Medical students speak (Student’s corner)

**COVID-19: Ethical and epidemiological issues with clinical trials**

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**Running title:** Ethics in COVID-19 clinical trials

**Abstract**

Among the various questions raised regarding the national and global strategies employed for the management of the current coronavirus disease (COVID-19) pandemic, are ethical and epidemiological issues surrounding clinical trials. The prospect of a vaccine is still far away, and current care standards are unable to guarantee the recovery of severe COVID-19 cases. Due to the tense situation arising from the urgency to care for infected patients and the uncertainty regarding the existence and proper use of treatments, questions have arisen that cannot be resolved solely by scientiﬁc expertise, but rather from an ethical and epistemological reflection on the best strategy to implement during this crisis.

**Keywords:** COVID-19, ethics, SARS-COV-2, clinical trials

**Introduction**

In the current public health crisis arising from the coronavirus disease (COVID-19) pandemic, past experiences (with AIDS, Ebola, etc.) and a flexible framework can be used to quickly and effectively determine the best drug response. 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?**

This is the most pressing question, and the one that leads to all others. There are currently several hundred clinical trials [1] underway around the world to assess the effects of various treatments for COVID-19. For example, the Discovery trial [2], 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 care are as follows: Remdesivir (used to treat Ebola), lopinavir/ritonavir (LPV/R) (a drug combination used to treat AIDS), LPV/R, 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 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.

**Where is the knowledge deficit currently?**

There have been promising results reported in studies on treatments for COVID-19. 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, etc.). 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.

**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 [3].

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

Clinical trials are not only subject to methodology [4, 5, 6] but also to legislation, which guarantees respect for individuals, non-maleﬁcence, and justice [7]. In the current crisis arising from the pandemic, the clinical and practical experience gained through past crises (AIDS and Ebola, among others) combined with a more flexible framework could be used to quickly and effectively develop an optimal drug response for COVID-19. 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 is not only lower but is also more difficult to establish since the total number of cases not yet known, and lethality is very 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 [2, 8]. 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 [9] and to continue only with those treatments that show promise.

**Conclusion**

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

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**Conflict of interest**

The authors declare no conflicts of interest.

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