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**Ethical considerations of the dynamics of clinical trials in an epidemic context: studies
on COVID-19**

*Réflexion éthique sur la dynamique de la recherche clinique en contexte épidémique : à
propos des études portant sur la COVID-19*

Short title: Clinical research in the COVID-19 pandemic: ethical reflections

Titre court : Recherches en contexte de pandémie COVID-19 : réflexions éthiques

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Abstract

The COVID-19 epidemic has led to the intense mobilization of all health professionals, including those involved in research. From the very beginning, research ethics committees (RECs) have been called upon and mobilized to carry out the scientific and ethical evaluations of research projects to achieve a sound analysis of their risk/benefit balance.

The aim of this article is to present an ethical reflection on the challenges and consequences of the fast-track procedure for the evaluation of COVID-19 research projects in the context of a public health emergency. Indeed, a large number of protocols of reduced rigor were hastily prepared without collaboration between researchers and in the absence of national regulation. As a result, a number of ethical dilemmas have emerged concerning the opposing needs of pragmatism imposed by the emergency context and the ethical principles that should govern the conduct of research. Moreover, the dispersion of these individual projects, aggravated by excessive media coverage of specific treatments, has resulted in a weakened impact of the research in the epidemic context.

This article provides suggestions for the ethical management of ongoing and upcoming research, giving RECs the opportunity to adapt their evaluations to avoid allowing the pragmatism of the emergency context to subvert the inviolability of the epistemological and ethical principles of research on humans. This reflection may strengthen the ethical basis for the formulation of their decisions.

Keywords : Clinical trial; COVID-19; Emergency; Ethics; Research ethics committee

INTRODUCTION

The emergence of COVID-19 has placed clinical research at the centre of attention of society. Indeed, faced with this unknown disease, it is essential to have a scientifically based response to the need for knowledge that will enable the protection of populations through prevention and treatment. During the first part of the COVID-19 epidemic (spring 2020), more than 550 clinical studies on humans were carried out in France following the unprecedented mobilization of all actors involved in clinical research [1]. Among them, research ethics committees (RECs), whose mission is to assess the conditions of validity of any research project involving humans, were massively mobilized to enable the rapid implementation of these studies. However, such rapidity has not been free of pejorative and counter-productive consequences. A number of projects, very similar if not identical, have been unable to achieve the inclusion objectives required to guarantee the reliability of their results within an acceptable timeframe to enable their take-up by the community and will, at best, lead to publications on partial results or on results which will be communicated too late to be of any benefit.

The increase in the number of research projects that include few collaborative approaches and lack prioritization or coordination, along with the demand for the prolongation of such studies to achieve the recruitment of a sufficient number of participants, raises ethical questions concerning the relevance of such research, the competition for recruitment, the possible over-solicitation of patients to participate, and the nature, content, and timeframes for obtaining results. In addition, the over-mediatization of certain scientific opinions, given the same level of credibility and reliability as the research itself, has not been without consequences in terms of the difficulty of recruiting participants for clinical trials. The role of scientific experts, the research projects submitted for authorization, and information, as well as the communication of research, merit examination in the current context of the COVID-19 epidemic.

Our reflection focuses on identifying and discussing the ethical issues related to the numerous research studies on COVID-19 submitted to the RECs under the emergency fast-track procedure set up during the first wave of the epidemic. Those ethical issues report to the principles of the Declaration of Helsinki which funded the modern basis of medical research: respect for human dignity, charity and non-maleficence, justice, equality and scientific integrity [2]. First, we will present the RECs' missions of evaluating and authorizing research involving humans based on a detailed and complex analysis of the risk/benefit balance. Second, we will discuss the issues and consequences of the conditions for developing COVID-19 research in such an emergency context. Finally, we will present proposals that could be added to the ethical reflections of the RECs concerning future research projects that will be proposed during the evolution of the pandemic, as well as the requests for extensions of ongoing projects.

1- Missions of the RECs: evaluation and authorization of research on humans based on a detailed and complex analysis of the risk/benefit balance.

Health research involving humans can only be justified by a favourable benefit-risk-constraint balance based on a detailed and complex analysis between the individual interest of the participant and that of society. As set out in the original text of the French Huriet-Serusclat law, which regulates research [3], participation in a research project is at the sole discretion of the participant, except for rare exceptions specified in the text, such as inclusion in research protocols of individuals in emergency situations. It is in this context in which consent, informed by prior information, takes on its full value, guaranteeing the free will and free choice of the individual according to his or her own personality, based on sociological, cultural, and life-history elements, within the anxiety-provoking, if not traumatic, context of the disease.

