medRxiv preprint doi: https://doi.org/10.1101/2020.03.23.20041533. The copyright holder for this preprint (which was not peer-reviewed) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
All rights reserved. No reuse allowed without permission.

Core Outcome Set for Traditional Chinese and Western Medicine Clinical Trials of COVID-19

Ruijin Qiu,[1] Chen Zhao,[2] Tengxiao Liang,[3] Xuezeng Hao,[4] Ya Huang,[1] Xiaoyu Zhang, [1] Zhao Chen, [1] Xuxu Wei,[1] Mengzhu Zhao,[5] Changming Zhong,[1] Jiayuan Hu,[1] Min Li,[6] Songjie Han,[1] Tianmai He,[1] Jing Chen,[7]* Hongcai Shang[1]*

1. Key Laboratory of Chinese Internal Medicine of Ministry of Education and Beijing, Dongzhimen Hospital, Beijing University of Chinese Medicine.
2. Institute of Basic Research In Clinical Medicine, China Academy of Chinese Medical Sciences
3. Emergency Department, Dongzhimen Hospital, Beijing University of Chinese Medicine.
4. Cardiology Department, Dongzhimen Hospital, Beijing University of Chinese Medicine.
5. First Teaching Hospital of Tianjin University of Traditional Chinese Medicine.
6. Beijing University of Chinese Medicine Third Affiliated Hospital
7. Baokang Affiliated Hospital of Tianjin University of Traditional Chinese Medicine, Tianjin China.

Abstract

Background: There are a large number of clinical trials for COVID-19. But the heterogeneity of outcomes may result in some clinical trials cannot be compared or merged. It is emergency to develop a core outcome set (COS) for clinical trials.

Methods: A preliminary list of outcomes were developed after a systematic review of protocols of clinical trials for COVID-19. Then two rounds of Delphi survey was conducted. The stakeholders included traditional Chinese medicine (TCM) experts, Western medicine experts, nurses and the public. Patients with confirmed COVID-19 were also invited to participate in a questionnaire with simple language. Frontline clinicians (including TCM and Western medicine clinicians), nurse, methodologist, evidence-based medicine researcher and staff from Chinese Clinical Trials Registry participate in video conference to vote.

Results: 97 eligible study protocols were identified from 160 clinical trials. 76 outcomes were identified from TCM clinical trials, 126 outcomes were identified from Western medicine clinical trials. In the end, 145 were included in the first round of Delphi survey. In the end, a COS was developed for clinical trials of TCM and Western medicine was developed. The COS includes Clinical outcome (recovery/ improvement/ progression/ death), etiology (SARS-CoV-2 nucleic acid tests, viral load), inflammatory factor (CRP), vital signs (temperature, respiration), blood and lymphatic system outcomes (lymphocyte, virus antibody), respiratory outcomes (chest imaging, blood oxygen saturation, PaO2/FiO2, arterial blood gas analysis, mechanical ventilation, oxygen intake, pneumonia severity index), clinical efficacy (rate of preventing mild to moderate type patients from progressing to severe type), symptoms (clinical symptom score). The outcomes were

medRxiv preprint doi: https://doi.org/10.1101/2020.03.23.20041533. The copyright holder for this preprint (which was not peer-reviewed) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
All rights reserved. No reuse allowed without permission.

recommended according to different types of disease. Outcome measurement instrument/definition were also recommended.

Conclusion: A COS for COVID-19 may improve consistency of outcome reporting in clinical trials, which may help identify valued interventions after comparing different trials when the researchers report the same outcomes.

1. INTRODUCTION

Since the first case of novel coronavirus pneumonia was reported in Wuhan, China, it is rapidly spread in China and other countries. The disease was temporarily named as 2019 novel coronavirus (2019-nCoV) on January 12, 2020, and it was officially named as coronavirus disease (COVID-19) on February 11, 2020 by the World Health Organization (WHO).

Until 0000 hours, March 18, 2020, 191 127 cases have been reported to the World Health Organization (WHO), 7 807 of them have died [1]. In China, up to 0000 hours, March 18, 2020, according to the website of the National Health Commission of the People's Republic of China (NHC-PRC), 80 928 confirmed cases have been reported from all areas of China [2].

Now COVID-19 is a globe threat, so that its outbreak has been declared as a pandemic on March 11, 2020 by WHO. There are significant knowledge gaps in the epidemiology, transmission dynamics, investigation tools and management of COVID-19 [3], and no specific drug or vaccine has been approved to treat it, so it is still a challenge for clinicians and researchers all over the world.

Since the first clinical trial of COVID-19 was registered on January 23, 2020 [4], an increasing number of clinical trials of COVID-19 have been registered, including traditional Chinese medicine and Western medicine clinical trials. Until March 18, 2020, 585 protocols were searched form all the databases of International Committee of Medical Journal Editors (ICMJE)-accepted clinical trial registry platforms.

