PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	From registration, protocol to report: are COVID-19 related RCTs in mainland China consistent? A systematic review of clinical trial registry and literature
AUTHORS	Chen, Yu; Yan, Ruiqing

VERSION 1 – REVIEW

REVIEWER	Banno, Masahiro Seichiryo Hospital, Department of Psychiatry
REVIEW RETURNED	21-Oct-2021

GENERAL COMMENTS	This study aimed to perform analysis on the transparency of COVID-19 related RCTs performed in China mainland in terms of trial registry information, published trial protocols, and reports. The strength of this study was to conduct analysis using a rigorous method of systematic reviews. However, there was some weakness in this study. I attached the full-text and two supplementary files of the previous study, “Kataoka Y, Oide S, Ariie T, Tsujimoto Y, Furukawa TA. COVID-19 randomized controlled trials in medRxiv and PubMed. Eur J Intern Med. 2020 Nov;81:97-99. doi: 10.1016/j.ejim.2020.09.019.”, which they had better cite. First, the authors had better describe and cite the similar study “Kataoka Y, Oide S, Ariie T, Tsujimoto Y, Furukawa TA. COVID-19 randomized controlled trials in medRxiv and PubMed. Eur J Intern Med. 2020 Nov;81:97-99. doi: 10.1016/j.ejim.2020.09.019.” (Introduction) Second, they had better describe the interpretation of their results, compared with the results from a similar study “Kataoka Y, Oide S, Ariie T, Tsujimoto Y, Furukawa TA. COVID-19 randomized controlled trials in medRxiv and PubMed. Eur J Intern Med. 2020 Nov;81:97-99. doi: 10.1016/j.ejim.2020.09.019.” They had better compare table 1 in the previous study with their results. (Discussion) Third, they had better describe the discussion about the generalizability, Item 21 in the STROBE statement. For example, they can describe that the results may not be applicable for pre-print articles about COVID-19 because their study focused on journal articles about COVID-19. (Discussion) Fourth, they had better add the reference to the following sentences: “Principal investigators have the responsibility to ensure that the trial has been registered before first participant is enrolled and that registration record is updated timely whenever

	the trial protocol is modified; Journal editors and peer reviewers need to carefully check submitted manuscripts and corresponding registration information, demanding explanation whenever discrepancy occurs." (Discussion)

REVIEWER	DeVito, Nicholas University of Oxford Department of Primary Care Health Sciences, Primary Care Health Sciences
REVIEW RETURNED	21-Dec-2021

GENERAL COMMENTS	Many thanks for the opportunity to review this article concerning discrepancies between registrations and publications of Chinese RCTs on COVID-19. I know from my own work that this is an issue worth examining. Overall I think this is valuable and generally seems a good analysis but needs a bit of work before it is ready for publication. Introduction: I appreciate the author's attempt to make the introduction a bit punchy and less rote than standard but it reads a bit awkward right now to me. There should be a citation to support the claim of "mandatory submission of trial protocol enforced by journals with high impact factors. References for the next sentence on "suboptimal reporting" is also probably warranted. I think the authors should give themselves a bit more credit in the work that they did in the title and aim of the paper. While the outcome analysis may indeed by the primary outcome and the most consequential finding, the authors are also offering a very comprehensive view of the landscape of Chinese RCTs during COVID and I think they should emphasize that as a second main aim of the paper. Methods: Are the authors claiming they did searches for all 300+ trials in their sample in a single day? That seems incredible to me having done hundreds of these searches myself over the past two years. I think the authors need to provide more information on their search strategy in general. If they only used registration ID as a search term I'd have serious concerns about how complete their dataset is as these are often either not included or inaccessible for many of the search methods used. Do the authors have plans to make their dataset available? I don't see any reason why they couldn't and it may be useful to others. Probably no need to list all the variable again in the last paragraph of the Methods after you listed them all earlier. Results: Given that the authors used two databases for Chinese language publications, would they be able to include how many they were able to find per database, or at least per Chinese language database? Having a baseline for this reported would be of interest

