Review Protocol

Objective

To evaluate the transparency of COVID-19 related RCT reporting in mainland China through comparing trial registrations with publications.

Ethics Approval

The study is exempt from ethics approval because only publicly available databases and registries will be used as data source. No human participants and animal subjects will be involved in the study.

Eligibility Criteria for Registrations

Registered randomized controlled trials related to prevention, treatment or prognosis of COVID-19 in mainland China will be included. Case report, case series, cross-sectional study, case-control study, cohort study, survey and other observational studies will be excluded. Studies will be excluded if randomization is not used or without a control group. For multicenter trials, all registered centers must be within mainland China to meet eligibility criteria.

Data Source and Search Strategy for Registrations

International Clinical Trials Registry Platform (ICTRP), Chinese Clinical Trial Registry (ChiCTR), ClinicalTrials.gov (NCT), the ISRCTN registry (ISRCTN) and EU Clinical Trial Register (EUCTR) will be searched. For ICTRP and ChiCTR, complete lists of COVID-19 clinical trial registrations will be downloaded. Filters will be applied to identify studies which meet eligibility criteria. For NCT, the page listing COVID-19 studies will be accessed and eligible studies will be identified using website filters and the map panel. ISRTCN and EUCTR will be manually searched with the keywords “COVID-19”, “Sars-Cov-2”, “covid19” and “2019-nCov”. All search results will be examined manually to ensure their eligibility.

Data Source and Search Strategy for Publications

PubMed, Embase, Cochrane Library, CNKI.net and Wanfangdata will be searched using trial

registration IDs of eligible trials. Only publications in English and Chinese will be included.

Data Extraction

From trial registrations, registration ID, date of registration/first submission, date of last update, date of first enrollment, scientific/official titles, primary purpose, recruitment status, intervention, source of funding, primary sponsor, ethics approval information, setting, randomization and masking methods, inclusion and exclusion criteria, primary/secondary outcomes and time frame of outcome measurement will be extracted.

From publications, title, estimated/actual enrollment, center name, inclusion/exclusion criteria, masking, primary outcomes and time frame of outcome measurement will be extracted.

Risk of Bias Assessment

Risk of bias assessment will be performed with RoB 2 for full reports of trials.

Data Synthesis

The screening process of registrations will be presented with a flow diagram. Characteristics of included trial registrations will be presented with descriptive statistics, in count and proportion for categorical data, or with median, max value, minimum value and interquartile range for quantitative data. The trend of registrations from early 2020 will be presented with line chart. Estimated/actual enrollment, center name, inclusion/exclusion criteria, masking method, primary outcome and time frame of primary outcome measurement information extracted from trial registrations and publications will be compared, and count and percentage of inconsistency within each domain will be presented. Risk of bias assessment results will be presented with figure.

Review Process

The screening process, data extraction, risk of bias assessment, registration-publication comparison will be independently completed by two reviewers, and the results will be compared. Disagreements will be resolved through discussion.

Protocol Amendments

May-2021

For trials which are repeatedly registered on two or more clinical trial registries, if they have any publication, the registration not cited by publication will be excluded from the analysis. If all or none of the repeated registrations are cited by publications, the record with most recent update time will be included in the analysis. Repeated registrations will be detected by reviewing the title, objective and name of principle investigator.

Publications citing an eligible trial registration identifier but declared to be of non-RCT design will be excluded from the analysis. The number of such publications will be reported.

Feb-2022

Google Scholar will be searched for publications to ensure the completeness of search results.

Information extracted from protocols and corresponding full reports will also be compared to evaluate protocol-report consistency.

Search Strategy

Clinical Trial Registration

International Clinical Trials Registry Platform (ICTRP, https://www.who.int/clinical-trials-registry-platform) was accessed and a list of COVID-19 trials (updated on 22-Jan-2022) in csv format was downloaded. The file was opened with Microsoft Excel. The following filters were applied to "Study type" column: "intervention" "interventional" "interventional clinical trial of medicinal product" "interventional study" "treatment study" "prevention" "prognosis study". The following filters were applied to "Countries" column: "China" "China?" "Chinese" "The People's republic of China". From the "Study design" column, "Case study" "Case-control study" "Cohort study" "Cross-sectional" studies, non-randomized/quasi-randomized studies and studies with single arm or historical control were excluded.

Chinese Clinical Trial Registry (ChiCTR, http://www.chictr.org.cn/enIndex.aspx) was accessed and index of studies of COVID-19 (updated on 22-Dec-2021) in csv format was downloaded. The ChiCTR index was then mapped to the ICTRP COVID-19 trials list to identify any studies listed in ChiCTR but not in ICTRP. Studies registered after 22-Dec-2021 were screened manually.

List of COVID-19 related studies from ClinicalTrials.gov was accessed (https://clinicaltrials.gov/ct2/results?cond=COVID-19). The filter "Study type - Interventional (Clinical Trial)" was applied, and studies registered in mainland China were identified using the "On Map" panel. The listed studies were downloaded and compared with ICTRP records in case of omissions.

In ISRCTN registry (ISRCTN, https://www.isrctn.com/) and EU Clinical Trial Register (EUCTR, https://www.clinicaltrialsregister.eu/), the registry was searched with the following search string: "covid19 or COVID-19 or SARS-Cov-2 or 2019-nCov", and the country of recruitment was set to "China" and "Outside EU/EEA", respectively. Search results were also compared with ICTRP records.

All above-mentioned registries were accessed on 1-Feb-2022.

Publication

Search was performed in PubMed (https://pubmed.ncbi.nlm.nih.gov/), Embase (https://www.embase.com/), Cochrane Library (https://www.cochranelibrary.com/search), Google Scholar (https://scholar.google.com/), CNKI.net (https://www.cnki.net/) and Wanfangdata (https://www.wanfangdata.com.cn/) using the trial registration number with exact match method.

Literatures

This systematic review identified 85 reports[1-85] and 20[86-105] protocols from 415 clinical trial registration records. For further analysis, 8 reports[78-85] were excluded because non-RCT study design was adopted.

1. Cao B, Wang Y, Wen D, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. *N Engl J Med.* 2020;382(19):1787-1799.
2. Che Y, Liu X, Pu Y, et al. Randomized, double-blinded and placebo-controlled phase II trial of an inactivated SARS-CoV-2 vaccine in healthy adults. *Clin Infect Dis.* 2020.
3. Chen J, Liu D, Liu L, et al. A Pilot Study of Hydroxychloroquine in Treatment of Patients with Moderate COVID-19. *Journal of Zhejiang University (Medical Sciences).* 2020;49(2).
4. Chen J, Xia L, Liu L, et al. Antiviral Activity and Safety of Darunavir/Cobicistat for the Treatment of COVID-19. *Open Forum Infect Dis.* 2020;7(7):ofaa241.
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Med (N Y). 2020;1(1):105-113 e104.

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double-blind, placebo-controlled, phase 1/2 clinical trial. *The Lancet Infectious Diseases*. 2021;21(6):803-812.

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