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Bioethics in the COVID-19 Pandemic Research: Challenges and Strategies

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ABSTRACT

As all other aspects in times of the coronavirus disease (COVID)-19 pandemic, carrying-out quality clinical research has been challenging. Many well-established paradigms have shifted as a consequence of the rapid demand for new knowledge. New treatments are fast-moving, informed consent forms are difficult to obtain, a competitive invitation from researchers to participate in different studies is common, and non-COVID-19 research protocols are suffering continuity. However, these challenges should not imply taking shortcuts or accepting deficiencies in bioethical standards, but rather enhance the alertness for rigorous ethical approaches despite these less than ideal circumstances. In this manuscript, we point out some interrogates in COVID-19 research and outline possible strategies to overcome the difficult task to continue with high-quality research without violating the ethical principles. (REV INVEST CLIN. 2020;72(5):265-70)

Key words: Coronavirus disease-19. Informed Consent. Research Ethics Committees. Ethics.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) is a new kind of extremely contagious coronavirus that can produce severe respiratory failure and death[1]. Given the worldwide spread of the disease and the lack of available treatments, hasty research has emerged in many medical, biomedical, and technological fields. Many bioethical challenges have tailed this rapid pursuit of knowledge[2]. Given the imperativeness of the emergency and the lack of information, the need for acquiring immediate applicable data may jeopardize some of the ethical principles[3]. In fact, some of the most recommended drugs at the beginning of the pandemic were outdated in subsequent more robust studies[4], and many publications were retracted after a thorough second examination. Unfortunately, many of these treatments were not innocuous. Thus, the correct selection of the participants and the disclosure of the foreseen risks are crucial.

Research in global health emergencies unavoidably takes place in non-ideal circumstances[3]. (Table 1) Balancing the search of beneficence against non-maleficence, respecting the autonomy of the participants

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Table 1. Ethical challenges for the clinical research in the COVID-19 pandemic

– Withstand disruptions from the relative stable norm
– Endure raised risks to physical and/or mental well-being
– Bear pressures of time
– Cope with uncertainty
– Recognize fear, distress, or panic in patients and coworkers
– Lessen tensions between clinical care and research ethics
– Pinpoint uncertain scientific soundness of protocols
– Provide honest communication-avoid false expectations
– Ascertain fair distribution of resources
– Recognize proper motivations for performing research
– Develop and sustain resources
– Identify hazards in adherence to standard practices
– Justify reasons for departing from standard practices

to decide if they would like to contribute to experimental or observational trials in such difficult times, and trying to involve all possible candidates to achieve justice, is an ability that should prevail despite the urgency. The aims of this article are to describe some challenges in coronavirus disease (COVID)-19 research, outline possible strategies to overcome such difficulties, and recognize the endeavor to preserve high-quality research without violating the ethical principles.

ACCURATE VERSUS FAST-MOVING INFORMATION

There is a tremendous uncertainty on COVID-19 information. At present, there is not enough evidence for the optimal care of infected patients. This has triggered the use of many pharmacological agents, some with serious side effects. The design of randomized controlled studies in this context is difficult. The selection of the reference group is complex since some pre-existing conditions and the time since the appearance of the symptoms are the main determinants of the outcomes, including survival. The use of a placebo has been eliminated in many trials based on the absence of an effective therapy[5]. However, the proper allocation of side effects implies the use of a placebo in controlled studies[6]. Furthermore, for some therapeutic options, such as plasma from recovered patients, the use of a placebo cannot be avoided. Several alternatives had been used (i.e., saline solutions or plasma from patients without COVID-19 infection), but its usefulness is intricate, as some of them may have a non-specific effect that may alter the evolution of the control group[7]. A very frequent mistake in many COVID-19 studies is the lack of control of the support therapies (pronation, oxygen therapy, corticosteroids, fluid reposition, etc.). These interventions have a major effect in response to therapy; if the type and intensity of such interventions are not the same in the groups to be compared, it will interfere with the results of the clinical trial[8]. As a result, efficacy has been overestimated in some cases (as in the use of hydroxychloroquine)[9], and some side effects have halted the use of others, but most of the time this occurs after some time of its use. Many pharmacological therapies employed have daily updates based on rapid emerging literature, mostly constructed using a "trial-error" approach. Challenges in interpreting what is happening in real life cannot be avoided.

Possible measures to lessen risks

A) The Research Ethics Committees (RECs) should update and adapt procedures to evaluate research projects in a short period of time, without affecting the quality of the reviews[10].

B) RECs should emphasize that at all time, the patients' safety continue to be at the forefront of considerations.

C) RECs should follow-up closely with the studies admitted under hypothetical backgrounds. Frequent or periodical safety reports must be requested.

D) Selection criteria should identify the population with the biggest likelihood to obtain some benefit without major safety concerns.