	to English-only researchers like myself to know how much of the literature would only be accessible via non-English databases. Even if this is simply put in a supplement, it would be useful from a methods point of view for similar future research. The authors should represent their exclusions for duplicates in Figure 1. Related to my point below about subheadings, the first paragraph of the results is over a page long and is simply listing out proportions. This is difficult to stick with as a reader. By the end you're saying "As for…" for each new area which feels redundant. I think how this section is presented generally need to be rethought. The authors report how many trials had 0, 1, or >1 primary outcome but I think the total number of outcomes should be reported somewhere. I really don't think the authors need to cite every study they found. That really explodes the size of the citation section unnecessarily. If they simply shared their dataset, anyone interested would be able to see the exact studies linked to the extracted data. You could even list them in a supplement if need be but there really is no need to add over 40 citations to the paper. You say you excluded 5 reports because they were "case series studies or retrospective studies" Did they look like RCTs but then the reports showed they actually weren't? Were they incorrect linkages of a study to a registration? Were they other secondary analyses related to the RCTs? I don't quite understand what happened here and how it impacted the analysis. So it looks like you report your outcome measures on a "per study" level but, perhaps as a sensitivity analysis or just additional information, it would be interesting to also report your results "per outcome". Some studies have many registered primary outcomes and secondary outcomes so seeing how those were reported overall would be interesting. Did you account for people declaring their outcome switches? CONSORT allows switches so long as it is disclosed. Did the authors take this tact or simply count any switch as a switch disclosed or not? Did the authors have any protocol/publication pairs that they also could have compared? The complete journey from registration to protocol to publication may be interesting to document. Discussion: I realise the authors were not assessing publication bias, and their methods were not designed to detect it (there was not cutoff in what trials are likely to be completed before searching, for instance), but only around 10% of registered Chinese RCTs being reported it the literature seems a notable incidental finding. Might be interesting to see just how many of these say they were completed and report/discuss that as an area for future research. Starting the second paragraph of Page 15, much of the background language here and examinations of specific studies

	feels like it belongs in the Introduction as the authors aren't relating it back to their own work. It's not putting their results in context, it's just stating the existing literature. Also, the authors don't cite 2 key reviews on this topic that I believe they should review and incorporate: Jones et al on Outcome Switching: 10.1186/s12916-015-0520-3 Li et al on deviations from registrations and protocols: 10.1186/s12874-017-0465-7 As stated earlier, I disagree with the authors that the number of publications that wouldn't include a trial ID, at least not in a way the search engines used could pick-up, is a rare issues. If they included something like Google Scholar as an additional search engine which does a good job indexing full text, I might feel more comfortable, but I think this is a major limitation and give me pause about the completeness of their results. I don't understand the statement that not considering the historical changes to the registry "tended to overestimate, but not underestimate, the overall transparency." It's not immediately apparent to me why that would be so, so it should be expanded upon. Minor issues: I would replace "China mainland" with "mainland China" throughout. I would strongly recommend the authors add some sub-heading to their Methods, Results, and Discussion. This will make things much easier to follow. Page 6, lines 45-46: First sentence of third paragraph is awkward in both structure and syntax. Page 10, lines 12-13: "Illustrated" is a typo. Page 12, lines 32-33: "Until" not "till" Overall, I think the report needs a strong proof on resubmission as there is some awkward syntax and typos throughout.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1 [inc. attachments]

Dr. Masahiro Banno, Seichiryo Hospital, Nagoya University Graduate School of Medicine

Comments to the Author:

This study aimed to perform analysis on the transparency of COVID-19 related RCTs performed in China mainland in terms of trial registry information, published trial protocols, and reports. The strength of this study was to conduct analysis using a rigorous method of systematic reviews. However, there was some weakness in this study. I attached the full-text and two supplementary files of the previous study, "Kataoka Y, Oide S, Ariie T, Tsujimoto Y, Furukawa TA. COVID-19 randomized

controlled trials in medRxiv and PubMed. Eur J Intern Med. 2020 Nov;81:97-99. doi: 10.1016/j.ejim.2020.09.019.", which they had better cite.

First, the authors had better describe and cite the similar study "Kataoka Y, Oide S, Ariie T, Tsujimoto Y, Furukawa TA. COVID-19 randomized controlled trials in medRxiv and PubMed. Eur J Intern Med. 2020 Nov;81:97-99. doi: 10.1016/j.ejim.2020.09.019." (Introduction)

Thanks for the suggestion. We have cited and described the above-mentioned article in introduction. "Kataoka et al. have examined COVID-19 RCT articles in medRxiv and PubMed, revealing problems in research methods……"

Second, they had better describe the interpretation of their results, compared with the results from a similar study "Kataoka Y, Oide S, Ariie T, Tsujimoto Y, Furukawa TA. COVID-19 randomized controlled trials in medRxiv and PubMed. Eur J Intern Med. 2020 Nov;81:97-99. doi: 10.1016/j.ejim.2020.09.019." They had better compare table 1 in the previous study with their results. (Discussion)

We have cited the study and compared our results to Table 1 in the study, in Discussion section. "Previously, Kataoka et al. reported research methods and reporting problems in medRxiv and PubMed publications related to COVID-19 RCTs, and inconsistency with trial registration was identified in 62% of 13 medRxiv literatures and 30% of 16 PubMed articles……"

Third, they had better describe the discussion about the generalizability, Item 21 in the STROBE statement. For example, they can describe that the results may not be applicable for pre-print articles about COVID-19 because their study focused on journal articles about COVID-19. (Discussion)

Thanks for your suggestion. We have added discussion about limitation of generalizability, as our study results could not be reliably generalized to manuscripts posted on preprint servers and literatures in languages other than English and Chinese. "Last, our search results were limited to peer-reviewed English and Chinese literatures, and the findings could not be reliably generalized to literatures which were not peer reviewed (for example, manuscripts posted on preprint servers) or studies published in other languages."

