand researchers' perceptions and attitudes about the impact of COVID-19 pandemic on clinical trials in China", and yet the word "researchers" refers to research personnel, i.e. a broad meaning of researchers, not only the investigators/co-investigators but also many other roles of staff in the research team, like nurse, pharmacist, CRC, etc. Therefore, trial staff involving different roles were invited in our survey. And we've changed the ambiguous wording in the revised manuscript.

2) Secondly, CRCs in China are practically involved in every important event in clinical trials, except for medical judgement or intervention. Their responsibilities mainly include assisting with screening patients to ensure rapid and accurate enrollment, managing subject scheduling and follow-up, preparing the site for implementation of the treatment, recording and verifying data in the Case Report Form (electronically or in paper), ensuring study supplies are properly inventoried, stored and reordered as necessary, keeping study files and records, and assisting investigators with internal and external communication. In other words, many of the investigator's responsibilities are primarily the CRC's operational responsibility, just like what are demonstrated in the references. So CRCs are representative as first-line performers and indispensable participants in clinical trials both before and after the outbreak of COVID-19.

3) In addition，the regulation mechanism of clinical trial in China is somewhat different from those in other regions. All drug clinical trials must be conducted in the superior and accredited hospitals approved by the government, where investigators are usually occupied by heavy medical tasks due to the imbalanced medical resources distribution in China. Chinese investigators may rely more than those in other countries on the skills,

knowledge, and abilities of competent, trained, professional CRCs. So the role of CRCs is particularly central to the successful conduct of a clinical trial in China.

References

[16]JB Zheng, YL Chen, XY Shi. Investigation and Analysis on the Status of Clinical Research Coordinator in Drug Clinical Trials. Journal of Strait Pharmaceutical 2021, 33(11):223-225. (Chinese journal article)

[17] Y Zhou, M Tang, YC Chen, et al. Exploring the introduction of clinical research coordinator management model in drug clinical trial institutions. Chinese Journal Of Clinical Pharmacy 2017, 26(1):28-50. (Chinese journal article)

Comment 4: What was the main reason to exclude these regions? Any ideological or political reasons behind it? Historical relations with other countries or beliefs? (Macau -> Portugal; Hong Kong -> England; Taiwan and Tibet -> Zones of local conflicts with Chinese authorities)

Reply 4: There is no ideological or political factors for the reason why we excluded those regions as you mentioned. Instead, the supervision system and implementation practicality were the main reasons we considered in our study. The clinical trial management systems in Hong Kong, Macao and Taiwan are different from those in Chinese mainland, neither do they follow the same COVID-19 pandemic control policies. To avoid the heterogeneity of our study result, respondents from these regions were not invited in the survey. Regarding Tibet, few clinical trials are conducting there due to the relatively poor economics and insufficient medical resources, and we failed to find suitable respondents to participate in the questionnaire survey. Up to now, only 2 trials in total are registered in the official trial registration platform (http://www.chinadrugtrials.org.cn).

Comment 5: There are other limitations that can be pointed out in addition to those described in the manuscript:

- The observational nature of the study design and the fact that surveys are subject to recall and response bias are considerable limitations.
- Most respondents were relatively young, possibly indicating selection bias which may have influenced the results.
- Given the heterogeneous centres organisations and COVID-19 burden across

China, it would have been interesting to compare practices between the various regions.

 Absence of a survey conducted early in the pandemic in China (i.e., first quarter of 2020), which would have permitted comparison with the current survey conducted later in the pandemic.

Reply 5: Thank you so much for the comments, and we have added them into the limitation section in our revised manuscript. The updated discussion about study limitations is as below:

There are some limitations in our study. First, CRCs account for most respondents, and most respondents were relatively young, possibly indicating selection bias, which may have influenced the results, and our study stands for the CRCs more than other roles in clinical trials, though the comprehensive perceptions are obtained. Differences between varied roles and ages were further compared by rank sum test and discussed. Second, the observational nature of the study design and the fact that surveys are subject to recall and response bias are certain limitations. Moreover, although questionnaire-based survey studies are intended to provide data that is generalizable to a bigger population, it is often argued that they are limited in terms of rich and thick description. Third, the use of a cross-sectional design is unable to make causal inferences because it did not control for all possible confounding variables, so the differences between groups just indicate the relevance. Fourth, as the number of distributed questionnaire at filled out each site was different, we had one site that sent back several surveys, while others only sent back one, the opinions would reflect what happened at that one site more than the others. Our study was conducted on a convenience sampling of research team members of clinical trials, thus the sample would represent the population with bias. Furthermore, given the heterogeneous centre organisations and COVID-19 burden across China, it would be interesting to compare practices between the various regions of China. Our study revealed no significant ($P<0.05$) difference among the east, center and the west in general, and yet investigation on specific regions, like provinces, will be carried out in the future study. In addition, the absence of a survey conducted early in the pandemic in China, i.e., first quarter of 2020, may be another limitation of the study, which would have permitted a comparison with the current survey. (See Page 20, Line 326)

Comment 6: Consider to include other studies that evaluated the real impact of COVID-19 in the clinical and experimental practice:

1. Alpuim Costa D, Nobre JGG, Fernandes JP, Batista MV, Simas A, Sales C, et al. Impact of the COVID-19 Pandemic on Breast Cancer Management in Portugal: A Cross-Sectional Survey-Based Study of Medical Oncologists. Oncol Ther. 2022 Mar 21:1–16. doi: 10.1007/s40487-022-00191-7. Epub ahead of print. PMID: 35312952; PMCID: PMC8935098.
2. Saini KS, Tagliamento M, Lambertini M, McNally R, Romano M, Leone M, et al. Mortality in patients with cancer and coronavirus disease 2019: a sys- tematic review and pooled analysis of 52 studies. Eur J Cancer. 2020;139:43–50.
3. Lambertini M, Toss A, Passaro A, Criscitiello C, Cremolini C, Cardone C, et al. Cancer care during the spread of coronavirus disease 2019 (COVID-19) in Italy: young oncologists' perspective. ESMO open. 2020;5(2):e000759.
4. Desai A, Sachdeva S, Parekh T, Desai R. COVID-19 and cancer: lessons from a pooled meta-analysis. JCO Glob Oncol. 2020;6:2.
5. Poggio F, Tagliamento M, Di Maio M, Martelli V, De Maria A, Barisione E, et al. Assessing the impact of the COVID-19 outbreak on the attitudes and prac- tice of Italian oncologists toward breast cancer care and related research activities. JCO Oncol Pract. 2020;16(11):e1304–14.
6. Lara Gongora AB, Werutsky G, Jardim DL, Nogueira-Rodrigues A, Barrios CH, Mathias C, et al. Impact of the COVID-19 pandemic on oncology clinical research in Latin America (LACOG 0420). JCO Glob Oncol. 2021;7:649–58.

Reply 6: Thank you for the suggestion. These articles you listed are very helpful in understanding and evaluating the impact of COVID-19 on clinical trials, and we have cited them in the background and discussion sections of the revised manuscript as references [36, 1, 39, 37, 3, 25]

Reviewer C

Comment: Your paper represents a needed and interesting undertaking which was to survey clinical trial staff (mostly CRCs) in Chinese clinical trial programs, which appear numerous and robust. However, the main problem with this manuscript is that the findings are not at all clear from what is written in the abstract, the results and discussion. In the results, there is no clear description to a non-statistician investigator or CRC as to what survey responses were statistically significantly meaningful and therefore reflect what the impact of the Covid pandemic on clinical trials actually was in China. After reading the paper word by word twice, I still do not understand exactly what the results of the survey really show. There are few sentences in the discussion about "positive comments" related to trial conduct made by the respondents and the use of technology during the pandemic, but that's it! I also don't understand how the authors reach these conclusions. In the discussion there is no summary of the results, nor is there any comparison of these results to what is known currently in the literature about how clinical trials faired during the Covid pandemic. Some of this is discussed in the Introduction, but it is not relevant there since it is not compared to results found by the investigation in the rest of the paper. Overall, from reading this paper, an individual interested in clinical trials will not have any understanding of the impact the pandemic had in China. Other problems include agrammatical and a syntactical use of English which may be the results of translation from Chinese (?) Above and beyond this, however, the author's style often present ideas in a vague and wordy manner which results in a lack of clarity and leaves the reader questioning what the point is of statements or references made to tables/figures b the authors. I would assume the authors themselves have some idea, but if a paper is not written with clarity, it is useless, even to aa clinically and scientifically specialized audience.

Reply:

Thanks a lot for your interest in our study. In this study, we analyzed the respondents' perceptions and attitudes toward the impact of COVID-19 on clinical trials through a questionnaire survey in different regions in Mainland China, and compared the differences in attitudes and perceptions of different respondents in four dimensions, so as to find out which aspects of clinical trials were positively or negatively affected by COVID-19 and to further make policy suggestions on the implementation of clinical trials in China under the pandemic.

According to your requirements, we have revised the abstract, the results and discussion to make the findings clearer. Please refer to the revised manuscript for the specific changes, and we hope to get your approval.

(1) The section of Abstract.

First, a description of the statistical method has been added to the Methods section of the Abstract as follows:

A nationwide cross-sectional questionnaire was distributed to respondents in the 272 study sites throughout mainland China between September and October 2021. The participants assessed the impact of COVID-19 pandemic on clinical trials based on a 5-point Likert-type scale, and exploratory factor analysis (EFA) was used to confirm the factor structure. Statistical analyses were performed to discover the differences between different groups. (see Page 2, Line 29)

Second, we have revised the results section of the Abstract as follows:

A total of 2,393 questionnaires from 272 hospitals were collected in mainland China. Factor analysis resulted in four factors, with a cumulative explained variance of 64.93 %, as follows: subjects enrollment; patient care; study supplies & data management; and research milestones & quality management. The scores (Mean ± SD) for 29 items ranged from 2.87 ± 0.89 to 3.67 ± 0.80, and the research team members, represented by most of Clinical Research Coordinators (CRCs), disagreed that the pandemic was associated with more serious adverse events (SAE), missed reports of safety events or any increase of unscheduled unblinding in clinical trials (scoring below 3.00). In addition, significant differences were revealed in different age, gender and role groups of respondents based on their views on the impact of the pandemic. (see Page 2, Line 34)

(2) The section of Results.

