Editorial

Research ethics in COVID-19 pandemic

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The recent turbulence caused by the coronavirus diseases 2019 (COVID-19) pandemic has prompted an urgent need to execute clinical trials to combat the spread of the deadly virus. Nobody knows how long this plague will last, and in the meantime, the mortality increases at a tremendous rate. To make things worse, no known effective prophylactic or therapeutic agent has been invented until now. To overcome these problems, scientists must prepare and execute clinical trials rapidly. Consequently, they need to recognize some ethical problems as described below.

Just like other pandemic situations, the current COVID-19 outbreak is characterized by a significant shortage of diagnostic, life-supporting equipment, various medical devices, and human resources. All these medical care facilities should be primarily dedicated to the patients, and should not be reduced for the sake of clinical trial execution. The investigator team should always remember that, when doing a clinical trial, they are automatically confronted with problems of conflict of interest. As the investigator team, they have to do their best to execute their research plans. However, as doctors or health caregivers, they have to prioritize the care and wellbeing of their patients. The Declaration of Helsinki clearly emphasizes that in these conflicting interests, the patient's interest should be their highest priority.[1]

Another interesting highlight in the COVID-19 disruption is its strong force that pushes scientists to plan and execute trials. Typically, research groups develop their own research protocols. Although research interests are always appreciated, these may also be related to ethical issues. Small scale clinical trials usually recruit a small number of trial subjects, which consequently reduces their power to detect an existing significant difference.[2] Thus they may yield false negative results. Another ethical problem is that many research groups may have the same research objectives, and thus duplication of research occurs and this causes waste of time and research resources. Many of these trials may perhaps focus their attention on trivial or less important research questions, and forget that the most urgent research questions to answer in this critical situation are how to reduce the spread of the virus and how to reduce the mortality of the patients infected by this virus. To optimize the work of enthusiastic investigators, it is highly recommended that they work collaboratively to set up objectives which can give real clinical benefits to society. An even more recommended and realistic idea is participation in international or multi-national clinical trials.

During the COVID-19 outbreak, various research groups want to immediately commence their research. Though this is understandable, the quality of the study and the protection for the research subjects should not be compromised. Subject recruitment with no informed consent and substandard procedure is a major ethical problem. A lack of sponsor is also a serious ethical problem because this means that no one will be responsible for providing research funds, health care and compensation for research-related injuries, procurement of high-quality investigational drugs, monitoring, auditing, and investigators' brochures, among others. All deficiencies in these respects may impair the safety of research subjects. Some people may ask that in an emergency setting, is it possible if investigators take over the role of the sponsor? The answer is no because of several reasons. If the investigators want to provide research funds or paying research-related injuries, most likely it is not realistic because a huge amount of money required is unlikely covered by the investigators. Monitoring and auditing should also be done by an independent party of the investigator team. High-quality trial drugs are best prepared by the manufacturer of the trial drugs, not by the investigators. Of course, in certain conditions, the investigators may purchase the agents from the market, but their quality might be questionable. In sum, the role of the sponsor in good clinical practice-standard trials is indispensable.[3]

The substandard research methodology is also closely related to misleading and biased conclusions. Some examples of such substandard research methodology include trials without a control arm, insufficient sample size, lacking randomization, major protocol deviations without an acceptable reason, data manipulation, and inappropriate statistical analysis. Open trials can still be acceptable if the study outcomes such as the case fatality rate, length of hospitalization, length of viremia, and viral count are measured objectively. These methodological weaknesses, if combined with the investigators' propensity of bias, may result in misleading conclusions. This may further induce ineffective and unsafe use of anti-COVID-19 drugs in society. Besides, this also wastes time, money, and the sacrifice of research subjects.

In search of effective antimicrobial agents against COVID-19, investigators might think that it is unethical to carry out a placebo-controlled trial. Some might say that single-arm studies would be appropriate, while others may insist that two or more arm-controlled studies would be better. However, placebo should not be given to the control group; rather, antibiotic or antiviral agent should be given to the control group. These 'anti-placebo' concepts need further rethinking. In a single-arm study, there is no control group, therefore it is impossible to draw any objective conclusion. The door then is widely open for investigators' bias. This design becomes obviously unethical because despite all patients' sacrifice, time and energy, the study design would never be able to produce a valid conclusion. In research involving diseases having no known specific treatment, the use of placebo is not only ethically acceptable but also should be encouraged because this is the only way to measure the absolute benefit and risk of the test drug. Needless to say, both treatment and control groups should receive the same standard treatments. So this is an 'add on' intervention.

An intriguing ethical issue is the inclusion of vulnerable subjects in COVID-19 studies. It is quite common that pregnant women, children, and the elderly are not included in the study for ethical reasons. Despite this contention is understandable, this conventional thought needs to be challenged. The fierce COVID-19 can attack anybody, including these vulnerable subjects. If these subgroups of patients are not included in the clinical trial, the clinicians may not know anything about the safety and efficacy of the test drug in these subpopulations. This would become a really expensive price to pay. The tragedy of thalidomide has taught us a clear lesson on this issue. Therefore, the correct and ethical principle is not to deny their participation but to give them special protection during and after the study.[4] In certain conditions, however, when the trial drug has been established of having harmful effects to a particular subset of patients, they should not be included in the trial. For example, a clinical trial involving favipiravir should not include pregnant women because of the well-known teratogenic effect of this drug.[5]

Finally, it is worth mentioning that all the information obtained in various clinical studies need to be shared immediately.[6] All data, including those that provide a tiny hope to reduce the COVID-19 mortality rate must be disseminated in a timely manner.[6] Multi-national collaborative studies are highly effective to increase the efficiency of trial execution and sharing of information. All these efforts need to be done for the sake of humanity.

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