In previous research, we found that there were many problems of protocols of clinical trials of COVID-19, such as unclear objectives of design, the heterogeneity of outcomes choosing, the small sample of population [5], all of these problems may reduce the value of clinical trials. Whilst, clinicians' understanding for the disease characteristics is changing when they treated much more patients. The Diagnosis and treatment plan of corona virus disease 2019 is also keeping changing. We believe that some inappropriate outcomes may be chosen by researchers. To improve the consistency of outcomes and include more clinical trials in systematic reviews, it is

medRxiv preprint doi: https://doi.org/10.1101/2020.03.23.20041533. The copyright holder for this preprint (which was not peer-reviewed) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
All rights reserved. No reuse allowed without permission.

urgent to develop a core outcome set (COS) for COVID-19.

A COS is an agreed standardised set of outcomes that should be measured and reported, as a minimum, in all clinical trials in specific areas of health or health care [6]. When researchers reported outcomes in a COS, they also can report other outcomes.

The scope of the COS are as follows:

1. Population with confirmed COVID-19, including mild type, ordinary type, severe type and critical type.
2. The interventions include traditional Chinese medicine (TCM) and Western medicine.
3. The COS will be applied in randomized controlled trials (RCTs) and observational studies.

2. METHODS

2.1 Registry

This COS has been registered in Core Outcome Measures in Effectiveness Trials (COMET) database [7]. This research was conducted and reported following COS-STAndards for Development (COS-STAD) [8] and COS-STAndards for Reporting (COS-STAR) [9].

2.2 Participants

Steering group

A steering group was formed by TCM expert, a Western medicine expert, a methodologist, a nurse and a statisticians. They conducted the research protocol, made decisions when there was confusion and attended the consensus meeting to facilitate the development of the COS.

Stakeholders in Delphi survey

The stakeholders in Delphi survey included TCM experts (clinicians and researchers), Western medicine experts (clinicians and researchers), nurses, patients and the public.

COVID-19 is a new, urgent infectious disease. In China, a large number of clinicians are trained to face the emergency, no matter if they are in the frontline. More than 40 000 clinicians and nurses from other areas of China to Hubei province to support the local medical system. Not all of these clinicians and nurses are in the field of respiratory and critical medicine. To obtain perspectives on a larger scale, we used snowball sampling to extend the sample size. We invited members from *Clinical Research Information Association of China Information Association for Traditional Chinese Medicine and Pharmacy* to participate in the Delphi survey and asked them to send the questionnaire to their colleagues.

We believe that the perspectives of patients and public are important. So we send the questionnaire

medRxiv preprint doi: https://doi.org/10.1101/2020.03.23.20041533. The copyright holder for this preprint (which was not peer-reviewed) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
All rights reserved. No reuse allowed without permission.

to social media (Wechat, Tencent) to invite the public to participate in.

To obtain patients' perspectives, the clinicians of Dongzhimen Hospital who were in frontline invited and helped patients who consented to participate in survey to complete questionnaire.

Stakeholders in consensus meeting

The stakeholders in consensus meeting included TCM and Western medicine clinicians, nurse, methodologist, evidence-based medicine researcher and staff from Chinese Clinical Trials Registry.

2.3 Information Sources

All the databases of International Committee of Medical Journal Editors (ICMJE)-accepted clinical trial registry platforms [10] were considered. Search terms for ChiCTR included the following: "COVID-19," "2019-novel Corona Virus (2019-nCoV)," "Novel Coronavirus Pneumonia (NCP)," "Severe Acute Respiratory Infection (SARI)," and "Severe Acute Respiratory Syndrome - Corona Virus- 2 (SARS-CoV-2)." Search terms for Netherlands National Trial Register (NTR) included "nCoV," "Coronavirus," "SARS," "SARI," "NCP," and "COVID." Search terms for other databases included "2019-nCoV OR Novel Coronavirus OR New Coronavirus OR SARS-CoV-2 OR SARI OR NCP OR Novel Coronavirus Pneumonia OR COVID-19 OR Wuhan pneumonia." The search was conducted on February 14, 2020. The details of inclusion criteria, exclusion criteria, study identification, date extraction, dropped/combined outcomes were described in the systematic review of protocols of clinical trials COVID-19 [11].

2.4 Consensus Process

In this research, two rounds of Delphi survey for professionals and the public as well as one round of Delphi survey for patients were conducted. After the Delphi survey were completed, a consensus meeting was conducted to determine the final COS.

Delphi survey

The questionnaire for professionals and the public was sent by smartphone. It included individual outcome in different outcome domains and scoring. In the end of the questionnaire, there were two open-ended questions: ① what outcomes do you think are important but not included in the questionnaire? ② What is your opinion on this questionnaire?

