



Editorial

The ethics of COVID-19 clinical trials: New considerations in a controversial area



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In December 2019, coronavirus disease 2019 (COVID-19) was discovered in Wuhan, Hubei province, China, which has caused severe illness and death.¹ China is the most populous country in the world with a population of 1.428 billion.² With 11 million inhabitants, Wuhan is the largest transportation hub in central China, which is known as Chicago of China.^{2,3} China has taken a series of public health interventions to control the epidemic.³ The outbreak of COVID-19 has become a public health event of global concern.⁴ Due to its relatively high infectivity, the rapid progression of the disease and the lack of clear and effective treatment, it has caused international anxiety.^{4,5} In fact, it has also caused illness in a significant proportion of exposed medical personnel.⁶ Since identification of COVID-19 was confirmed in December 2019, the number of cases has shown an upward trend, and the epidemiological picture is changing every day. With lack of any effective vaccine or drug currently available, scientists and doctors are conducting a series of clinical studies involving affected patients.^{7,8} Although Chinese researchers are struggling to find effective treatments and preventive measures, and actively conduct clinical trials, one aspect of the clinical trials has been surprisingly overlooked. That's the ethics of clinical trials. In 2016, the World Health Organization (WHO) released the "Guidance for Managing Ethical Issues in Infectious Disease" to ensure the safety of participants during the outbreak of disease.⁹ The guidance notes that it is morally obligatory to conduct scientific research in a timely manner. As of April 5, 2020, the Chinese Clinical Trials Registry (www.chictr.org.cn) has registered a total of 556 COVID-19 clinical trials. Most of these studies are interventional studies, which included randomized controlled trials (RCTs), followed by observational studies, diagnostic studies and other types.¹⁰ Although the design of some studies may be flawed due to the lack of time. However, it is the ethics of trials that need special attention. We have a few comments on this issue.

On the one hand, the focus of ethical issues is the protection of the subjects' rights and interests. In clinical trials, the investigator or applicant should first consider how to protect the rights of the subjects. Specifically, the subjects' rights of voluntary participation, the right to know, the right to privacy, the right to

security, the right to timely treatment and other rights should be protected.^{9,11,12} Clinical trials of drugs are usually divided into four phases: phases I, II, III and IV. Each phase has different requirements and objectives, and the number of cases required is also different.⁹ Some of the drugs currently registered are only effective in vitro, and the safety has not been proven.¹⁰ For example, the study of Chinese patent medicine Shuang-Huang-Lian oral liquid, according to preliminary experiments, in vitro cell experiments showed that it could effectively inhibit COVID-19. However, it has been used in randomized, open-label, blank-controlled, and multi-center clinical trials.¹³ It should be noted that many laboratories have conducted preliminary experiments and hope to enter clinical trials as soon as possible. Whether this conforms to the standardized process of drug clinical trials, this is a matter of concern. From the perspective of study design, it should be confirmed to be safe and reliable from the perspective of efficacy and safety. Meanwhile, staging can also achieve the purpose of protecting participants. Some studies lack the statistical basis for sample-size calculation. For example, one study treated COVID-19 by atomizing a Chinese medicine injection.¹⁴ Because this is a new route of administration, a phase I clinical trial should be conducted. The sample size is usually less than 100, and the sample size in this study is 119.¹⁴ During the COVID-19 outbreak, doctors may use experimental drugs on infected participants, relax the inclusion and exclusion criteria, and fail to provide reasonable compensation or inform vulnerable patients about the risks of the trials, the ethics committee should pay special attention to these issues.¹⁵ Specifically, ethical issues may also need to be resolved based on the characteristics of patients, including elderly patients and people with disorders of consciousness.^{9,15} In addition, special attention should be paid to the biosafety level of the laboratory, which may lead to virus leakage.

On the other hand, if a drug is effective for COVID-19 patients, then patients randomly assigned to the control group may lose the right to timely treatment. Even if the trial is successful, many participants' benefits and even their lives could be lost. As a physician, the main task is to cure patients as soon as possible, and it is not humanist to give blank treatment or placebo treatment when there is no established effective conventional treatment for critically ill patients. This also increases the psychological burden of patients and the fear of disease, and increases the uncertainty of treatment. The experiment of the treatment group and the control group should be carried out on the basis of routine treatment. Research

participants' risks should be minimized and timely psychological counseling should be given.

Furthermore, from the participant's perspective, the questions to be answered in the design of a clinical trial should also be safe. Investigators must not expose participants to any inappropriate risks/harm.¹² Human experiments conducted before or during World War II impressively remind us that when designing RCTs, it is important to obtain participants' voluntary informed consent and ensure their health.¹³ Randomized controlled trials are also useful for studying the effectiveness and/or safety of diagnostic and screening tests. Clinical studies also need to carefully combine short-term efficacy evaluation with long-term efficacy indicators. For example, a clinical study is about nebulized Xiyanping injection in the treatment of COVID-19.¹⁴ Xiyanping injection is the extract of *Andrographis paniculate*, which is a Chinese patent medicine approved by China to treat bronchitis.¹⁶ However, the use of Xiyanping still remains a controversial issue since the safety impacted factors are not completely clear. The study indicated that age and the combination of Xiyanping and Ribavirin were independent risk factors for the severity of adverse drug reactions.¹⁶ According to the drug instructions, the administration route of Xiyanping is intramuscular injection and intravenous drip, without atomization.¹⁶ Unreasonable use of traditional Chinese medicine may cause some potential adverse reactions, so the potential risks may outweigh the benefits. Besides, in order to evaluate the efficacy and safety of the drug, researchers need to conduct long-term statistics on some indicators, after the participants are discharged from the hospital, such as disability rate, mortality rate and quality of life.