In order to provide a clear description to a non-statistician investigator or CRC, we have added some explanations on the results of factor analysis in the section of Results as follows:

The exploratory factor analysis results showed that the 29 attitudes attributes regarding the impact of COVID-19 on clinical trials could be classified into four dimensions. (see Page 9 ,Line 177)

In addition, in order to show the results of comparison, we also have added some P values in the section of Results as follows:

The results showed that there were significant differences between males and females in all four factors, with P values of <0.001, 0.009, 0.019, 0.024 for factors of SE, PC, S&D and R&Q, respectively. In the meantime, except the factor SE, all the other factors showed significant (P＜0.05) differences in the median scores among different age groups and respondent groups. (see Page 16, Line 223)

(3) The section of Discussion.

We have revised the manuscript accordingly. And the positive comments were discussed in discussion section, paragraphs 5, 6 and 7. The disagreement of the negative impact scenarios (Q15, Q17, Q18), the approval of positive impact scenarios (Q21, Q22, Q24, Q26~Q29), and the most frequently mentioned suggestions in our survey, were discussed to show the positive attitudes made by the respondents and how technology is used more during the pandemic.

In addition, we revised the discussion section with a summarized results in the first paragraph, followed by some comparisons with the published literature. The updated first two paragraphs of our discussion are as follows:

Our study shows that over 2,000 research members from study sites covering the east to the west of China accepted the nationwide survey, and the results exhibited the general attitude and perceptions objectively and soundly. Generally, the respondents had a negative attitude towards subject recruitment and patient care, blaming the difficulties of enrollment and medical oversight to the COVID-19, and these opinions are consistent with similar studies from some other countries. More protocol deviations were reported during the COVID-19 pandemic, since delays in followed-up visits were inevitable and management procedures of investigational products were challenged by numerous inconveniences caused by the pandemic. Nevertheless, the respondents also saw some positive impacts of the pandemic on clinical trials, such as telemedicine, online meetings, and remote monitoring, which were the consensus reached by research staff.

Unlike some other previous studies reported, we investigated the perceptions of all research staff, including varied roles. During the conduct of our survey, many CRCs responded actively, and opinions and attitudes of this new force in Chinese Clinical trials were firstly explored extensively. Different perceptions of varied roles in clinical trials were compared, and significant (P<0.05) differences were demonstrated among different role, age and gender groups. Furthermore, it was found in our survey that most

respondents supported the government's routine policy against COVID-19, and took the view that these measures would be helpful for future clinical trials. We speculated it may be attributed to the effectiveness of COVID-19 controlling situation of China, and the strict policy was accepted by the public.

(See Page 16, Line 240)

(4) The section of Conclusion.

In order to make an individual interested in clinical trials will have enough understanding of the impact the pandemic had in China, we reorganized our manuscript to make each part section more clear, revised the section of Results and Discussion. Specially, we summarized the main findings in the section of the Conclusion as follows: This study explored the impact of COVID-19 pandemic on clinical trials in China from the perspectives of research team members. The current pandemic situation has indeed posed a significant impact on clinical trials, especially in terms of subject recruitment and protocol compliance, but the research team members are still confident and positive to the policies to offset the negative impacts. As mentioned in our study, many new technologies and some pragmatic suggestive measures have and will continue to change the way in which clinical trials are conducted.

(See Page 20, Line 345)

(5) The grammatical and syntactical use of English.

The manuscript was written by the Chinese authors, and some grammatical errors may have been caused by the Chinese language habits, rather than directly translated from Chinese to English. To improve the language quality of our manuscript, we hired a professional English proofreader to check and polish it thoroughly. All the grammar mistakes we found, as well as overused words or phrases, and vague or ambiguous wording were revised in the updated manuscript. We wish it meets the criteria now.

Reviewer D

Comment 1： Analysis or additional information on the open question (section 4) of the survey should be provided. You are only now bringing up the open ended question. You should present results from this in the results section. For example, if you saw common themes in the responses, you should note that in the results. No analysis (even qualitative) on these was presented. Did the open question responses provide any insight into the question responses?

Reply 1: Thank you for your useful suggestions. We added "suggestions proposed" into the results.

Changes in the text:

Suggestions proposed

In section IV of the questionnaire, providing the suggestions regarding how to ensure efficient and qualified implementation of clinical trials were welcome but not mandatory. There was 40.2% (962/2393) of the respondents voluntarily filling out their answers. Suggestions proposed in high frequency fell in the aspects of strengthening communication between clinical trial stakeholders, i.e. sponsors and investigators, and making full use of the internet for remote monitoring and medical oversight by telemedicine. The remaining suggestions covered many aspects of clinical trial. Some respondents advised reinforcing the training and education of subjects and stressing the awareness of COVID-19 prevention and control. Some people suggested simplifying the bureaucratic requirements and processes related to clinical trials, like EC reviewing and approval in an expedited manner, establishing specialized pathways for clinical trial subjects, and so on. Besides, it was considered crucial by respondents that the study sites could actively and promptly issue their specific guidelines relevant to the conduct of clinical trials.