The questionnaire for patients was sent by smartphone, too. It included outcomes/outcome domains that were easily understand by patients. The patients were asked to vote which outcomes/outcome domains are important to them. There was one open-ended question: what

medRxiv preprint doi: https://doi.org/10.1101/2020.03.23.20041533. The copyright holder for this preprint (which was not peer-reviewed) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
All rights reserved. No reuse allowed without permission.

outcomes do you think are important but not included in the questionnaire?

Outcome Scoring

The questionnaire for professionals and the public was used a 9-point scoring system, which has been used in previous COS [12, 13]. **A** score of '1–3' means the outcome is not important to include in the COS, '4–6' means the outcome is important but not critical to include in the COS and '7–9' means the outcome is critical to include in the COS. The outcome that was scored less than 7 by 50% or less participants in all of the stakeholders were removed from the next consensus process. The outcomes recommended by participants were added in the second round of Delphi survey after discussing by the steering group.

Consensus Definition

For the professionals and the public's Delphi survey, the consensus definitions are as following:

1. consensus in: 70% or more of the participants in all stakeholders scored outcome as 7–9, and <15% of the participants in all stakeholders scored the outcomes as 1–3.
2. consensus out: 50% or less of the participants in TCM experts and Western medicine experts scored the outcome as 7–9.
3. no consensus: anything else.

The patients' voice should be considered totally. So for the patients' survey, the consensus definitions are as following:

Outcomes that were voted by more than 50% patients.

For the consensus meeting, the consensus definitions are as following:

1. Consensus in: outcomes that were voted by 70% or more participants.
2. Consensus out: outcomes that were voted by less than 70% participants.

Consensus meeting

The consensus meeting was held by teleconference. The contents of the consensus meeting covers

1. reporting background and methods of the research;
2. reporting the results of Delphi survey of professionals and the public, and the results of patients' questionnaire;
3. discussing the candidate outcomes and their instruments/definition.
4. Voting on the outcomes and reaching a consensus.

2.5 Ethics and Consent

medRxiv preprint doi: https://doi.org/10.1101/2020.03.23.20041533. The copyright holder for this preprint (which was not peer-reviewed) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
All rights reserved. No reuse allowed without permission.

The entire project was belong to a clinical trial of COVID-19, which h was approved by the Ethics Committee of Dongzhimen Hospital, Beijing University of Chinese Medicine (DZMEC-KY-2020-09). Because of the special circumstance, participants who completed the questionnaire were believed consent.

3. RESULTS

A total of 160 protocols from 19 different clinical trials registry platforms were searched. After reading the titles and study details, 63 non-relevant or ineligible study protocols were excluded. In the end, 97 eligible study protocols were included from the ChiCTR and ClinicalTrials.gov. 34 clinical trials were for TCM therapy and 63 clinical trials were for Western medicine therapy. All of clinical trials will be conducted in China. These clinical trials include 75 RCTs (53 for Western medicine and 22 for TCM) and 22 non-RCTs (10 for Western medicine and 12 for TCM). For 34 protocols of TCM clinical trials, there were 76 individual outcomes from 16 outcome domains after merging and grouping outcomes. For 63 protocols of western medicine clinical trials, there were 126 individual outcomes from 17 outcome domains after merging and grouping. The list of outcomes can be obtained from [11] There were more than 40 duplicated outcomes between the TCM and Western medicine clinical trial protocols.

After removing duplicated outcomes, we developed the first round of Delphi survey. After reviewed by the steering group, a total of 145 were included in the questionnaire.

3.1 Round 1 of Delphi survey

We had incentive measures to improve response of Delphi survey (randomized rewards after completing and submitting the questionnaire). The planned time for the round 1 of Delphi survey was from March 4, 2020 to March 12, 2020. Until March 9, 2020, a total of 176 participants completed the questionnaire. After reviewing, 51 questionnaire were invalid. On March 8 and March 9, 2020, no more than 5 questionnaire completed per day, and almost all of them were invalid.

The majority of invalid questionnaire were completed by the public, who finished within 5 min (it was impossible for people who were unfamiliar with COVID-19 to complete), or who chose the same score for all of the outcomes. After discussing with steering group, we decided to stop the Delphi survey.

In the end, 125 valid questionnaire were analysed. The characteristics of participants in the round 1 of Delphi survey is shown in Table 1. The number of outcomes that achieved consensus and no consensus in different stakeholders are shown in Table 2. The list of outcomes is shown in Supplement 1.

medRxiv preprint doi: https://doi.org/10.1101/2020.03.23.20041533. The copyright holder for this preprint (which was not peer-reviewed) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
All rights reserved. No reuse allowed without permission.