Fourth, they had better add the reference to the following sentences: "Principal investigators have the responsibility to ensure that the trial has been registered before first participant is enrolled and that registration record is updated timely whenever the trial protocol is modified; Journal editors and peer reviewers need to carefully check submitted manuscripts and corresponding registration information, demanding explanation whenever discrepancy occurs." (Discussion)

Two publications were cited to support our assertion: 10.1186/s12874-017-0465-7 and 10.1186/s12916-015-0520-3.

Reviewer: 2

Mr. Nicholas DeVito, University of Oxford Department of Primary Care Health Sciences

Comments to the Author:

Many thanks for the opportunity to review this article concerning discrepancies between registrations and publications of Chinese RCTs on COVID-19. I know from my own work that this is an issue worth examining. Overall I think this is valuable and generally seems a good analysis but needs a bit of work before it is ready for publication.

Introduction:

I appreciate the author's attempt to make the introduction a bit punchy and less rote than standard but it reads a bit awkward right now to me.

Thanks for pointing this out. The introduction has been completely overhauled and hopefully it will read better.

There should be a citation to support the claim of "mandatory submission of trial protocol enforced by journals with high impact factors. References for the next sentence on "suboptimal reporting" is also probably warranted.

The BMJ requires authors of clinical trials to upload a protocol for their study (https://www.bmj.com/about-bmj/resources-authors/article-types). Also, JAMA requires submission of trial protocol along with manuscripts (https://jamanetwork.com/journals/jama/pages/instructions-for-authors#SecManuscriptSubmission). However, as it was difficult to define "journals with high impact factors", we decided to delete this statement. Also, we revised the manuscript to support the next sentence of "suboptimal reporting" with more study results.

I think the authors should give themselves a bit more credit in the work that they did in the title and aim of the paper. While the outcome analysis may indeed by the primary outcome and the most consequential finding, the authors are also offering a very comprehensive view of the landscape of Chinese RCTs during COVID and I think they should emphasize that as a second main aim of the paper.

Thank you so much for giving us the credit. We have specified it as a part of our aim now. "In this study, we aimed to provide a comprehensive review of characteristics of registered COVID-19 related RCTs in mainland China, and evaluate the level of transparency and selective reporting by comparing trial registration with published protocols and full reports."

Methods:

Are the authors claiming they did searches for all 300+ trials in their sample in a single day? That seems incredible to me having done hundreds of these searches myself over the past two years.

I fully understand your concern. As the COVID-19 pandemic is a major public health issue, ICTRP offered index of all COVID-19 clinical trials (https://worldhealthorg-

my.sharepoint.com/:x:/g/personal/karamg_who_int/EReItiDVLS5HuSNOVB21VRAByz3zAv-jxPoNS3cgtTywkA?rtime=Meeju1K52Ug), making it possible to identify eligible studies on one single day with Excel. Searches for literature with registration ID was carried out later, but we used the day of registration record search as cut-off date, so we thought it was equivalent to state that search for literature was performed on the same day. Now we recognize the statement was not appropriate because it may raise concerns of methodological integrity. This part of the manuscript has been revised.

I think the authors need to provide more information on their search strategy in general. If they only used registration ID as a search term I'd have serious concerns about how complete their dataset is as these are often either not included or inaccessible for many of the search methods used.

Details of search strategy are now provided in supplementary. In this revision, we also included search results from google scholar, as this search engine is more efficient in full-text search.

Do the authors have plans to make their dataset available? I don't see any reason why they couldn't and it may be useful to others.

We are happy to share our dataset with anyone interested in this topic. A copy of it will be submitted along with the revised manuscript.

Probably no need to list all the variable again in the last paragraph of the Methods after you listed them all earlier.

The last paragraph of the Methods was edited to avoid such repetition.

Results:

Given that the authors used two databases for Chinese language publications, would they be able to include how many they were able to find per database, or at least per Chinese language database? Having a baseline for this reported would be of interest to English-only researchers like myself to know how much of the literature would only be accessible via non-English databases. Even if this is simply put in a supplement, it would be useful from a methods point of view for similar future research.