(See Page 16, Line 227)

Comment 2： Assess if there were any hospitals that had more responders compared to others which could be a limitation. There may be limitation if any one or few hospitals comprised the majority of responses in a region.

Reply 2: Although the distribution of the respondents was uneven, it was consistent with the regional distribution of clinical trial centers and the number of clinical trials undertaken. In other words, which regions had more clinical trial centers, we sampled

more study sites in these regions, and which study sites carried out more clinical trials, we had more respondents in these sites. But we still realized that this could be a limitation, so we have modified the limitations as advised.

Changes in the text: “Fourth, as the number of distributed questionnaire at filled out each site was different, we had one site that sent back several surveys, while others only sent back one, the opinions would reflect what happened at that one site more than the others. Our study was conducted on a convenience sampling of research team members of clinical trials, thus the sample would represent the population with bias.” (See Page 20, Line 334)

Comment 3： Review/edit for language/grammatical errors. Consistent formatting (eg. spacing) should be used.

1. Line 24: Recommend different phrasing. For example, "The number of Chinese clinical trials has continued to grow even under...."
2. Line 25: Change “to” to “toward”
3. Line 33: Change "Our" to "The"
4. Line 34: Change "set to" to "organized into"
5. Line 38: Change "Besides" to "Additionally"
6. Line 40: Change "Our" to "Study". Change "to" to "toward"; Line 41: Recommend changing to "...and confirmed 7 positive scenarios impacting trials, including quality management..."; Line 42: Change "visit" to "visits"; Line 43: Remove "as"; Line 42: What is meant by "anti-pandemic"?
7. Line 47: Remove "The" and start with "COVID-19"
8. Line 49: Change "development" to "progression"
9. Line 52: Reword: "Thereafter, a total of..."
10. Line 54: Remove space between Clinical and Trial. Awkward wording” the rollout of vaccine hadn’t changed the trends of re-increased number of suspended trials”
11. Line 55: Reword to "which accounts for"
12. Line 58: Change “level” to "levels"
13. Line 59: Remove "nowadays". “is never the same as before” reword to “ has not resumed to where it was before“
14. Line 62: Change to "and in what ways"
15. Line 68: Add space before (CRCs)

16. Line 72: Change "helped" to "help"
17. Line 76: Change the two "were" to "are"
18. Line 127: "Data was analyzed..."
19. Line 130: Add space before (KMO)
20. Line 142: Add space after 125. Before presenting the (%) make sure you are consistently adding a space. Sometimes you do, sometimes you don't.
21. Table 4: Recommend putting an * for those in the table that were statistically significant.
22. Line 207: Reword to "As can be seen"
23. Line210: Change "were" to "are"
24. Line 216: Change “world widely” to “worldwide”
25. Line 227: Not "no approval" rather "no negative impact on these by COVID-19"
26. Line 246: Spell out esp.
27. Line 247: Prevention and control of what? COVID-19?

Reply 3: Thanks for your advice. The grammatical issues listed in the “review-comments” were already modified.

Changes in the text:

1. “Chinese clinical trials are soaring up…”was changed to “The number of Chinese clinical trials has continued to grow…” (See Page 2, Line 24).
2. “to” was changed to “toward” (See Page 2, Line 25).
3. This sentence was deleted.
4. This sentence was deleted.
5. "Besides" was changed to "In addition" (See Page 2, Line 39).
6. We rewrote the conclusion paragraph as follows:

   The current pandemic situation has actually had a negative impact on clinical trials, especially in terms of subject recruitment and protocol compliance, while the research team members feel confident that some effective measures proposed in the study can alleviate these impacts. (See Page 2, Line 42).
7. "The" and start with "COVID-19" was removed (See Page 3, Line 48).
8. "development" was changed to "progression" (See Page 3, Line 50).
9. “totally” was removed. (See Page 3, Line 54).
10. The space between Clinical and Trial was removed. “the rollout of vaccine hadn’t changed the trends of re-increased number of suspended trials” was changed to

"the rollout of COVID-19 vaccination hadn't changed the increasing number of suspended trials". (See Page 3, Line 55).

11. "which is accounted for" was changed to "which accounts for" (See Page 3, Line 57).
12. "level" was changed to "levels" (See Page 3, Line 60).
13. "nowadays" was removed. "the conduct of clinical research is never the same as before" was changed to "the conduct of clinical research has not resumed to where it used to be" (See Page 3, Line 61).
14. "how it does" was changed to "in what ways" (See Page 3, Line 72).
15. Space was added before (CRCs). (See Page 4, Line 77).
16. "helped" was changed to "help" (See Page 4, Line 81).
17. the two "were" were changed to "are" as follows:
    Numerous well-trained CRCs are active in the front line of clinical research, which are also the main force of clinical research teams. (See Page 4, Line 85).
18. "was" was added between "Data" and "analyzed". (See Page 6, Line 143).
19. Space was added before (KMO). (See Page 6, Line 147).
20. Space was added after 125. A space was added uniformly before presenting the (%). (See Page 7, Line 160).
21. The statistically significant values in Table 4 were added with *. (See Page 15).
22. "As is can be seen from our study" was changed to "Our study showed that…" (See Page 16, Line 240).
23. "were" was changed to "are". (See Page 17, Line 257).
24. This sentence was deleted.
25. "no approval of these impacts" was changed to "no negative impact on these by COVID-19". (See Page 18, Line 278).
26. "esp." was changed to "especially". (See Page 18, Line 286).
27. "of COVID-19" was added after "Prevention and control policies". (See Page 17, Line 271).