E) The selection criteria of the study participants should include a validated clinical stratification tool. This tool should consider the peculiarities of the populations. The contribution of the pre-existing conditions is different between ethnic and age groups.

F) Good clinical practices should always be met to minimize risks and safeguard the health and well-being of patients, regardless of the emergency.

G) Only one investigational agent should be used in each patient.

H) If the patient gives his/her consent, he or she may participate in more than one observational or experimental study (for example, looking for different biological markers), but extraordinary efforts must be made to link the research projects and avoid wearing-off the patient, drawing excessive blood samples, or performing redundant studies.

I) Interim analyses coordinated by independent safety boards should be requested for every new therapeutic agent under study.

J) Concomitant therapies are as important as the active principle under study. All study groups should receive the same supportive treatment as needed. The use of concomitant therapies should be regularly measured and reported.

K) A major necessity is the active surveillance of the execution of the study protocols to assure that good clinical practices are preserved. New resources should be created to facilitate the communication between study participants and RECs. Preventive programs should be actively put in place to detect and correct the most common deviations and violations of the study protocols.

INFORMED CONSENT FORMS

Defies to adequately inform patients about the investigations include the rapid progression and severity of the disease, and the lack of availability of relatives or dependable witnesses, as the patients are usually isolated to avoid transmission of the infection. Poor understanding of the investigation due to their critical state of health, and despair to access medical treatment, may push patients to consent in almost any term. Despite the severity of symptoms, the rapid spread of the infection, lack of effective treatments, personnel shortage, and the hazards of communication when using the personal protective equipment, competent care for the ethical principles of autonomy should always prevail[3]. There is an urgency to create dedicated, dynamic, and particular informed consent forms for patients with COVID-19 participating in clinical trials and observational studies[11]. Because conducting research on COVID-19 has a window of opportunity, RECs have the responsibility of making timely but thorough reviews of COVID-19 protocols. Another important issue to consider is that concurrent studies may compete to reach the study sample size. Patients and their relatives lack the necessary knowledge to be able to decide which is the best option. Finally, a large amount of retrospective papers have been published. Some are based on hospital charts or electronic records, in which informed consent is seldom requested. However, privacy issues should not be underscored. In some cases, private information of participants could be leaked if preventive regulations are not put in place[12], particularly in the current pandemic, where cases must be reported on a regular basis.

Possible measures to lessen risks

A) A simplified, universal informed consent form can be used for all patients admitted to the institution/hospital for observational studies.

B) Tailored informed consent forms must be adapted to the patient's ability to understand. If the patient is unable to write, a special permit should be granted to record verbal consent.

C) Information regarding the nature of the procedure or of the investigation, the expected benefits, the alternatives, and the consequences derived from the subject's refusal to participate in the study should be clearly exposed[3].

D) For clinical trials:

   a. Concerns about rapidly changing information can be documented in the consent form and strategies to overcome this issue must be made explicit (for example, cessation of the trial if some characteristics are met).

   b. Protocols should be followed-up strictly and any changes should be documented and made public as soon as possible.

c. Safety boards and interim analyses should be systematically requested for any new therapy under study[13].

d. In emergencies, when a decision must be made urgently, particularly when the patient is unable to make the decision and the patient's next of kin is unavailable, the treatment may be initiated without prior informed consent[2].

PARTICIPATION IN SEVERAL CONCOMITANT STUDIES

More than ever, patients are being recruited aggressively in clinical trials, in an extraordinary effort to provide the fastest evidence on the pathogenesis of the disease to plan new therapies. The basic approach of assuming that benefits outweigh the risks for some treatments has not proven to be valid in most cases. Challenges in interpreting what is happening in real-time can generate continuous changes to the original protocols. Understanding that we are bearing with many unknown factors requires flexibility for changes. On the other hand, in the context of the COVID-19 pandemic, patients may be exposed to several investigators offering invitations to their research protocols. At the same time, patients may be eager to participate because it may be the only opportunity to receive treatment. When a multitude of protocols are being carried out simultaneously, it may be difficult to objectively give informed consent.

Possible measures to lessen risks:

a) The patient's comfort should continue to be the high-ranking consideration. The investigator should be sure that the patient's participation is voluntary and will not deteriorate the patient's physical or mental health.

b) Several scenarios should be considered in the case of multiple invitations to participate in research protocols such as (in no order in particular): assignment to the protocol that may have most potential benefit, randomization, or, if possible, the patient's decision[14].

c) Institutions and RECs should work together to prevent competition between clinical trials[13]. Only one option should be presented to the patients. The selection of the option should be previously done by a consensus group, based on the best option available to the characteristics of the participant. If the patient declined to participate in the selected trial, a second one could then be offered[15].

