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LETTER TO THE EDITOR

Tugolbai Tagaev [1(ABCDF)], Vityala Yethindra [2(ABCDFG)], Altynai Zhumabekova [3(ABCD)], Yogesh Parihar [4(ACD)], Alenur Narasimharaj [4(ABD)]

Coronavirus disease 2019: ethical and epidemiological issues with clinical trials

[1] Department of Public Health and Healthcare, I.K. Akhunbaev Kyrgyz State Medical Academy, Bishkek, Kyrgyzstan
[2] Department of Pathology, International Higher School of Medicine, International University of Kyrgyzstan, Bishkek, Kyrgyzstan
[3] City Maternity Hospital No. 2, Bishkek, Kyrgyzstan
[4] International Higher School of Medicine, International University of Kyrgyzstan, Bishkek, Kyrgyzstan

Dear Editor,
In the current public health crisis arising from the coronavirus disease 2019 (COVID-19) pandemic, past experiences (with Acquired Immune Deficiency Syndrome (AIDS), Ebola, etc.) and a flexible framework can be used to quickly and effectively determine the best drug response. In clinical trials, the investigator or applicant should initially take care about rights protection of the subjects. Eventually, 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.[1,2] The balance between taking the necessary precautions and making the decision to administer an experimental treatment to a large proportion of the population is unique to each crisis.

Are any treatments showing encouraging signs?
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.[3] Some of the drugs currently registered are only effective *in vitro*, and the safety has not been proven.[4] This is the most pressing question, and the one that leads to all others. There are currently several hundred clinical trials[5] underway around the world to assess the effects of various treatments for COVID-19. For example, the Discovery trial,[6] carried out by European health centers on 3,200 patients, including 800 in France, is testing the effects of four treatments that have been used previously against other diseases. The four treatments that will be compared to standard protocol are as follows: Remdesivir (used to treat Ebola), lopinavir/ritonavir (a drug combination used to treat AIDS), interferon beta-1A (interferon added to stimulate immune defenses), and hydroxychloroquine (used to treat rheumatoid arthritis and lupus). These treatments have been included in this article because they have previously demonstrated potent antiviral actions against

Corresponding author: Tugolbai Tagaev, e-mail: ttagaev22.kg@gmail.com

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viruses and *in vitro* actions against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). They have also been the subject of preliminary studies; however, to date, the effects described in both publications and pre-publications have not been conclusive. A small fraction of these publications comprised reports of prospective clinical trials (0.25%), and many of these trials have imparted conflicting conclusions, leading to confusion among the public and the scientific community.[7]

Drug repurposing is also an impressive idea for treating COVID-19 as it involves low cost and rapidly available in the pharmacies. This idea alleviates some steps of clinical trials, especially those concerning the strenuous diligence and time needed for phase 1 and 2 trials.[8]

Where is the knowledge deficit currently?

Although the pressure and urgency for conducting COVID-19 research abounds during this worldwide crisis, this should not preclude scientific principles and ethics.[9] Pandemics create issues regarding scientific and ethical questions for research and understanding what ethical concerns remain the same and differs is essential for conducting clinical trials. There have been promising results reported in studies on treatments for COVID-19. If one study found a treatment which was effective in vitro against viruses that showed similarities to SARS-CoV-2 in terms of their function. This indicates that preliminary studies are headed in the right direction. Unfortunately, a few encouraging results does not guarantee with any certainty the efficiency and safety of these treatments. The questions that arise are related to the effectiveness of each treatment and their side effects when used in patients who may be in respiratory distress or have other diseases. Additionally, the use of an appropriate protocol is equally vital: the dosage, when to administer treatment, and in which patients (age, sex, comorbidity factors, undergoing other treatments). However, there is also an important issue in the comparative evaluation of these treatments from the point of view of their risks and benefits. Indeed, even if a promising and effective treatment is found with moderate risks, the research environment arising from the current pandemic is strongly encouraging the scientific community to initiate studies to determine which of these treatments maximizes the benefits and minimizes the risks. This is due to the fact that this pandemic is calling for the treatment of hundreds of thousands of individuals globally. Any approximation in this regard could otherwise result in a significant number of victims, who would have reacted better with treatments that were more effective or better tolerated. Therefore, the current knowledge deficit concerns the absolute efficacy and safety of each treatment, as well as the comparison among treatments. The interventions selected for testing should consist of the most promising therapies, as determined by existing data. The value of clinical trials depends on the quality of information produced and the relevance of the data to address public health needs.[10]

Should the knowledge deficit be set aside given the urgency of the situation?

This point of tension arises directly from the uncertainty regarding the treatments being tested during an ongoing crisis in which many lives are at stake. Hydroxychloroquine is at the center of a controversy in France and several other countries, where many are wondering about the benefits of systematically treating patients with hydroxychloroquine, even if this means postponing scientific certainty. However, even in a case where a patient's condition deteriorates, and an uncertain treatment appears to be more acceptable (so called "compassionate use"), the administration of this treatment to all those affected remains questionable. This holds true if the implemented protocol targets patients at an early stage, thus calling for the systematic treatment of any person that tests positive or presents moderate symptoms. Since the overwhelming majority of COVID-19 patients do not progress to severe forms, treating them with hydroxychloroquine or other treatments with side effects or potentially dangerous effects poses a serious public health risk.[11]

What are the general provisions, and how are they adapted to the circumstances?

Clinical trials are not only subject to methodology but also to legislation, which guarantees respect for individuals, non-maleficence, and justice.[12-15] However, the balance between taking the necessary precautions, which are typically already in use, and the decision to administer an experimental treatment to a large proportion of the population is unique to each crisis. The mortality rate of AIDS was extremely high during the initial years of the epidemic, similar to that of Ebola. Thus, the lethality of these diseases justified the administration of treatments in the absence of proof of their superiority and without a placebo group. Compared to AIDS and Ebola, the lethality of COVID-19 appears to be lower, but is more difficult to establish since the total number of cases is not yet known, and lethality is dependent on age and the healthcare system. Therefore, the administration of non-validated treatments remains problematic, especially since a large majority of the total cases are asymptomatic or have more mild forms of the infection. Despite these challenges, several factors have already helped to adapt the clinical standards to the circumstances in this pandemic.

First, clinical trials have been set up in record time and making agreements among several healthcare centers that have the capacity to analyze large amounts of

samples rapidly.[6,16] Second, these trials are making use of relatively recent methodologies with several arms, allowing for the observation of the effects of several treatments simultaneously and adapting them accordingly. This last point allows researchers to stop one of the arms quickly if it demonstrates ineffectiveness and to continue only with those treatments that show promise.[17]

Conclusion

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. The medical and research professions have the means to reconcile care and implement rigorous testing for COVID-19, with the possibility of making initial results available in a few days. During the situation of COVID-19, the review standards for clinical studies should not be lowered.

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