Comment 4:

Line 49: Not sure what is meant by "strong variability". Are you referring to its rapid mutation rate? Perhaps reword to "its rapid mutation and transmission".

Reply 4: “its strong variability and rapid transmission” was changed to “its rapid mutation and transmission”. (See Page 3, Line 49).

Comment 5：

Line 60: I think it would be good to note what these guidances covered. Some covered monitoring activities and how to do off-site patient visits. Some general info would be valuable here.

Reply 5: Thanks for your good advice. We have modified this paragraph as advised.

Changes in the text: “It is well noted that many regulatory and research organizations, e.g. the US Food and Drug Administration and European Medical Agency, issued special guidance and developed new policies and procedures to address the conduct of clinical trials during the COVID-19 public health emergency, as did the Chinese government. These guidelines stress ensuring health and safety of trial participants, and suggest alternative measures proportionate and based on benefit-risk considerations with adequate documentation. For instance, where a trial participant is unable to attend the site, home nursing, contact via phone or telemedicine, and location assessment, etc. may be required to identify adverse events and ensure continuous medical care and oversight for patients, which may be helpful for avoiding further burden in terms of time and staffing in clinical trials during the COVID-19 pandemic. ” (See Page 3, Line 61).

Comment 6：

Line 62: Has any impact or continues to impact? I think it is know that there was impact, but that you are looking to see if the impact remains today.

Reply 6: Yes, you’re right. We are wondering if the impact remains today.

Changes in the text: “It is crucial to understand whether the current pandemic situation continues to impact on clinical trials in China and in what ways” (See Page 3, Line 71).

Comment 7：

Line 64: “And the research team members, who carried out the trials should feel the impact first-handed and straightforward, so we would like to survey the attitudes and perceptions of people in the front line of clinical trial implementation towards the erupt of COVID-19 pandemic…”

This sentence needs to be reworded so it is clearer that what you are saying is that the research staff experience the impacts first hand, and therefore their assessment is critical to understanding the impact of COVID-19 on trials.

Reply 7: We have modified this paragraph as advised and deleted the sentence "so we would like to survey the attitudes and perceptions of people in the front line of clinical trial implementation towards the erupt of COVID-19 pandemic…"

Changes in the text: "As the research staff conducted the trials and experienced the impacts first hand, their assessments were critical to understand the impact of COVID-19 on trials. Research staff in China generally refers to all team members in clinical trials in sites, including physicians…" (See Page 3, Line 74)

Comment 8:

Line 66: "we would like to survey the attitudes and perceptions of people in the front line of clinical trial implementation towards the erupt of COVID-19 pandemic"

Not sure what is meant by "erupt" but I don't think it is the right word here.

Reply 8: This sentence was removed.

Comment 9:

Line 72: Define CT.

Reply 9: "CT" was changed to "computerized tomography". (See Page 4, Line 82)

Comment 10:

Line 72: "Chinese CRCs have taken, or rather, helped with the tasks of most non-medical judgment". Do you mean that don't require medical judgment?

Reply 10: Correct. And we reworded the sentence as follow:

"Chinese CRCs often help with most tasks that do not require medical judgment…" (See Page 4, Line 81)

Comment 11:

Line 105: "Questionnaires were piloted with three experts and one investigator for face validity with the questionnaire amended prior to further reliability piloting with 10 research investigators and 20 CRCs to test the internal consistency of measures."

Who were these experts and how where they chosen? Language needs to be cleaned up a bit, but I believe you are saying that following the initial pilot, the questionnaire was amended and then sent out for further validation.

Reply 11: We added a description of how to select experts and reorganized the sentence. Changes in the text: "Initially, four experts from well-known study sites with years of clinical trial experience, including two physicians, one pharmacist and one administrator, conducted the pilot survey, and we further amended and optimized the questionnaire to achieve high internal consistency reliability (Intraclass Correlations (ICC) 0.869 for 29 items in the questionnaire), indicative of good reliability."(See Page 5, Line 115).

Comment 12:

Line 111: "The respondents were recruited from 272 study sites throughout mainland China, i.e., all tertiary hospitals with GCP qualifications in 121 cities in 30 provinces, autonomous regions, and municipalities (Tibet, Hong Kong, Macao, and Taiwan were excluded) between September and October 2021."

How were these sites identified? Did you use a database containing lists of study sites? If you sent the survey to 272 hospitals, does that mean that you sent them to more than one individual at the sites in order to get 377 responses? So, the question is, how many surveys could each site fill out? The problem here is that if you had one site that sent back several surveys, while others only sent back one, the opinions would reflect what happened at that one site more than the others.