Table 1 The characteristic of participants in the round 1 of Delphi survey

Characteristics	No. of population
Identification	
TCM experts	76 (76/125, 60.8%)
Western medicine experts	16 (16/125, 12.8%)
Nurses	6 (6/125, 4.8%)
Public	27 (27/125, 21.6%)
Frontline working	
Yes	48 (48/125, 38.4%)
No	77 (77/125, 61.6%)
Designing or Participating in research of COVID-19	
TCM research	32 (32/125, 25.6%)
Western medicine research	6 (6/125, 4.8%)
None	87 (87/125, 69.6%)

Only 15 (15/125, 12%) participants were from Hubei province. But the IP that the electronic questionnaire obtained showed that 30 (30/125, 24%) participants were in Hubei province. The regions of participants are shown in Figure 1.

More than 20 participant provide outcomes or significant propose for the round 1 of Delphi survey. After discussing with steering group, 6 of them were added to round 2 of Delphi survey. No "consensus out" outcomes by all of the stakeholders. The steering group discussed the results of round 1 of Delphi survey, they believed that for nurses and the public, it is too hard to give up some outcomes because of the knowledge gap. They decided that all of the outcomes entered in the round 2 of Delphi survey.

Table 2 The number of outcomes that achieved consensus and no consensus in round 1 of Delphi survey

Stakeholders	Consensus in	Consensus out	No consensus
TCM experts	34	50	61
Western medicine experts	50	47	48
Nurses	126	2	17
Public	106	0	39

3.2 Round 2 of Delphi survey

According to the significant propose from the participants in the round 1 of Delphi survey, the steering group decided to add more personal information. To reduce invalid questionnaire, the participants would get a randomized reward if the completed questionnaire was considered as valid. The participants were also asked if they agreed to be mentioned in acknowledge section

medRxiv preprint doi: https://doi.org/10.1101/2020.03.23.20041533. The copyright holder for this preprint (which was not peer-reviewed) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
All rights reserved. No reuse allowed without permission.

when the research was published. CT of hip and MRI of hip were grouped as hip imaging. There were total 150 individual outcomes in the round 2 of Delphi survey.

The feedback from participants in round 1 of Delphi survey showed that it is difficult to score for some outcomes. So in the round 2 of Delphi survey, the participants had chance to choose "unclear" for any outcomes that were difficult to determine. The median score of each outcomes from each stakeholder group were shown in the round 2 of Delphi survey. The steering group would like a larger number of participants could participate in the Delphi survey, so that the questionnaire were sent to potential participants (no matter if they attend the round 1 of Delphi survey) and asked them to invite their colleagues who were interested in the research. The round 2 of Delphi survey was conducted from March 11, 2020 to March 13 2020.

A total of 110 questionnaire were completed. 7 of them were invalid. 103 valid questionnaires were analysed. The characteristics of participants in the round 2 of Delphi survey is shown in Table 3.

Table 3 The characteristic of participants in the round 1 of Delphi survey

Characteristics	**No. of population**	**Characteristics**	**No. of population**
Identification		Frontline working	
TCM experts	60 (60/103, 58.3%)	Yes	42 (42/103, 40.8%)
Western medicine experts	22 (22/103, 21.4%)	No	61 (61/103, 59.2%)
Nurses	13 (13/103, 12.6%)	Designing or Participating in research of COVID-19	
Public	8 (8/103, 7.8%)	TCM research	25 (25/103, 24.3%)
Education background		Western medicine research	2 (2/103, 1.9%)
Doctor	35 (35/103, 34%)	None	76 (76/103, 73.8%)
Master	50 (50/103, 48.5%)	Participating in round 1 of Delphi survey	
Undergraduate	14 (14/103, 13.6%)	Yes	26 (26/103, 25.2%)
Others	4 (4/103, 3.9%)	No	77 (77/103, 74.8%)
Professional qualification			
Senior	30 (30/103, 29.1%)		
Intermediate	46 (46/103, 44.7%)		
Junior	17 (17/103, 16.5%)		
None	10 (10/103, 9.7%)		

The IP that the electronic questionnaire obtained showed that 28(28/103, 27.2%) participants were in Hubei province. The regions of participants are shown in Figure 2. The number of outcomes that achieved consensus and no consensus in different stakeholders are shown in Table 4.The list of outcomes is shown in Supplement 2.

Table 4 The number of outcomes that achieved consensus and no consensus in round 2 of Delphi

medRxiv preprint doi: https://doi.org/10.1101/2020.03.23.20041533. The copyright holder for this preprint (which was not peer-reviewed) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
All rights reserved. No reuse allowed without permission.

survey

Stakeholders	Consensus in	Consensus out	No consensus
TCM experts	91	35	24
Western medicine experts	57	44	49
Nurses	141	0	9
Public	104	31	15

After the results of round 2 of Delphi survey reviewed by the steering group, the outcomes achieved “consensus out” by TCM experts and Western medicine experts were excluded. The outcomes achieved “consensus in” between all of the stakeholders were grouped and presented according to the classification of disease type and interventions. They were presented to consensus meeting participants with “no consensus outcomes” before the consensus meeting was held.