We believe that the most needed clinical studies of drugs are based on efficacy and safety at present, and mainly focus on cohort studies, observational studies, and real-world studies, not RCTs. We have some reasons as follows. First, RCTs are rigidly designed and the researchers require a lot of time to carefully study clinical issues, resulting in a protocol of very clear, well-defined, specific, feasible, measurable, ethical, and clinically important question.¹⁷ Due to the urgency of the COVID-19 epidemic, the design of RCTs may not be perfect, ignoring the protection of patients' interests, and fail to offer reasonable compensation or to inform vulnerable participants of trial risks.¹⁵ Second, RCTs based on preliminary observational clinical trials are more conducive to protecting patients' rights and saving medical resources. Third, the intervention to be studied and comparator intervention are the key components of RCTs. The comparator intervention group usually uses routine treatment. This limits the right of these patients to use other newly discovered drugs that may be effective.

In terms of study design, patients' rights should be primarily considered, followed by scientific value and commercial interest. Multidisciplinary international cooperation should be conducted to reduce the harm to patients' rights and interests. In conclusion, during the outbreak of COVID-19, the review standards for clinical studies should not be lowered.

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Conflict of interest

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Ethical statement

No ethical approval was required for this manuscript as this study did not involve human subjects or laboratory animals.


Data availability


Not applicable.

References

1. Paules CI, Marston HD, Fauci AS. Coronavirus infections – more than just the common cold. *JAMA* 2020, <http://dx.doi.org/10.1001/jama.2020.0757> [Epub ahead of print].
2. Rahman Qureshi UU, Saleem S, Khan A, Afzal MS, Ali MS, Ahmed H. Outbreak of novel Corona virus (2019-nCoV); implications for travelers to Pakistan. *Travel Med Infect Dis* 2020:101571, <http://dx.doi.org/10.1016/j.tmaid.2020.101571> [Epub ahead of print].
3. Tian H, Liu Y, Li Y, et al. An investigation of transmission control measures during the first 50 days of the COVID-19 epidemic in China. *Science* 2020:eabb6105, <http://dx.doi.org/10.1126/science.abb6105> [Epub ahead of print].
4. The, Lancet. COVID-19: learning from experience. *Lancet* 2020;395:1011.
5. Velavan TP, Meyer CG. The COVID-19 epidemic. *Trop Med Int Health* 2020;25:278–80.
6. Sookaromdee P, Wiwanitkit V. COVID-19 among medical personnel in operation room. *Infect Control Hosp Epidemiol* 2020:1–3, <http://dx.doi.org/10.1017/ice.2020.106> [Epub ahead of print].
7. Zhang K. Is traditional Chinese medicine useful in the treatment of COVID-19? *Am J Emerg Med* 2020, <http://dx.doi.org/10.1016/j.ajem.2020.03.046> [Epub ahead of print].
8. Jin YH, Cai L, Cheng ZS, et al. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). *Mil Med Res* 2020;7:4.
9. Guidance for managing ethical issues in infectious disease. *World Health Organization website*. Published October 27; 2016. Available from <https://www.who.int/tdr/news/2016/ethical-issues-in-inf-dis-outbreaks/en/>. Accessed February 2, 2020.
10. Zhang T, He Y, Xu W, Ma A, Yang Y, Xu KF. Clinical trials for the treatment of Coronavirus disease 2019 (COVID-19): a rapid response to urgent need. *Sci China Life Sci* 2020, <http://dx.doi.org/10.1007/s11427-020-1660-2> [Epub ahead of print].
11. Wendler D, Rid A. In defense of a social value requirement for clinical research. *Bioethics* 2017;31:77–86.
12. Annas GJ. Beyond Nazi war crimes experiments: the voluntary consent requirement of the Nuremberg Code at 70. *Am J Public Health* 2018;108:42–6.
13. A randomized, open-label, blank-controlled, multicenter trial for Shuang-Huang-Lian oral solution in the treatment of novel coronavirus pneumonia (COVID-19). Available from <http://www.chictr.org.cn/showproj.aspx?proj=49051>. Accessed April 5, 2020.
14. Clinical study of nebulized Xiyanping injection in the treatment of novel coronavirus pneumonia (COVID-19). Available from <http://www.chictr.org.cn/showproj.aspx?proj=49222>. Accessed April 5, 2020.
15. Zhang H, Shao F, Gu J, Li L, Wang Y. Ethics committee reviews of applications for research studies at 1 Hospital in China during the 2019 novel coronavirus epidemic. *JAMA* 2020:e204362, <http://dx.doi.org/10.1001/jama.2020.4362> [Epub ahead of print].
16. Zheng R, Tao L, Kwong JSW, et al. Risk factors associated with the severity of adverse drug reactions by Xiyanping injection: a propensity score-matched analysis. *J Ethnopharmacol* 2020;250:112424.
17. Bhide A, Shah PS, Acharya G. A simplified guide to randomized controlled trials. *Acta Obstet Gynecol Scand* 2018;97:380–7.

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