Reply 12: These study sites were identified from the drug clinical trial institutions approved by National Medical Products Administration (NMPA) in mainland China. Yes, we used a data base containing lists of study sites. The clinical trial management research system database was developed by NMPA. The information of the database included the name, address, contacts, telephone number and principal investigators of the 1500 clinical trial institutions. The website of this database was as follows: https://beian.cfdi.org.cn/CTMDS/apps/pub/drugPublic.jsp

Based on the sample size calculations, the minimum sample size was 377 responses. In order to get enough responses, we sent the questionnaires to more than one individual at the sites. Due to different size of each study site, the numbers of distributed questionnaires at each study site were different. The initial aim of this survey was to

complete 5-20 questionnaires at each study site, with a goal of 2500 respondents in total. Convenience sampling was conducted at each study site, and the research assistants distributed questionnaires to the appropriate respondents by online tools. .Therefore, the number of distributed questionnaire at each site was different, which could be a limitation of our study. We have added it in the section of Limitation.

We have revised this paragraph as follows:

These study sites were identified from the clinical trial management research system database, which was developed by National Medical Products Administration (NMPA) in mainland China. The information of the database included the name, address, contacts, telephone number and principal investigators of the 1500 clinical trial institutions. In order to get enough responses, we sent the questionnaires to more than one individual at any individual study site. Due to different size of each study site, the number of questionnaires distributed at each study site varied. The initial plan of this survey was to collect 5-20 questionnaires at each study site, with the goal of 2500 respondents in total. (See Page 5, Line 123)

We have revised the section of Limitation as follows:

As the number of distributed questionnaire at filled out each site was different, we had one site that sent back several surveys, while others only sent back one, the opinions would reflect what happened at that one site more than the others. (See Page 20, Line 334)

Comment 13：

Line 218: “These difficulties made patients reluctant or objectively prohibited to go to hospital.”

Not sure you can make that conclusion. I think they could be reasons, but there may be other reasons as well. You didn't collect the reasons, so you can't definitively say.

Reply 13: We reviewed the sentence, which is indeed supposed to be the cause of the recruitment difficulties, so we revised the sentence.

Changes in the text: “The reasons for difficulties in subject enrollment and patient care are multifaceted. One main reason was that the patients were reluctant or objectively prohibited to go to hospital during the pandemic.” (See Page 17, Line 265).

Comment 14：

Line 229: “The phenomenon may reflect the clinical trial members’ optimism to the trial conduct.”

What do you mean by this? Would their optimism before COVID-19 and after COVID-19 for clinical trials be different?

Reply 14: The sentence “The phenomenon may reflect the clinical trial members’ optimism to the trial conduct” was not appropriate, so we deleted it.

Comment 15:

Line 234: “And elder people might feel more integrated towards entire process of trials and be more sensitive to the impact”

Possibly. If you collected years of experience in clinical trials, that would perhaps help you verify this. Just because someone is older doesn't necessarily mean they have more experience.

Reply 15: In fact, the elderly respondents were mainly investigators, and Chinese regulations stipulate that investigators should have certain professional titles and relevant work experience. The principal investigator is required to have participated in at least three clinical trials. So it is true that they have more experience than the young CRCs.

Changes in the text:

This was due to the fact that CRCs are mostly in the 21-30 age group, the other respondents (non-CRCs), namely fellows in healthcare institution, were relatively older. The older respondents were mainly investigators, who are usually required by higher level of qualifications with more years of education, experience and training than CRCs. So older respondents might feel more integrated towards the entire process of trials. (See Page 18, Line 289)

Comment 16:

Line 238: Is telemedicine viewed positively...in that it is a good thing, or did they just respond positively that they believe telemedicine, for better or worse, will continue? Were their negatives to telemedicine in this study?

Reply 16: There is no doubt that telemedicine is a positive measure in clinical research. Especially during the pandemic, formal COVID-19 mitigation policies were adopted in many study sites, including telemedicine, and it was recommended as part of clinical

trials' routine in the future. Of course, we believe that telemedicine cannot replace on-site visits, it is only a supplement. It also has limitations, on the one hand, some important information cannot be transmitted without face-to-face communication, on the other hand, telemedicine does not facilitate biospecimen collection and physical examination, and in addition, in some rural areas, the necessary equipment for telemedicine may not be available.

We added some points to the discussion.

Changes in the text: "By telemedicine, remote drug distribution and continuous medical oversight of adverse events during trials are realized, , which not only reduces hospital visits, decreases the risk of nosocomial infections and dropout rate, alleviates the pressure on medical resources, but also further ensures the quality of clinical trials. Although there are some limitations in telemedicine, such as biospecimen collection, physical examination, and the availability of the required equipment in poor areas, it is still recommended to be part of future clinical trials' routine." (See Page 19, Line 302)

Comment 17：

Line 249: "People with a star may be directly rejected or restricted to the entry, which brings some obstacles to the normal implementation of clinical trials."

Those not familiar with the process will not know what the star represents. Does the star denote someone with COVID-19 or someone with symptoms?

Reply 17: We are very sorry for the confusion caused by the lack of clear explanation. In order to avoid misunderstanding, we have deleted this sentence.

Comment 18： Line 262: Were there any suggestions on how to improve the negative items, such as safety reporting?

Reply 18: In the discussion of the manuscript, we mentioned some suggestions to offset the negative impact of the pandemic on clinical trials. At the same time, we reviewed the relevant literature and added some new suggestions for the negative items as follows. First, strengthen communication between clinical trial stakeholders. Second, issue and update guidelines on risk areas timely. Third, integrate clinical trial resources and simplify the bureaucratic requirements and processes related to clinical trials. Forth,

make full use of information technologies. Fifth, take more frequent quality control, and finally, reinforce the training and attention to subjects.