3.3 Patients’ survey

From the response of nurses and the public, we found that it is difficult for them to score because they may misunderstand for the terminology. So we developed a simple questionnaire with understanding language for patients. There were 43 outcomes/outcome domains in the questionnaire. The list of outcomes is in Supplement 3. The patients were recruited by the frontline clinicians in our team on March 12, 2020 and March 13, 2020. In the end, 10 cured patients agreed to participate in the survey. They were asked to choose what outcomes are important to themselves. The characteristics of the patients are shown in the Table 5.

Table 5. The characteristics of the patients in the survey

Characteristics	No. of population	Characteristics	No. of population
Gender		Type of disease	
Male	6 (6/10, 60%)	Mild	4 (4/10, 40%)
Female	4 (4/10, 40%)	Ordinary	4 (4/10, 40%)
Age		Severe	0
≤18	0	Critical	2 (2/10, 20%)
18-29	3 (3/10, 30%)	Type of therapy	
30-39	5 (5/10, 50%)	TCM	0
40-49	1 (1/10, 10%)	Integrated TCM and Western medicine	9 (9/10, 90%)
50-59	1 (1/10, 10%)	Western medicine	1 (1/10, 10%)

There were 7 outcomes were chosen by 50% or more patients (chest imaging, pulmonary function, respiratory symptom, fever, SARS-CoV-2 nucleic acid tests, recovery rate, psychological outcomes). All of these outcome were presented in the consensus meeting to experts.

medRxiv preprint doi: https://doi.org/10.1101/2020.03.23.20041533. The copyright holder for this preprint (which was not peer-reviewed) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
All rights reserved. No reuse allowed without permission.

3.4 Consensus meeting

The consensus meeting was held on March 18, 2020. It was a video conference. 6 frontline clinicians (1clinician is from Western medicine hospital, 5 clinicians are from TCM hospital) and 1 frontline nurse, 1 methodologist and 1 researcher who participate in the design of clinical trials of COVID-19 were invited to attend the consensus meeting. The participants are from Shanghai (1), Beijing (5), Tianjin (2) and Guizhou (1). All of them were voting participants. All of the clinicians and nurse have working experience in Hubei province after COVID-19 outbreak. Two additional participants (one coordinator and one staff from Chinese Clinical Trial Registry) attended the meeting but did not participate in the discussion or voting.

After reporting the results of Delphi survey and patients' survey, participants discussed some outcomes they believed that should measure or should not measure in clinical trials. After discussing, the voting participants were invited to vote what outcomes should be included in COS of COVID-19. The outcomes that voted by 70% or more participants were included in the COS. The voting results is shown in Supplement 4. The COS of COVID-19 is in Table 4.

4. DISCUSSION

4.1 Limitations

There are several limitations in the study. First, due to the infectious of COVID-19, patients and the public did not participate in the design and the development of preliminary list of outcomes. Second, the preliminary list of outcomes were developed from protocols of clinical trials, when there were knowledge gaps in the prevalence, therapy, prognosis, clinical characteristics of COVID-19. So the COS must be updated in the future. Third, the number of patients may be insufficient. All of them are from Hubei province. The perspectives may not reflect different region characteristic. Fourth, almost all of stakeholders were from China. Though 1 participants in round 1 of Delphi survey was from Canada, the one's opinion reflected the perspective of Chinese, because the questionnaire was in Chinese.

4.2 Conclusions

This COS was rapidly and rigorously conducted and report for the emergency in a special environment. It can be used in any type of disease, any intervention any type of design. There is a specific outcome for TCM clinical trials, which is clinical symptom score. Researchers can measure it according to different TCM syndromes. For some individuals, there are several measurements, because no evidence to show which measurement is the best one. We hope researchers of clinical trials can use this COS to reduce heterogeneity of outcome reporting. Furthermore, it is useful to help decision makers to approve new medicines for COVID-19 when researchers report important outcomes. However, researchers can report other outcomes according to their purpose of research.

medRxiv preprint doi: https://doi.org/10.1101/2020.03.23.20041533. The copyright holder for this preprint (which was not peer-reviewed) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
All rights reserved. No reuse allowed without permission.

Author Approval

All authors read and approved the final manuscript.

Funding

This work was supported by the National High-level Personnel of Special Support Program (W02020052).

Competing interests

The authors declare that there is no conflict of interest.

Data sharing statement

The data is from public database and does not include identifiable patient data.