Evaluation of databases was beyond the scope of this study, so we decided not to report number of search results per database formally in the manuscript. For your reference, 24 entries of publications were found in Wanfangdata, while 46 entries were found in CNKI. One Chinese language publication was found uniquely in CNKI. So, we suggest CNKI should be searched if you want to review literatures in Chinese language.

The authors should represent their exclusions for duplicates in Figure 1.

The Figure 1 has been updated and exclusions for duplications are now presented.

Related to my point below about subheadings, the first paragraph of the results is over a page long and is simply listing out proportions. This is difficult to stick with as a reader. By the end you're saying "As for…" for each new area which feels redundant. I think how this section is presented generally need to be rethought.

We have added subheadings to the Results section. Also, the paragraph was revised to make it easier to follow.

The authors report how many trials had 0, 1, or >1 primary outcome but I think the total number of outcomes should be reported somewhere.

The total number of registered primary outcomes was 1048. We have revised the Results section and Table 1 to include this information.

I really don't think the authors need to cite every study they found. That really explodes the size of the citation section unnecessarily. If they simply shared their dataset, anyone interested would be able to see the exact studies linked to the extracted data. You could even list them in a supplement if need be but there really is no need to add over 40 citations to the paper.

Thanks for the advice. Citations of included literatures are now provided in a supplementary file.

You say you excluded 5 reports because they were "case series studies or retrospective studies" Did they look like RCTs but then the reports showed they actually weren't? Were they incorrect linkages of a study to a registration? Were they other secondary analyses related to the RCTs? I don't quite understand what happened here and how it impacted the analysis.

While it might sound confusing, the situation actually took place. Let's take ChiCTR2000031955 for an example. (Screenshots taken on 4-Mar-2022)

Study for prevention of novel coronavirus pneumonia (COVID-19) in high risk population by Chinese medicine

download

Registration number:	ChiCTR2000031955		
Date of Last Refreshed on:	2020-09-21		
Date of Registration:	2020-04-16		
Registration Status:	Prospective registration		
Public title:	Study for prevention of novel coronavirus pneumonia (COVID-19) in high risk population by Chinese medicine		
English Acronym:			
Scientific title:	Study on the prevention of COVID-19 with Chinese medicine regulating constitution		
The registration number of the Partner Registry or other register:			
Applicant:	Lingru Li	Study leader:	Lingru Li
Applicant telephone:	+86 13426096071	Study leader's telephone:	+86 13426096071

Target disease:	Novel Coronavirus Pneumonia (COVID-19)		
Target disease code:			
Study type:	Interventional study		
Study phase:	0		
Objectives of Study:	In this study, the high-risk population with a history of COVID-19 was selected as the study object.Selecting positive nucleic acid or IgM or IgG of new coronavirus as the outcome.The effect of the preventive measures of traditional Chinese medicine was observed by basic and traditional Chinese medicine, and by tracking, follow-up, antibody and nucleic acid detection.At the same time, we conducted a survey on the awareness and needs of covid-19 prevention for many occupational groups.		
Description for medicine or protocol of treatment in detail:			
Study design:	Parallel		
Inclusion criteria	(1) novel coronavirus pneumonia has not been stopped since the outbreak of COVID-19; (2) the co worked personnel were diagnosed as COVID-19 or asymptomatic infection or SARS-CoV-2 IgM positive within 14 days; (3) the detection of nucleic acid, IgM and IgG of SARS-CoV-2 was negative within 1 weeks; (4) between 18-70 years old; (5) voluntarily accepted clinical observation and signed informed consent.		
Exclusion criteria:	(1) Patients diagnosed with COVID-19; (2) positive nucleic acid test; (3) positive IgM of SARS-CoV-2; (4) positive IgG of SARS-CoV-2; (5) pregnant or preparing pregnant women, lactating women, men preparing for pregnancy; (6) major diseases such as malignant tumor, end-stage renal disease, serious Alzheimer's disease; (7) those who have participated in or are participating in other clinical trials within one month; (8) Mental disorders can not express their own feelings; (9) there are other circumstances that are not suitable for inclusion in the study.		
Study execute time:	From2020-04-01To 2020-12-31	Recruiting time:	From2020-04-01To 2020-12-31

Interventions:	Group:	control group	Sample size:	2380
	Intervention:	General basic epidemic prevention measures	Intervention code:	
	Group:	sachet group	Sample size:	476
	Intervention:	General basic epidemic prevention measures + Traditional Chinese medicine sachet	Intervention code:	
	Group:	Oral and nasal spray group	Sample size:	476
	Intervention:	General basic epidemic prevention measures + Oral and nasal spray	Intervention code:	
	Group:	Oral Chinese medicine group	Sample size:	476
	Intervention:	General basic epidemic prevention measures + Traditional Chinese medicine for epidemic prevention in high risk groups	Intervention code:	

