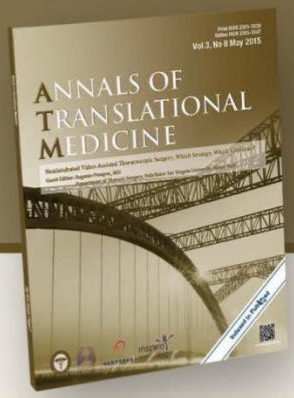
ANNALS OF TRANSLATIONAL MEDICINE



Peer Review File

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Reviewer A:

The authors studied an interesting topic, assessing the methodological rigorousness and feasibility of clinical studies registered in Clinical Trials Registry Platforms. Below are my comments for it.

1. The paper is poorly written. Language editing is necessary for revisions.

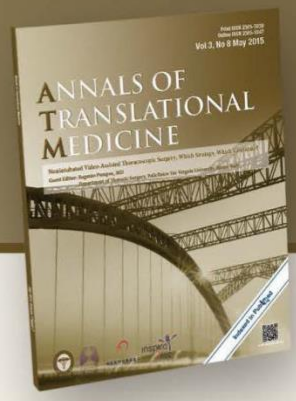
Reply 1: Thanks to the reviewer's suggestions, we have made the language editing. And the editorial certificate has been uploaded.

2. Clinical studies search is limited, resulting in possible selection bias. ChiCTR, ClinicalTrials. gov and other popular platforms should also be searched.

Reply 2: Thanks to the reviewer's valuable suggestions. According to WHO's instructions, there was 11 international clinical trials registry platforms in the WHO, see details in https://www.who.int/ictrp/network/primary/en/. We searched clinical studies from the WHO search portal, including ChiCTR, ClinicalTrials. gov and other popular platforms' registration information. We believe that our search results are not limited.

3. For assessing different types of clinical studies, existing "risk of bias" assessments should be adopted. The current assessment is very crude and inaccurate. For example, Jadad or Cochrane risk of bias for RCT, QUADAS-2 for diagnostic tests, and NOS for observational comparative studies.

Reply 3: Thanks for your advice. Your suggestion is very good, and it should be advocated to evaluate the quality of the research protocols as well as the included literature in the systematic review. However, the purpose of the study protocol registration is to publish the information such as study type, interventions and outcomes on the Internet before the study, so as to prevent the violation of the study protocol in the process of the study. Only part of the summary information is provided in the registration process of the research scheme, and the information is not very comprehensive. When the Cochrane risk of bias tool was used, the bias due to missing outcome data included in the tool could not be carried out in the study protocol. At present, there is no quality evaluation standard or quality evaluation guideline for clinical study registration protocol



in the academic world, which is also one of the contents that future clinical research methodologists need to study.

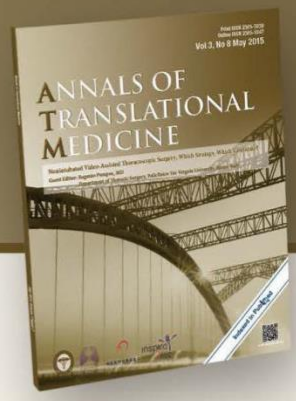
4. The current assessment for feasibility is also very questionable. The rationale must be clearly clarified.
Reply 4: Thanks for your advice. There is currently no unified standard for the assessment of research feasibility. We comprehensively evaluated the feasibility of the study in terms of the location of the study site, the sample size of the study, the number of officially announced COVID-19 patients in the area, and the number of research centers, et.al.

5. Please update the search of registered studies when submitting this revision, you may have known that some studies have been suspended or canceled due to difficulties in recruiting.
Reply 5: Thanks for your advice. This study focused on the registration of covid-19 clinical studies in China, and the retrieval date was March 10, 2020. Since then, the covid-19 outbreak in China has been basically under control, with the daily number of new patients in single digits, the number of inpatients required for research has been sharply reduced, and the number of registered studies has barely increased. Unfortunately, the registrants of the study did not promptly announce the suspension or cancellation of the study on the website, we cannot currently obtain the exact cancellation status at this time.

Reviewer B:
1. In line 74-75, you may be mixed the virus"SARS-CoV-2" and the disease "COVID-19". We should describe them clearly.
Reply 1: Thank you for your suggestion. We noticed the difference between viruses and diseases. We put them together to try to search the registration studies as thoroughly as possible. Thanks again for your advice.

2. In line 78, some asymptomatic infection cases are not "patients", they are just "COVID-19 cases".
Reply 2: Thank you for your valuable suggestion. We have modified this problem in the manuscript.

3. In line 90，the "broke out" often is used to the war or something, the "outbreak" is better?



Please mention the word choice in this manuscript.

Reply 3: Thank you for your valuable suggestion. We have modified this problem in the manuscript.