Acknowledgements

Reference

1. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200318-sitrep-58-covid-19.pdf?sfvrsn=20876712_2

2. http://www.nhc.gov.cn/xcs/yqfkdt/202003/e644c2fc18b4448db7ed4b30f68b91a6.shtml

3. Khot WY, Nadkar MY. The 2019 Novel Coronavirus Outbreak - A Global Threat. J Assoc Physicians India. 2020, 68(3):67-71.

4. Huang C. A randomized, open-label, blank-controlled trial for the efficacy and safety of lopinavir-ritonavir and interferon-alpha 2b in hospitalization patients with novel coronavirus pneumonia (COVID-19). http://www.chictr.org.cn/showproj.aspx?proj=48684.

5. Zhang X, Zhao C, Sun Y, et al. [Promoting the Establishment of a Collaboration and Sharing Mechanism for Clinical Trials: perspectives from the Outbreak of COVID-19]. Journal of Traditional Chinese Medicine :1-12[2020-03-21]. http://kns.cnki.net/kcms/detail/11.2166.r.20200219.1436.002.html.

6. http://www.comet-initiative.org/

7. Available: http://www.comet-initiative.org/Studies/Details/1507 (Accessed 14 Feb 2020)

8. Kirkham JJ, Davis K, Altman DG, Blazeby JM, Clarke M, Tunis S, et al. Core outcome set-standards for development: the COS-STAD recommendations. PLoS Med. 2017,14(11):e1002447.

9. Kirkham JJ, Gorst S, Altman DG, Blazeby JM, Clarke M, Devane D, et al. Core outcome set-standards for reporting: The COS-STAR Statement. PLoS Med. 2016;13(10):e1002148.

10. ICMJE. Which trials registries are acceptable to the ICMJE? http://www.icmje.org/about-icmje/faqs/clinical-trials-registration/ (Accessed 14 Feb 2020)

11. Qiu R, Wei X, Zhao M, Zhong C, Zhao C, Hu J, et al. Outcome reporting from protocols of clinical trials of Coronavirus Disease 2019 (COVID-19): a review. DOI: https://medrxiv.org/cgi/content/short/2020.03.04.20031401v1

12. Qiu R, Li M, Zhang X, Chen S, Li C, Shang H. Development of a core outcome set (COS) and

medRxiv preprint doi: https://doi.org/10.1101/2020.03.23.20041533. The copyright holder for this preprint (which was not peer-reviewed) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
All rights reserved. No reuse allowed without permission.

selecting outcome measurement instruments (OMIs) for non-valvular atrial fibrillation in traditional Chinese medicine clinical trials: study protocol. Trials. 2018,19(1):541.

13. Qiu R, Zhong C, Han S, He T, Huang Y, Guan M, et al. Development of a core outcome set for myocardial infarction in clinical trials of traditional Chinese medicine: a study protocol. BMJ Open. 2019, 9(12):e032256.