In the trial registration record, the study leader specified that the study design was parallel interventional study, with information regarding eligibility and each arm provided. However, the report citing this registration number did not look like RCT.

frontiers in Public Health

ORIGINAL RESEARCH
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Effect of Knowledge/Practice of COVID-19 Prevention Measures on Return-to-Work Concerns; Attitudes About the Efficacy of Traditional Chinese Medicine: Survey on Supermarket Staff in Huanggang, China

Lingru Li[1†], Yue Meng[1,2†], Ji Wang[1†], Ying Zhang[2], Yong Zeng[3], Huiqun Xiao[4], Jiangming He[5], Zhenquan Liu[1], Shujuan Hou[1], Tianxing Li[1,2], Jingbo Qin[1,2], Yini Fang[1,2], Wenqian Guo[1,2], Li'an Liu[6], Hui Luo[7], Yingshuai Li[1], Yanfei Zheng[1*] and Qi Wang[1*]*

[1] National Institute of Traditional Chinese Medicine Constitution and Preventive Treatment of Diseases, Beijing University of Chinese Medicine, Beijing, China, [2] College of Chinese Medicine, Beijing University of Chinese Medicine, Beijing, China, [3] Health Committee of Huanggang, Huanggang, China, [4] Huangzhou Maternity and Child Health Care Hospital, Huanggang, China, [5] Public Health Department, Huangzhou General Hospital of Huanggang, Huanggang, China, [6] College of Chinese Classics, Beijing University of Chinese Medicine, Beijing, China, [7] Institute for Tibetan Medicine, China Tibetology Research Center, Beijing, China

Objective: The objective of this study was to investigate how knowledge and practice of coronavirus disease 2019 (COVID-19) prevention measures affected concerns about returning to work among supermarket staff. Attitudes about the ability of traditional Chinese medicine (TCM) to prevent COVID-19 were also assessed.

Methods: A cross-sectional study was conducted in Huanggang, Hubei Province, China from April 23 to 25, 2020. Participants were invited to fill out an electronic questionnaire on their cell phones.

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Specialty section:
This article was submitted to Infectious Diseases - Surveillance, Prevention and Treatment, a section of the journal

Clinical Trial Registration: http://www.chictr.org.cn/, identifier: ChiCTR2000031955.

Keywords: COVID-19, traditional Chinese medicine, prevention, resuming work, knowledge and practice, concern, Hubei

Incorrect linkage was not likely because the first author of the paper was exactly the study leader in trial registration record. Also, the report did not look like a secondary analysis to RCT. All excluded reports had similar problems. We chose to exclude them from the analysis because they fundamentally diverged from the original design, so it was not necessary to make further comparisons.

So it looks like you report your outcome measures on a "per study" level but, perhaps as a sensitivity analysis or just additional information, it would be interesting to also report your results "per outcome". Some studies have many registered primary outcomes and secondary outcomes so seeing how those were reported overall would be interesting.

We agree that reporting the results on "per outcome" level would be interesting. However, as is shown in the dataset and Table 1, many of the included registrations had high numbers of registered outcomes (13 studies even registered more than 10 outcomes) and most of these outcomes are different. We would need a very long table to present these studies on "per outcome" level and it might exceed the page limit of the journal. So, we decided not to report per outcome analysis formally. Since our dataset is available along with the manuscript, readers who are interested in one or more outcomes can perform their own analysis with no difficulty.

Did you account for people declaring their outcome switches? CONSORT allows switches so long as it is disclosed. Did the authors take this tact or simply count any switch as a switch disclosed or not?

Thanks for the remind. We carefully checked all publications where discrepancies in primary outcome were identified. None of these publications was found to disclose their switch in outcomes.

Did the authors have any protocol/publication pairs that they also could have compared? The complete journey from registration to protocol to publication may be interesting to document.

This is definitely an interesting idea. We compared the protocols with corresponding full reports and the results were added to the Result section as well as Table 3.

Discussion:

I realise the authors were not assessing publication bias, and their methods were not designed to detect it (there was not cutoff in what trials are likely to be completed before searching, for instance), but only around 10% of registered Chinese RCTs being reported it the literature seems a notable incidental finding. Might be interesting to see just how many of these say they were completed and report/discuss that as an area for future research.

