HELLENIC NATIONAL BIOETHICS COMMISSION

RECOMMENDATION

for

Clinical Trials During the COVID-19 Pandemic

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The Hellenic National Bioethics Commission, in multiple meetings, examined the conduct of clinical trials (interventional clinical trials) during the COVID-19 pandemic (coronavirus, SARS-CoV-2) and the ethical issues that arise based on the COVID-19 Disease Expert Group's recommendation.

The present Recommendation aims to identify specific potential issues that are posed by clinical trials on COVID-19 and other diseases during the pandemiv, so as to avoid the repetition of standard, general principles followed in clinical trials. Therefore, the Commission has addressed the following issues:

1. Evaluation of clinical trials for the treatment of COVID-19 disease.

2. Selection of patients or participants in clinical trials.

3. Consent issues of participants in clinical trials.

4. Use of placebo.

5. Challenge studies.

6. Data sharing.

7. Priorities in the design of clinical trials.

8. Scarcity of resources and consequences of the pandemic on non-COVID-19 clinical trials.

The Commission's recommendations on each of the above issues are presented below.

1. Evaluation of clinical trials for the treatment of COVID-19 disease

The Commission recognizes the need for an immediate evaluation of the research protocols related to COVID-19 disease by the relevant Research Ethics Committees. Indeed the Commission recommends that priority is given in the review of these protocols by the competent Research Ethics Committees. However, in these cases, it is necessary to emphasize the clear distinction between urgency and propriety. Thus, all the applied ethical principles and standards must be followed to ensure safety, voluntary participation, and full respect of research participants' rights when evaluating these protocols.

Besides, concerning clinical trials for potential COVID-19 treatments, a thorough and ongoing risk assessment of the administered drugs is necessary, along with the medical staff's vigilance for better assessment of plausible risks. A relevant typical example was the immediate withdrawal of chloroquine and hydroxychloroquine from the US Food and Drug Administration (FDA), based on new scientific data on the drugs' efficacy and the manifestation of serious cardiac adverse events and other potential serious side effects. However, the Commission acknowledges that clinical trials of drugs in COVID-19 patients may lead to serious adverse events that cannot be priorly predicted. For this reason, it is considered appropriate to establish an independent Data Safety Monitoring Committee for each clinical trial, with the main task of monitoring patient safety throughout the clinical trial period and its timely termination in case of serious adverse events. The Commission also refers to relevant guidelines of the World Health Organization.

2. Selection of patients or participants in clinical trials

From the pandemic experience in our country to date, it appears that smaller reference centers/hospitals do not have the capacity to conduct clinical trials. This

situation is mainly due to practical reasons, such as the lack of experience of doctors, researchers, and funders in conducting clinical trials in regional hospitals, the limited availability of the tested pharmaceutical agents, the need for immediate daily supply of the tested pharmaceutical agents within a few hours from the pharmaceutical stores, etc. Consequently, the lack of experience and scarcity of resources for the tested drugs lead to inequalities in access to clinical trials for all COVID-19 patients from all over the country. To facilitate the resolution of this issue, the Commission recommnends that smaller/regional hospitals should be staffed with administrative, medical, and nursing staff, who will receive ongoing training on the support and conduct of clinical trials.

The Commission has especially considered the access of minority groups to clinical trials and their potential benefits. It emphasizes the importance of preparedness in order to design clinical trials that will include patients from minorities, without negative discrimination in terms of origin, culture, etc. This state of readiness includes the timely and valid provision of information to minorities through their representatives, as well as the participation of interpreters, mediators, and social workers in the process, who will better enhance communication between all involved parties. Although such preparedness should be planned for all clinical trials, the need is even more significant in pandemic times.

3. Consent issues of participants in clinical trials

In the case of COVID-19 patients who cannot consent due to their health condition, the usual practice of obtaining consent after informing their legal representative or parents in the case of minors is applied. However, particularly in COVID-19 clinical trials many participants do not have the capacity to consent to participation, and therefore, there must be a comprehensive and clear justification for their participation in the trial, which must be the case for both adult and juvenile patients. In case the patient recovers and has the ability to consent, obtaining a new informed consent by the patient himself/herself is recommended.

COVID-19 patients (or their legal representatives) are required to handle an emergency situation, combined with the hitherto non-existent treatment, and this carries the risk of the so-called "therapeutic misconception". In other words, patients may think that their participation in the clinical trial will have a direct therapeutic benefit for them, when in fact, this is extremely rare, as most clinical trials aim to help future patients with the same disease (if the treatment proves to be effective and safe). Therefore, it is necessary to make it clear and explicitly state in the consent form/information sheet that there may be no immediate therapeutic benefit for the participants themselves. Also, it should be clarified that if the experimental drug proves to have a benefit, the participants will only be benefited in the case that they were not included in the placebo group.

4. Use of placebo

The Commission realized that the use of placebo is unavoidable in COVID-19 clinical trials in order to ensure scientific validity through randomized clinical trials. After all, there is currently no alternative treatment available for COVID-19, and patients who are randomly assigned to the placebo group receive the standard of care, according to the clinical protocols of each country. In case a treatment proves to be effective, a possible approach is to include the treatment in the standard of care, in any future clinical trials.