Table 6 The COS of COVID-19

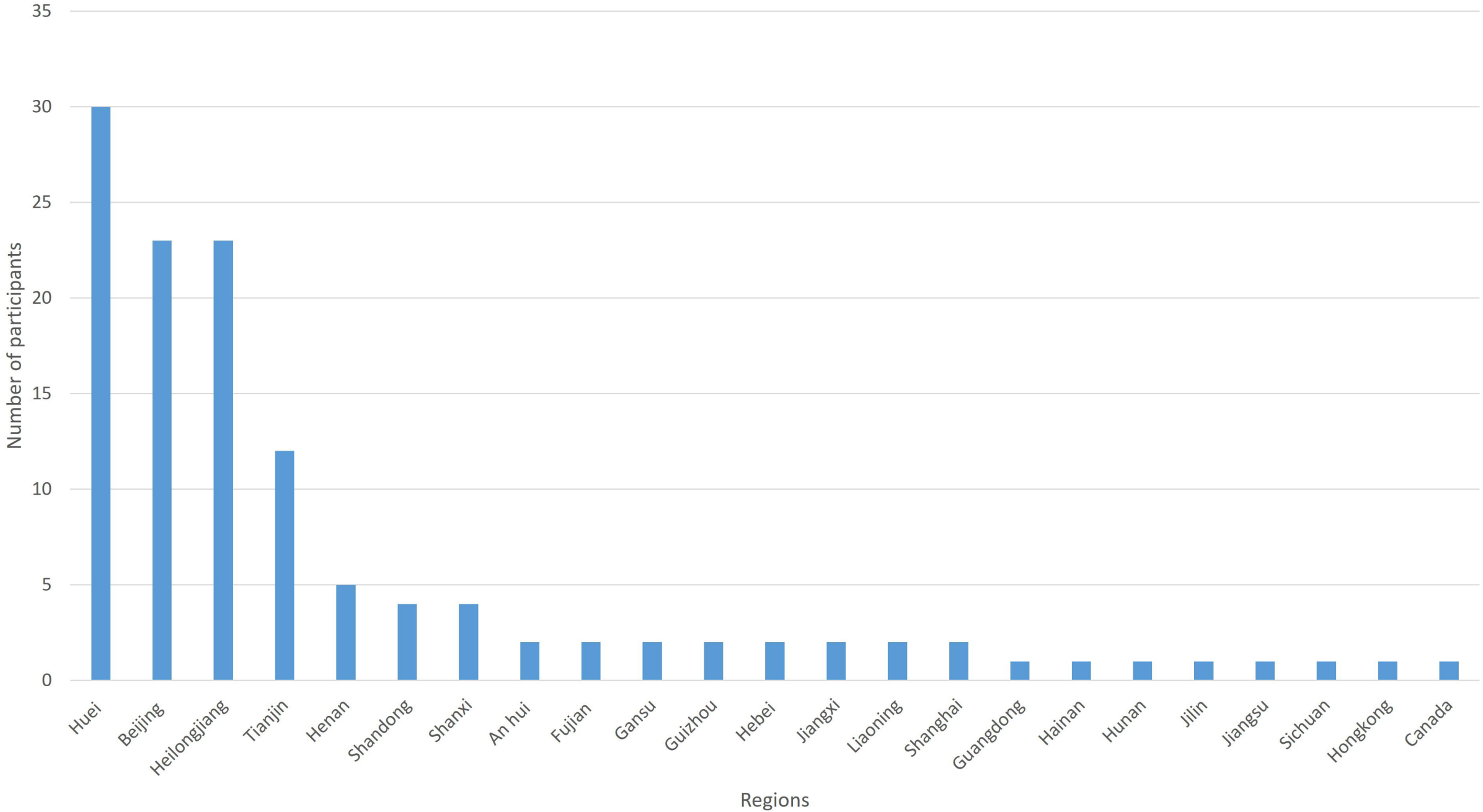
Outcome domain	Outcome	Outcome measurement instruments/definition	Type of disease				Interventions	
			Mild	Ordinary	Severe	Critical	TCM	Western medicine
Clinical outcome	Recovery/ improvement/ progression/ death	a. Recovery: recovery time or recovery rate b. Improvement: from severe type to ordinary type c. Progression: rate and time of progressing to the severe or critical type d: Death: mortality	√	√	√	√	√	√
Etiology	SARS-CoV-2 nucleic acid tests	a. Proportion of patients with negative SARS-CoV-2 b. Time taken by SARS-CoV-2 RNA to become negative c. Declining speed of SARS-CoV-2	√	√	√	√	√	√
	Viral load		√	√	√	√	√	√
Inflammatory factor	CRP	CRP level and time of CRP recovery	√	√	√	√	√	√
Vital signs	Temperature	Rate of fever and clearance time of fever	√	√	√	√	√	√
	Respiration	a. The incidence of dyspnea b. Improvement of respiratory rate c. Time to normal respiratory rate d. Clearance rate of dyspnea		√	√	√	√	√
Blood and lymphatic system outcomes	Lymphocyte	Lymphocyte count	√	√	√	√	√	√
	Virus antibody	Virus antibody level	√	√	√	√	√	√
	Chest imaging	Inflammation absorption or time to recovery	√	√	√	√	√	√
	Blood oxygen	Blood oxygen saturation level or improvement rate	√	√	√	√	√	√