Thanks for the advice. We recognize that 10% is a quite low publish rate, but when we update the search results to Feb-2022 according to the editor's demand, we found around 25% of registered

trials had published a report. So the publication rate was raising as time went by. On the other hand, the public health policy of China demanded COVID-19 patients be transferred to designated quarantine site, and some of the trials could not be finished because of this reason. So we could not confidently say that the current rate of publication was a result of publication bias. We added some sentences in Discussion to remind the readers that publication bias was potentially present and more work needs to be done to address the issue.

Starting the second paragraph of Page 15, much of the background language here and examinations of specific studies feels like it belongs in the Introduction as the authors aren't relating it back to their own work. It's not putting their results in context, it's just stating the existing literature. Also, the authors don't cite 2 key reviews on this topic that I believe they should review and incorporate:

Jones et al on Outcome Switching: 10.1186/s12916-015-0520-3

Li et al on deviations from registrations and protocols: 10.1186/s12874-017-0465-7

Thanks for the advice. This part has been moved to introduction. Also, the two reviews listed above have been cited and are mentioned in introduction.

As stated earlier, I disagree with the authors that the number of publications that wouldn't include a trial ID, at least not in a way the search engines used could pick-up, is a rare issues. If they included something like Google Scholar as an additional search engine which does a good job indexing full text, I might feel more comfortable, but I think this is a major limitation and give me pause about the completeness of their results.

We fully understand your concern. However, the approach of using trial ID as search keyword was not changed. Because without the trial ID, it would be very difficult, if not impossible, to set a standard and determine if the publication was from a certain registered trial or not. To ensure the completeness of our search results, we also searched Google Scholar in this revision, since it is more powerful in full-text searching. We also edited to avoid the statement "However, considering the requirement for RCT registration is common in journals, we considered these publications to be of a small number (if existed at all)". Instead, we specified that our results could not be generalized to reports that don't cite any trial registration ID.

I don't understand the statement that not considering the historical changes to the registry "tended to overestimate, but not underestimate, the overall transparency." It's not immediately apparent to me why that would be so, so it should be expanded upon.

Because registrations are sometimes modified to meet what is reported to fabricate consistency. This phenomenon was discussed by Jones et al.in 10.1186/s12916-015-0520-3. We have revised the discussion to expand upon this point and made it more understandable. "……this approach tended to overestimate, but not underestimate, the overall transparency, in that registrations are often modified after trial completion to display false consistency with publications."

Minor issues:

I would replace "China mainland" with "mainland China" throughout.

Done.

I would strongly recommend the authors add some sub-heading to their Methods, Results, and Discussion. This will make things much easier to follow.

Thanks for the advice. Sub-headings were added to Methods and Result. Also, we revised the structure of Discussion to make it easier to follow.

Page 6, lines 45-46: First sentence of third paragraph is awkward in both structure and syntax.

This sentence was replaced when revising the introduction.

Page 10, lines 12-13: "Illustrated" is a typo.

The typo was corrected.

Page 12, lines 32-33: "Until" not "till"

Corrected accordingly.

Overall, I think the report needs a strong proof on resubmission as there is some awkward syntax and typos throughout.

We have thoroughly revised the manuscript and rewritten most of it. However, as we are not native English speakers, there might be certain syntax errors and typos remain undetected. We appreciate if you could point out any issues in writing and thank you for helping us improving the quality of the manuscript.

VERSION 2 – REVIEW

REVIEWER	Banno, Masahiro Seichiryo Hospital, Department of Psychiatry
REVIEW RETURNED	20-Apr-2022

GENERAL COMMENTS	The author thoroughly responded to the comments. I have no additional comments.

REVIEWER	DeVito, Nicholas University of Oxford Department of Primary Care Health Sciences, Primary Care Health Sciences