Details can be found in paragraph 6 of discussion section in our revised manuscript.

(See Page 19, Line 308)

Second External Peer Review

Reviewer A

Comment 1: This revision of the manuscript shows great improvement especially since it is shorter, and the authors have made efforts to clarify what their objective in surveying clinical trials research staff (mostly CRCs) at various sites. In my read of this version, it seems to be to elicit their opinion as to whether they agree or disagree with 29 items in a questionnaire which the authors designed with items commenting on various aspects of clinical trial conduct. Their intent was to characterize respondents opinions, for each of these items about the nature of the impact of the Covid pandemic on clinical trials conduct ie did it negatively impact (meaning, I believe, damage or hurt the conduct of clinical trials) or positively impact (ie improve the conduct of clinical trials.)

Unfortunately, the authors do not do a good job explaining this nor do they succinctly write about their results in the abstract, in the body of the paper, or in the discussion. It seems to me that they are more concerned highlighting that most of their respondents were either neutral or positive about each item on the Likert scale. The range really hovered around 2.67 to 3.8 really between 3 neutral and 4 somewhat agree. An inspection of the percentages of response in the table of each item pretty much shows that. BUT it takes a long time for the reader to figure that out analyzing the table 3 and figure 3. So the paper suffers when the authors do not in the results state that most respondents agreed or were neutral regarding negative effects of the pandemic, except when they disagreed about AE reporting, etc. They also do not reporting prose that respondents saw some positive effects of the pandemic. They report about “negative” and “positive” effects without stating specifically what they mean by positive and negative when it comes to patient recruitment, data management, data quality, supplies study milestones etc. So the reader ends up reading the paper not understanding exactly how the respondents felt about which elements of clinical trials.

Reply 1: Thank you very much for your pertinent comments. To make our results clear and succinct, the following contents have been revised in the updated manuscript.

1) We deleted the original Table 2, Figure 2, and changed **Table 3** into three columns, showing the attitudes of disapproval (scoring 1 and 2), neutrality (scoring 3)

and approval (scoring 4 and 5) of the questioning scenarios we proposed in the survey. The revised Table 2 is as follows:

2) The description of **Table 2** (the original Table 3） in the results section was revised as follows:

Table 2 listed the pre-setting scenarios of impact of the COVID-19 pandemic on clinical trials with scales, showing respondents' perceptions and attitudes towards each item by mean scores and standard deviations (mean±SD). The attitudes of respondents were divided into three categories as disapproval (scoring 1 and 2), neutrality (scoring 3) and approval (scoring 4 and 5). It was noted that the approval was dominating for all items except Q15, Q17 and Q18. The neutral attitudes of these three questions accounted for the majority, and the disapproval of each item accounted more than the approval. This phenomenon indicates most respondents didn't agree that the pandemic caused these unfavorable events, including more SAE, missed reports of safety events or any increase of unblinding events in clinical trials. (see Page 7, Line 176)

3) Results in the abstract were revised as follows:

"The research team members, represented by most of clinical research coordinators (CRCs), basically agreed with all but three pre-set scenarios of the impact of COVID-19 on clinical trials. Most respondents didn't agree that the pandemic was associated with more serious adverse events (SAE), missed reports of safety events or any increase of unscheduled unblinding."(see Page 2, Line 35)

Comment 2: The findings in the paper appear to be mostly descriptive. The authors use statistics to do the factor analysis (which parses out in a way that they designed the questionnaire so it is not a surprise, and I wonder if again it is needed at all in the results). The only statistics are used to compare different groups (male vs female, younger and older etc.) but the differences are within a point difference on the Likert scale, so I wonder how significant those results are.

Reply 2: Thank you so much for your useful suggestions. We are opening ourselves to your criticism.

1) However, it was necessary to do the factor analysis in this study. There are some differences between the research hypotheses and final results in our study. In the first stage, the hypotheses were established based on an extensive literature review and the comments of experts. The questionnaire consisted of 29 items to assess the scale of

perceptions of different impacts of COVID-19 on clinical trials. In our hypotheses, the 29 items could be classified into 6 categories: a) Subject enrollment; b) Patient care; c) Study supplies; d) Data management; e) Quality management; f) Research milestones. In the second stage of the study, attempts were made to verify this hypothesis using Exploratory factor analysis (EFA) in this study. EFA is used to reduce the number of measured variables to analyze the structure between the variables, and the increasing statistical efficiency. It is used when the relationship between observed variables and factors has not been theoretically established [1]. Due to lack of theoretical foundations, we therefore used an EFA approach. In the final stage, after EFA work, the 29 attitudes attributes regarding the impact of COVID-19 on clinical trials could be classified into four dimensions: “Subject enrollment”(SE), “Patient care”(PC), “Study supplies and Data management”(S&D) and “Research milestones and Quality management”(R&Q). The validity, internal homogeneity (Cronbach’s alpha), and consistency (test–retest reliability) of the developed instrument also were measured. Therefore, by EFA test, the study’s hypothesis was partially confirmed. Based on the study’s hypothesis, six dimensions could be found, but in the results, according to the responses’ perceptions, only four dimensions were established. We can conclude that EFA is needed at all in the results.