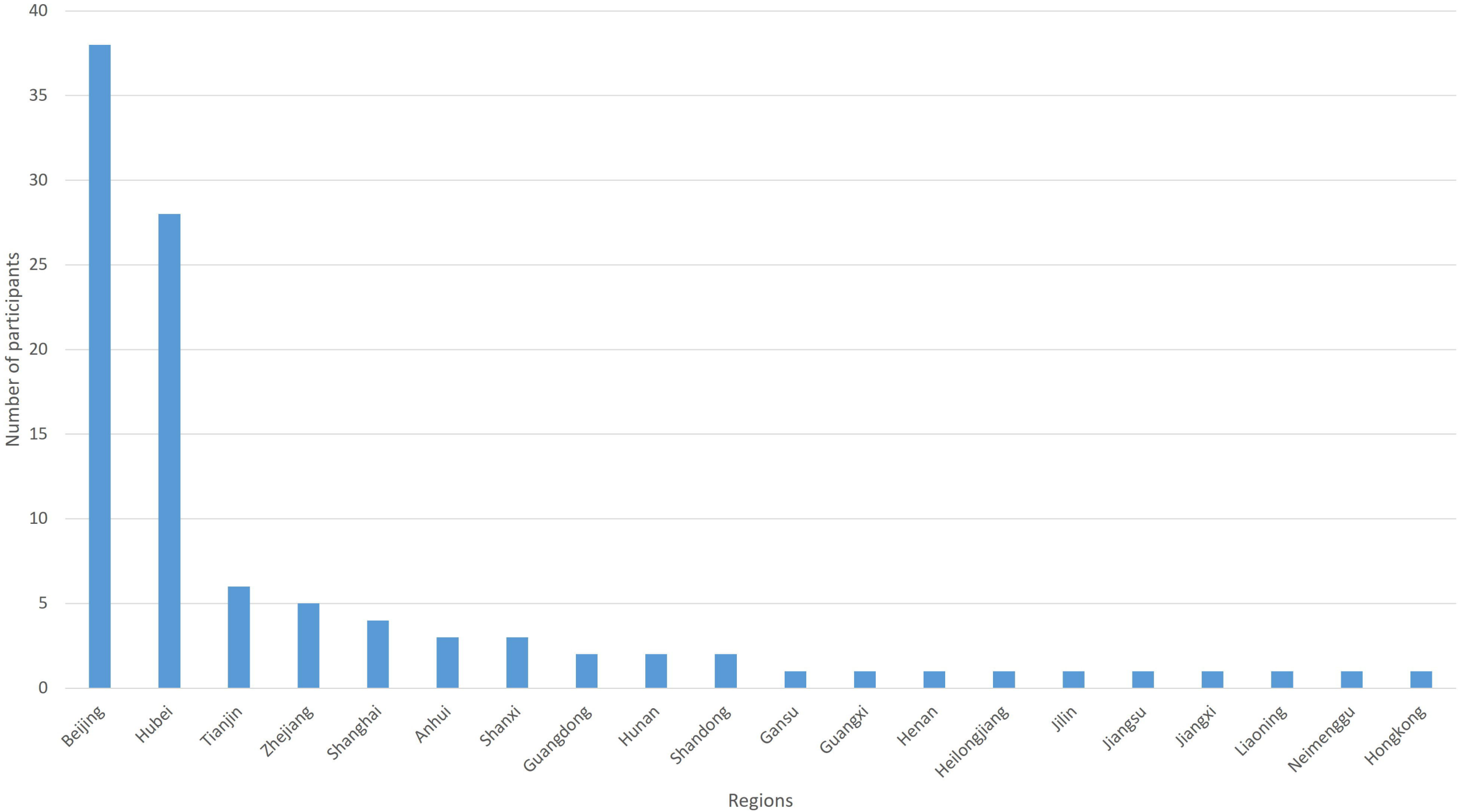
medRxiv preprint doi: https://doi.org/10.1101/2020.03.23.20041533. The copyright holder for this preprint (which was not peer-reviewed) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
All rights reserved. No reuse allowed without permission.

Outcome domain	Outcome	Outcome measurement instruments/definition	Type of disease					Interventions
	saturation							
	PaO2/FiO2	Arterial blood gas analysis	√	√	√	√	√	√
	Arterial blood gas analysis		√	√	√	√	√	√
Respiratory outcomes	Mechanical ventilation	a. Duration of mechanical ventilation b. Frequency of requirement for mechanical ventilation c. Rate of mechanical ventilation				√	√	√
	Oxygen intake	a. Duration of supplemental oxygenation b. Frequency of requirement for supplemental oxygen c. Rate of supplemental oxygen requirement c. Oxygen intake methods		√	√	√	√	√
	Pneumonia severity index			√	√	√	√	√
Clinical efficacy	Rate of preventing mild to moderate type patients from progressing to severe type		√	√			√	√
Symptoms	Clinical symptom score		√	√	√	√	√	

medRxiv preprint doi: https://doi.org/10.1101/2020.03.23.20041533. The copyright holder for this preprint (which was not peer-reviewed) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
All rights reserved. No reuse allowed without permission.

medRxiv preprint doi: https://doi.org/10.1101/2020.03.23.20041533. The copyright holder for this preprint (which was not peer-reviewed) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
All rights reserved. No reuse allowed without permission.


35
30
25
20
15
10
5
0
Number of participants
Huei
Beijing
Heilongjiang
Tianjin
Henan
Shandong
Shanxi
An hui
Fujian
Gansu
Guizhou
Hebei
Jiangxi
Liaoning
Shanghai
Guangdong
Hainan
Hunan
Jilin
Jiangsu
Sichuan
Hongkong
Canada
Regions


40
35
30
25
20
15
10
5
0
Number of participants
Beijing
Hubei
Tianjin
Zhejiang
Shanghai
Anhui
Shanxi
Guangdong
Hunan
Shandong
Gansu
Guangxi
Henan
Heilongjiang
Jilin
Jiangsu
Jiangxi
Liaoning
Neimenggu
Hongkong
Regions