REVIEW RETURNED	25-Apr-2022

GENERAL COMMENTS	Many thanks for the opportunity to review a revision of this paper. I think the authors have addressed many of my comments. I offer a few additional points and, at the author's request, some copy editing suggestions. For the "Publications from Registered Trials" section, please state in the text what the most common risks of bias in the literature were. When I suggested "per outcome" reporting, I did not mean to report the fate of each individual outcome. I meant adding something like "Overall we checked XX registered outcomes, including XX primary and XX secondary outcomes; xx (xx%) primary outcomes were reported correctly and xx (xx%) secondary outcomes were reported correctly." Something like that would add more welcome detail to your results rather than solely reporting data at the level of the whole study. It's good that you checked all the papers to see if any outcome changes were declared and found none. Please just state that you did this and what was found this in the manuscript. In your response to my prior review you said that without an ID "it would be very difficult, if not impossible, to set a standard and determine if the publication was from a certain registered trial or not." I strongly disagree with this. It should be very possible to do this. In fact, that's part of the entire point of registration. This is routinely done in similar work. To show a few examples: https://www.bmj.com/content/344/bmj.d7292 https://www.sciencedirect.com/science/article/pii/S0895435618310631?via%3Dihub https://publications.aap.org/pediatrics/article/149/4/e2021052557/185586/Early-Discontinuation-Results-Reporting-and In the first paragraph of your Discussion providing an overview of your results, I'd mention something about your Risk of Bias findings as well here. I think you need to revisit how you discuss this as a limitation. It's not simply that you can't generalize it. Copy edits (page and line numbers refer to those generated in the proof): Page 5, lines 36-40: "However, the overall transparency of RCTs remains suboptimal,..." Page 5 lines 54/55: Start a new paragraph at "To ensure" Page 5 lines 54/55: Spell out ICMJE acronym Page 6 lines 9-13: "Prospective registration is a powerful tool in reducing selective reporting as it reflects…" Page 6 lines 38-52: "Numerous clinical trials have been registered and published to address scientific questions regarding the prevention, treatment, and prognosis of the disease. Kataoka et al examined…" Page 8 Lines 44-46: New paragraph after the parenthetical and then re-do that sentence as: "We extracted registration ID, date of registration…and other relevant information from registration records.") First sentence in "Characteristics of registered trials" section on page 11: "Among all included studies, 303 (73.0%)...in ISRCTN and 243 (58.6% were registered before the date of first enrollment."

	Page 11 lines 27/28: “At the time of the most recent update…” Page 11 Lines 32-36: “The median estimated enrollment…” Page 12 Lines 23/24: add a semicolon between “were published” and “8 reports” Page 12 Lines 45/46: “did not specify who was masked in the text or registration.” Next sentence: “There were 11 (55%) discrepancies between the primary outcomes in the registrations and the protocols. This included introducing new primary outcomes….” Next sentence “Only 2 (10.0%) protocols were consistent in all domains.” Page 16, starting on lines 27/28: I would make the sentence “These results revealed compromised” a new paragraph and also please revise this sentence as it is currently a bit awkwardly constructed and long.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Dr. Masahiro Banno, Seichiryo Hospital, Nagoya University Graduate School of Medicine

Comments to the Author:

The author thoroughly responded to the comments. I have no additional comments.

We deeply appreciate your effort in helping us to improve the quality of this manuscript with your valuable suggestions.

Reviewer: 2

Mr. Nicholas DeVito, University of Oxford Department of Primary Care Health Sciences

Comments to the Author:

Many thanks for the opportunity to review a revision of this paper. I think the authors have addressed many of my comments. I offer a few additional points and, at the author’s request, some copy editing suggestions.

For the “Publications from Registered Trials” section, please state in the text what the most common risks of bias in the literature were.

Thanks for the advice. Now the top three most common risk of bias are specified in manuscript text.

When I suggested “per outcome” reporting, I did not mean to report the fate of each individual outcome. I meant adding something like “Overall we checked XX registered outcomes, including XX primary and XX secondary outcomes; xx (xx%) primary outcomes were reported

correctly and xx (xx%) secondary outcomes were reported correctly." Something like that would add more welcome detail to your results rather than solely reporting data at the level of the whole study.

Sorry for the misunderstanding. I have updated the manuscript text to report the total number of (primary/secondary) outcomes of all included registrations. "The 415 trials registered a total of 2951 outcomes, including 1048 primary outcomes and 1903 secondary outcomes……Among the 183 primary outcomes of the 74 registrations, 59 (32.2%) were correctly reported."

It's good that you checked all the papers to see if any outcome changes were declared and found none. Please just state that you did this and what was found this in the manuscript.

Thanks for the advice. I have added a few sentences in the results to specify this.

In your response to my prior review you said that without an ID "it would be very difficult, if not impossible, to set a standard and determine if the publication was from a certain registered trial or not." I strongly disagree with this. It should be very possible to do this. In fact, that's part of the entire point of registration. This is routinely done in similar work. To show a few examples:

https://www.bmj.com/content/344/bmj.d7292

https://www.sciencedirect.com/science/article/pii/S0895435618310631?via%3Dihub

https://publications.aap.org/pediatrics/article/149/4/e2021052557/185586/Early-Discontinuation-Results-Reporting-and

I totally understand your concern. In general, I think the core of the question is how should we set the standard. I've pasted some of the lines regarding literature searching from the articles above:

"If no citation was provided we manually searched Medline with the NCT number. If we did not identify a publication, we searched Medline again with the intervention, condition studied, and name of the principal investigator (when provided in response to the "study official" field). The articles identified through the search were matched to the corresponding trial (when possible) using the following information from ClinicalTrials.gov: detailed description, location, enrolment, study start and completion dates, and primary and secondary outcome measures."(https://www.bmj.com/content/344/bmj.d7292

)

"(1) The clinical trial identifier (NCT ID or DRKS ID) was entered on ClinicalTrials.gov/DRKS.de, and the earliest result publication linked in the registry was searched and checked if it was indeed a result publication for the trial. Reviews and other background literature were excluded. (2) The clinical trial identifier was entered on PubMed. (3) Google Scholar and (if no hit was found) Web of Science were searched by subsequently entering the following search terms: clinical trial identifier, official title, brief title (if available), intervention name, and principal investigator or primary sponsor.