4. In Table 3, the first column is unclear (location problem), and the percentage is not easy to understand for the common readers. Could you give more information to the readers in the note or in the title row?

Reply 4: Thank you for your valuable suggestion. We have added more information in the note.

Reviewer C:

1. The research is of great significance.
2. It is suggested to list the main results and add tables.
3. The conclusion shows that there are some problems. It is suggested to analyze the causes briefly and put forward the solutions.

Reply 1: Thank you for your valuable suggestion. Indeed, as you said, our conclusion has not been well summarized, and we have revised the conclusion based on your suggestions.

Reviewer D:

In this manuscript by Tao et al., the authors reviewed and summarized the registration protocols for clinical research of the novel coronavirus disease in China. They evaluated the scientific and feasibility of these studies. The manuscript is well written but there are a number of issues that dampen enthusiasm for the study in its current form.

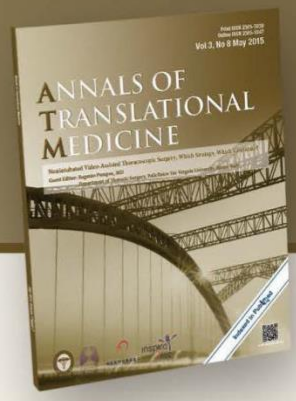
1. The authors briefly described the process and results of data extraction (in the methods and results). A flow diagram showing the details will be much better here.

Reply 1: Thank you for your valuable suggestion. We have added a flow diagram in the revision.

2. In the background, some information already well known about the COVID-19 should be less emphasized. Subsequently, as for the clinical trials for COVID-19 registered recently, more literature should be fully reviewed and introduced here.

Reply 2: Thank you for your valuable suggestion. We have revised the background based on your suggestions.

3. As for the therapeutic trials, the possible reasons for the limitation of the feasibility should be



well discussed. More tables (or supplements) should be displayed.

Reply 3: Thank you for your advice. In the current registration platform, the registration information about the feasibility is limited, such as whether the unit specifically carries out the research conditions, the method of generating random programs, the implementation conditions of the research, and the degree of cooperation of the research objects. Different clinical research registration platforms may need to strengthen the accuracy review of the completeness of the registration scheme. At the same time, this is also one of the shortcomings for this study, which we have already explained in the discussion.

Reviewer E:

This study aims to summarize and analyze the novel coronavirus pneumonia (COVID-19) related clinical trials. However, I have to reject it because of the following concerns.

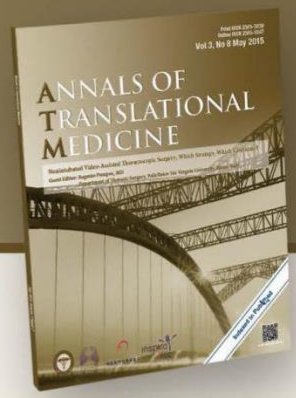
Comments:

1) In order to further standardize the clinical research work of listed drugs during the epidemic of COVID-19, the State Council issued the Circular on standardizing Medical institutions to carry out Clinical Research on COVID-19 Drug treatment. For the clinical research that violates the relevant regulations and requirements, and has obvious toxic and side effects or no clear therapeutic effect, it should be terminated. Could the authors comment on that? In the present study, how many studies have been terminated?

Reply 1: Thank you for your advice. a) We believe that the state council and the ministry of science and technology should standardize the management of the interventional research on covid-19 to avoid the duplication of the same drug and the same protocol, as well as the ethical issues arising from the exposure of patients to unsafe drug environments. b) We cannot get the specific number of studies terminated at present, because the registration information on the platform will lag.

2) According to current reports, the drugs to treat COVID-19 include anti-AIDS drugs, interferon, glucocorticoids, traditional Chinese medicine, stem cells and so on. In this study, what kinds of drugs are included in interventional or therapy studies, please clarify?

Reply 2: Thanks for your suggestions. The purpose of this study is to evaluate the registered studies from the perspective of the scientificity and feasibility of clinical research. The springboard is whether the clinical research registration method is reasonable and feasible. It is not the purpose of this study as to what kind of therapeutic drugs or interventions taking in therapeutic studies. However, the reviewers made very good suggestions, and we can consider



summarizing them in other follow-up studies.

3) The topic is not so novel.
4) The method of this paper is too simple.
Reply 3&4: Regarding the topic and method, the reviewers did not propose specific amendments. We have not made significant changes to this issue.

5) It is noted that your manuscript needs careful editing by someone with expertise in English editing paying particular attention to English grammar, spelling, and sentence structure so that the goals and results of the study are clear to the reader.
Reply 5: Thanks to the reviewer's suggestions, we have made the language editing. And the editorial certificate has been uploaded.