CONTINUE RESEARCH PROTOCOLS IN NON-COVID-19 PATIENTS

Continuity of care for other patients and study participants is a major challenge now. Reorganization of the hospital networks has been accommodated to fit the emerging number of severe cases of acute respiratory distress due to COVID-19, leaving almost no available facilities to treat other cases or to continue ongoing (non-COVID-19) research studies. Sick patients might not desire to attend the hospitals, and those that need urgent medical and/or surgical attention do not find optimal care. Study subjects may be reluctant to continue participating in studies that require their presence in health institutions. In addition, medical staff must a priori assume that any patient or study participant can be infected. Operating rooms are empty, partly due to the transformation of hospitals to COVID-19, and due to the high risk involved in operating on someone infected with SARS-COV-2[16]. Moreover, major concerns include the possibility of cross-contamination by asymptomatic health professionals or other staff to the research subject or vice versa.

Possible measures to lessen risks:

a) Assume that each participant is positive due to the high number of asymptomatic individuals and the relative high number of false negatives (or lack of) tests.

b) Defer elective visits at all costs until the pandemic is under control[17].

c) Continue medical attention to selected participants through calls.

d) Implement telemedicine for follow-up whenever possible[18].

e) Implement frequent testing to hospital staff and patients[19].

f) If possible, questionnaires may be filed electronically, and medications can be sent through courier services for a reasonable time.

COMPASSIONATE USE OF DRUGS

The lack of an effective therapy and the publication of preliminary observations with positive results has raised multiple requests for the compassionate use of experimental drugs outside of clinical trials. The European Medicines Agency defines "compassionate use as a treatment option that allows the use of an authorized medicinal product that is under development"[20]. Eighteen out of 28 European countries have defined regulations and procedures to face this critical situation[21]. Compassionate use of experimental drugs may require the supervision of an Ethics Commitee (EC). Guidelines have been built based mainly on the experience of new therapies against cancer. However, modifications of the existing guidelines will be required due to the characteristics of the COVID-19 outbreak. The large number of request may challenge the ability of the drug companies, researchers, and EC to preserve the fair access to the drugs.

Possible measures to lessen risks

a) Governments and institutions should work together with drug companies to design and implement compassionate use programs and prevent unethical conducts. An example is to follow the practices of the "Compassionate Use Advisory Committee (CompAC)" sponsored by Pharma companies but organized by an academic institution[22].

b) Compassionate use programs should be linked with Phase II or III research studies. Otherwise, the clinical experience derived from individual applications is not useful for future patients.

c) EC should have standardized procedures to evaluate compassionate use requests. Proposing physician, patents, and palliative care specialist should fulfil pre-specified criteria to prepare an application.

READING AND INTERPRETING PUBLICATIONS AHEAD OF PRINT

More than half of the pandemic publications correspond to editorials, opinions, letters to the editor, commentaries, or pharmaceutical industry-driven publications[23], and only the rest is original research. The exponential growth of COVID-19 papers responds to the need for experts and analysts to explain the situation's uniqueness. Some of these publications undermined rigorous evidence-based medicine to produce practical, up-to-date information. Usually, the publication process is long and includes two or more external peer reviews, followed by a careful revision of the internal editorial staff. For time optimization, some COVID-19 publications modified this process with expedited revisions done solely by the internal editors[24], resulting in a higher than the usual number of "pre-prints," "in process," or "accepted for publication" manuscripts. To obtain clear objective evidence, readers should be critical before practicing the literature's recommendations.

Possible measures to lessen risks

a) Clinicians can find reliable scientific conclusions in randomized controlled studies, systematic reviews, and meta-analysis. Therapeutic clinical trials provide less robust evidence. The degree in which the findings may be generalized will depend on the study's power, study population selection, and clinical setting similarities.

b) Researchers should look for the availability of open and accessible databases for consultation.

c) Readers should be aware of post-publication issues or possible article retractions, and the concerns, clarifications, or corrections emerging from the scientific community.

CONCLUSIONS

The COVID-19 pandemic will continue to evolve for months to come, creating some uncertainty, challenging the current health care system, and raising important ethical questions[3]. However, the ethical behavior in all aspects should continue to be at the front of considerations. The pandemic has changed some

regular medical activities, but the long-term consequences of ethical-based research should prevail. Adaptation or utilization of universal consent forms, electronic or voice recordings to transmit clear information, and documentation of these procedures may aid the difficulties in informing and supporting the voluntary and informed participation during the pandemic without violating ethical principles in research. Investigators must review more often than ever the outcomes of their investigations and must compare and confront their results on a day-to-day basis with the international literature, to prevent missing important side effects, to identify better options, and to prevent from embarking in ineffective or redundant research. Finally, this outbreak has shown that continuous training in good clinical practices for all members of the medical community is required. It is the first line to prevent unethical behaviors[25].

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