The first two result pages were screened. Publications were matched using a list of explicit criteria (i.e., study design, intervention, and outcomes). All criteria needed to be met to be counted as a match."(https://publications.aap.org/pediatrics/article/149/4/e2021052557/185586/Early-Discontinuation-Results-Reporting-and)

As you can see, when these researchers failed to identify a publication with the trial registration ID, they chose to match published literatures with other information, like detailed description, location, outcome measures, primary sponsors, interventions and many other domains. However, to me this method sounds a bit subjective/arbitrary, and might cause problems in practice. For example, should we demand exact match of such information? How much difference (usually there is some level of difference) can we tolerate before we conclude they are different studies? You might have note that the even the two examples above used different standards (*detailed description, location, enrolment, study start and completion dates, and primary and secondary outcome measures* in the first article OR *official title, brief title (if available), intervention name, and principal investigator or primary sponsor* in the second article), making this approach seem less robust. The second reason was that I wanted to be 100% certain. Selective reporting of outcomes in RCT is a severe "accusation" (if I may say so), and I only want to make this judgement with definitive evidence: a trial registration ID cited by the publication. Without registration ID, it is always possible that registrations could be linked to wrong publications. If this happens, the principal investigator might feel frustrated when reading this article.

In the first paragraph of your Discussion providing an overview of your results, I'd mention something about your Risk of Bias findings as well here. I think you need to revisit how you discuss this as a limitation. It's not simply that you can't generalize it.

I have added a few lines in the first paragraph of discussion to summarize risk of bias findings. The latter part of the comment is a little bit confusing for me (seems some sentences are missing). But I guess the comment is regarding the last paragraph of discussion where I discussed the limitation and generalizability of the study. So, I revised the paragraph to further elaborate these topics.

Copy edits (page and line numbers refer to those generated in the proof):

Page 5, lines 36-40: "However, the overall transparency of RCTs remains suboptimal,..."

Revised accordingly.

Page 5 lines 54/55: Start a new paragraph at "To ensure"

Revised accordingly.

Page 5 lines 54/55: Spell out ICMJE acronym

The ICMJE acronym was spelt out at its first occurrence.

Page 6 lines 9-13: "Prospective registration is a powerful tool in reducing selective reporting as it reflects…"

Revised accordingly.

Page 6 lines 38-52: "Numerous clinical trials have been registered and published to address scientific questions regarding the prevention, treatment, and prognosis of the disease. Kataoka et al examined…"

Revised accordingly.

Page 8 Lines 44-46: New paragraph after the parenthetical and then re-do that sentence as: "We extracted registration ID, date of registration…and other relevant information from registration records.")

Revised accordingly.

First sentence in "Characteristics of registered trials" section on page 11: "Among all included studies, 303 (73.0%)...in ISRCTN and 243 (58.6% were registered before the date of first enrollment."

Revised accordingly.

Page 11 lines 27/28: "At the time of the most recent update…"

Revised accordingly.

Page 11 Lines 32-36: "The median estimated enrollment…"

Revised accordingly.

Page 12 Lines 23/24: add a semicolon between "were published" and "8 reports"

Revised accordingly.

Page 12 Lines 45/46: "did not specify who was masked in the text or registration."

Revised accordingly.

Next sentence: "There were 11 (55%) discrepancies between the primary outcomes in the registrations and the protocols. This included introducing new primary outcomes…."

Revised accordingly.

Next sentence “Only 2 (10.0%) protocols were consistent in all domains.”

Revised accordingly.

Page 16, starting on lines 27/28: I would make the sentence “These results revealed compromised” a new paragraph and also please revise this sentence as it is currently a bit awkwardly constructed and long.

A new paragraph was made and the sentence was re-constructed. “These results revealed compromised transparency in COVID-19 related RCT reporting in mainland China, and also suggested the presence of selective reporting in RCTs in other fields of study. Such findings are noteworthy especially for peer-reviewers and journal editors, as compromised transparency might undermine the value of these trials.”