2) Analyses stratified by age, sex and respondent were conducted to reveal possible differences in the results between the study subgroups. The significance of this work were as follows:

First, five-point Likert scale was used in our questionnaire. Although the differences are within a point difference on the Likert scale, there were significant differences between males and females in all four factors, with P values of <0.001, 0.009, 0.019, 0.024 for factors of SE, PC, S&D and R&Q, respectively. Meanwhile, except the factor SE, all the other factors showed significant ($P < 0.05$) differences in the median scores among different age groups and respondent groups. It is demonstrated that the results are statistically significant.

Second, to our knowledge, this is the first study to discover the different attitudes towards the impacts of the COVID-19 pandemic on the conduct of clinical trials between different groups. In addition, especially for CRCs group, most of CRCs are female youngers. It is different from other roles in clinical trials. There were few studies that focused on the CRCs’ comprehensive view to the impact of COVID-19 on clinical

trials in China and other countries. In order to give rise to an objective, full-scale and comprehensive view to the impact of COVID-19 on clinical trials in China, it is significant to compare the CRCs' attitudes and perceptions with other roles' in clinical trials.

References

[1] Park JH, Kim JI. Practical Consideration of Factor Analysis for the Assessment of Construct Validity. J Korean Acad Nurs. 2021 Dec; 51(6):643-647. doi: 10.4040/jkan.51601. PMID: 35023854.

Comment 3: That's my biggest criticism. I also think the paper is too long. The section on 'proposed suggestions' I believe is not germane and not described in the methods or in the questionnaire until later. It should be deleted. I believe the prose part of the discussion should not contain information regarding data analysis – that should be either in the methods or footnoted in the tables and figures. To me Figure 3 and Table 3 report basically the same thing and are redundant. The discussion is weak as it suggests that the results of this questionnaire suggest a negative impact of the pandemic, but a lot of the respondents were neutral, so, really, weren't many of the CRCs of the opinion that there was little to no effect?

Reply 3： We appreciate your comments and this submitted version was further revised by cutting the redundant and possibly unnecessary contents in the main document.

Regarding the "proposed suggestions", which is the forth section of our questionnaire as mentioned in the "Method", it was suggested to be provided by another reviewer in previous reviewing comments. However, we have revised it shorter and clearer. Our study did confirm a general negative impact of the pandemic which was displayed contrastingly in **Figure 2** (the original **Figure 3**), since more questioning items resulted in the downward (i.e. negative) quadrant with the average scores over 3 than in the upward (i.e. positive) quadrant. In the updated version, **Table 2** (the original **Table 3**) shows the percentages of attitudes to each question, among which the neutrality indeed occupied quite some fractions, though generally the approval accounts the most.

Comment 4: Stylistically there are many phrases that are redundant and overly

informative and can be deleted this may be due to lack of proficiency in English or translation from the Chinese as has been pointed out by other reviewers.

IN summary, the paper in its current form should not be published. It still requires significant revision to make it shorter, simpler, and simply summarized per the 4 factors or categories of the questionnaire how CRCs felt about any negative impacts of the pandemic, and what they saw as a positive effect ie improving the conduct of trials, eg. better technology, telemedicine, home visits etc., brought on by the pandemic. The only table really needed is Table 3 and possible table 4 and demographics table. The rest of it could be cut and does not contribute to the questions the authors raise.

Reply 4: We have revised the manuscript thoroughly and cut out the redundant phrases to make it shorter and simpler. A total of 515 words, and the original Table 2 and Figure 2 were deleted.

Reviewer B

Comment 1：

28. Line 50: Instead of “an ordeal” consider using “challenges”.
29. Line 226: “providing the suggestions regarding how to ensure efficient and …” remove “the”
30. Line 227: "There was 40.2% (962/2393) of the respondents…" Instead of "There was", consider “For this section,”
31. Line 234: Instead of "Besides", consider "Additionally"
32. Line 278: Instead of "A research in the US", consider "In a study conducted in the US"
33. Line 315: "Fifth, CRAs couldn’t conduct on-site monitoring as planned," recommend changing to “Fifth, CRAs could not …”
34. Line 331: "Fourth, as the number of distributed questionnaire at filled out each site was different, we …"

    Sentence is awkward, consider rewording to “Fourth, the number of distributed and completed questionnaires differed by site, we…”

Reply 1: Thanks for your advice. The grammatical issues listed in the “review-comments” were already corrected.

Changes in the text:

28. “an ordeal” was changed to “challenges” (See Page 3, Line 50)
29. This sentence was deleted.
30. “There was 40.2%...” was changed to “For section IV, 40.2%...” (See Page 8, Line 197)
31. "Besides" was changed to "Additionally" (See Page 8, Line 203)
32. "A research in the US" was changed to "In a study conducted in the US". (See Page 10, Line 244)
33. "couldn’t" was changed to "could not" (See Page 11, Line 269)
34. The sentence was modified to “Fourth, the number of distributed and completed questionnaires differed by site.” (See Page 11, Line 282)