5. Challenge studies

Globally, there is intense concern about the so-called "challenge studies", which involve the deliberate infection of healthy volunteers with SARS-CoV-2 (coronavirus) and their subsequent involvement in clinical trials, mainly in testing novel vaccines against the coronavirus. It is noted that in some cases, the participation of healthy volunteers is accompanied by financial compensation, mainly in the United States of America (USA). Although several people consider the participation of healthy volunteers in such studies to be morally accepted, provided

that it is a manifestation of an individual's genuine personal autonomy (which should be ascertained through clearly defined and specific procedures), yet the conduct of these "challenge studies" is associated with critical ethical challenges, which make their utilization problematic. In the light of this debate and reflection, the Commission notes the following:

I. Unlike past cases of challenge studies conducted for other diseases (such as typhoid, malaria, cholera, etc.), there is no effective treatment to be provided to participants who may be severely infected with the SARS-CoV-2 virus and, given its high transmissibility, this may be life-threatening.

II. It is doubtful whether studies in healthy young adults (18-35 years old as generally suggested by advocates) will be able to predict the potential effectiveness of a vaccine in older people, or in adults with underlying diseases, or in people from high-risk groups.

III. It is uncertain whether these studies, with a small number of participants, actually accelerate the vaccine development process compared to the standard Phase III of clinical trials.

IV. It is possible that challenge studies may not detect (rare) side effects of the tested vaccine, while these can be serious and threatening to the recipients' health when the vaccine is given to millions of people. In conclusion, the criterion of "potential utility", which is exploited by the proponents of challenge studies, is ethically degraded by the severe uncertainties for both the safety of participants/volunteers and the overall risk assessment due to multiple scientific uncertainties concerning the new coronavirus.

Besides, due to increased uncertainties, potential participants may not be "fully and adequately informed" of the risks in order to provide genuine consent, as required to participate in any clinical trial. Due to the problems stated above, the Commission also points out the risk of threatening the public trust in clinical trials for the new disease. Such clinical trials are necessary to find an effective vaccine, but they could also raise public suspicion about the vaccinations. In any case, the Commission emphasizes that the basis of the decision to participate in any clinical

trial must be altruistic instead of financial. Also, the principles of both the protection of each individual's health and respect for their rights and interests should take precedence over the interests of society and science in general. The Commission also refers to relevant guidelines on challenge studies by the World Health Organization.[1]

6. Data sharing and data protection of participants

Here, the Commission has identified two points that require attention.

Firstly, concerning data sharing of COVID-19 clinical trials, the Commission encourages data sharing - when this is possible - to facilitate faster treatment and faster vaccine development. The Commission also recognizes that private-funded clinical trials (e.g. from pharmaceutical companies) have a legitimate interest in safeguarding and not sharing data, but this should be weighed with the public interest during a pandemic.

For easier and equal access of all citizens to potential treatments and vaccines to be developed, the Commission recommends to the State and policymakers to strengthen private-public cooperation and research co-funding. This will improve mass production and availability while making the treatment or vaccine's final cost affordable. Simultaneously, the rapid publication of clinical trial results is strongly recommended to enhance their utilization in a shorter time (including negative research results).

The second issue concerns the protection of the participants' personal data taking part in COVID-19 clinical trials. The Commission noted the need to inform clinical trial participants about who (e.g. other researchers, publicly available databases, etc.), and under which status (e.g. fully anonymized or pseudonymized) personal data collected during the clinical trial will be shared.

[1] WHO 6 May 2020. Key criteria for the ethical acceptability of COVID-19 human challenge studies. Available at https://apps.who.int/iris/bitstream/handle/10665/331976/WHO-2019-nCoV-Ethics_criteria-2020.1-eng.pdf?ua=1

7. Priorities in the design of clinical trials

Clinical trials for the SARS-CoV-2 pandemic should in no way suppress other clinical trials on diseasesfor which there is no available, effective treatment. However, a hierarchy should be applied to clinical trials for diseases for which there are effective treatments (e.g. bioequivalence studies), so as not to put participants at risk due to the pandemic. After all, when physical isolation, distancing and prevention measures are taken, especially in the event of a new wave of the pandemic, it is not appropriate for volunteers to visit the Centers to participate in such studies. Alternatively, such clinical trials may continue to be performed but with re-designed procedures and models, such as virtual and distance visits, etc., to the extent that the integrity and reliability of each study is certainly not compromised.

8. Scarcity of resources and consequences of the pandemic on non-COVID-19 clinical trials

The issue of whether and to what extent the pandemic resulted in the withdrawal of non-COVID-19-related clinical trial funds to invest in COVID-19 clinical trials was initially considered. Although no financial data are yet available to substantiate this, the *de novo* investment of large research funds (e.g. European and national) in COVID-19 research and the development of an effective vaccine is evident and is certainly justified by the urgency of the pandemic situation.

The Commission also examined the delays and postponements in the start of non-COVID-19 clinical trials that were noted during the pandemic. These delays are due to several reasons, such as: The lack of medical and nursing staff, who had to focus primarily on the management of COVID-19 patients, which resulted in them not being occupied in the non-COVID-19 clinical trials. Actually, in some cases, including our country, where the needs are exceptionally high, doctors of other specialties are called to offer their services to patients with COVID-19.

The Commission strongly recommends the simultaneous reinforcement of non-COVID-19 clinical trials that have to do with other diseases (e.g. rare diseases) for which effective treatments are not available.

Athens,

29 September 2020.