The law, which reflects the societal consensus and therefore its acceptance, is strictly anchored by the ethical reflection that preceded it and the conditions for obtaining such consent, as well as the introduction of limits to the free will of individual participants by stipulating additional protection for people from specific groups (minors, pregnant women, subjects under deprivation of liberty or legal protection, etc.) [3]. Thus, the text stipulates that research may be conducted on these specific groups only if results cannot be obtained by any other means, and therefore provides a framework for the recruitment of participants by investigators. The analysis of the established benefit-risk-constraint balance is not based solely on the individual therapeutic or scientific collective interest, but also the specific expected benefit for this group.

It is in this context that the RECs carry out their missions of evaluating and authorizing any research project involving human participants. There are 39 RECs distributed throughout France. They are composed of two multidisciplinary colleges of 14 members each, representing both the scientific community (first college) and civil society (second college). Each submitted dossier is subject to a scientific and ethical analysis by the committees, enabling them to give an opinion on the conditions of validity of the research projects (Article L.1123-7 of the Public Health Code). In particular, the following points are carefully examined: (i) the protection of participants, including the procedure to be followed to obtain informed consent from patients and the justification for research on individuals incapable of providing their consent, (ii) the relevance of the research, the expected benefit-risk balance, and expected validity of the conclusions, and (iii) the appropriateness of the means implemented to achieve the objectives.

2- Research on humans in the context of an epidemic health emergency, such as COVID-19 in France

a- Adaptation of the French regulatory system

Any emergency context requires adaptation of the regulations. Thus, a fast-track procedure for authorizing research projects, either therapeutic, physio-pathological, or epidemiological, specifically relating to COVID-19 had to be deployed. In France, this new procedure, known as the "fast track" procedure, made it possible to authorize more than 550 highly diverse projects covering all aspects of the pandemic within unprecedented timescales (median of 6 days versus 77 days during normal times) by virtue of the unprecedented mobilization of the various institutions involved (National Agency for the Safety of Medicines and Health Products and the RECs in conjunction with the General Directorate for Health) [4].

This exceptional effort by all the partners involved in medical research in France demonstrates the adaptability of our country's clinical structures, too often criticized for their administrative burden and their relative inertia to implementation.

b- Emergency research design

- Dispersion in the development of research projects

The lack of collaborative approaches between researchers, as well as the absence of national prioritization in this exceptional research effort, has considerably weakened its impact on the evolution of the epidemic. Indeed, about twenty studies have been carried out on the same molecule. Several monocentric studies have been organized on the same topic and populations [5-7]. It must be noted that the many projects, often too complex and/or ambitious, have only very (or too) belatedly been able to contradict and halt non-scientifically based alternative therapeutic treatments that have nevertheless been applied to patients suffering from more-or-less severe forms of COVID-19 in an unsupervised manner without any true analysis of the results in terms of either therapeutic benefit or tolerance. The only argument for these

treatments has often been based on the sole need to act. In this context, we were far from "*primum non nocere*" and closer to the search for the Holy Grail without any safeguards.

- Hasty development of protocols

The clinical studies submitted to the RECs showed the drafting of these research protocols to often be incomplete. The urgency rendered the designers incapable of considering all aspects related to the research: only the scientific rationales, contexts, and concepts were sometimes argued, as many dossiers were presented without having clearly envisaged the conditions of recruitment or providing information to participants and their relatives, thus calling into question the feasibility of the procedures for including the participants. Certain choices were sometimes based on conjecture concerning the evolution of the epidemic, such as the selection of the participating centres. Although the urgency of the situation probably encouraged innovation, it also prevented the true context of the studies from being taken into account and contributed to the fact that the recruitment conditions did not allow the defined objectives to be achieved.

The first wave of COVID-19 shattered well-established certainties in clinical research methodology, such as the need to conduct studies as monotherapies or against known and widely used references. This raises the question of whether scientific constraints have distanced research projects from the reality of the context of the medical clinic and care, making it difficult for patients to accept them, and thus their feasibility. Indeed, in addition to its value and scientific interest, the ethical dimension of a research project is also assessed by its level of acceptability by the population concerned and, more broadly, by society. A "perfect" research protocol based on well-established scientific criteria satisfies peer reviews much more than future participants.

b- Excessive media coverage

The media coverage of certain so-called "miracle" treatments may have been detrimental, by delaying the implementation of studies on other molecules. As the French Academy of Medicine has stated, "*Scientific truth cannot be decreed by applause. It does not emerge from political discourse, petitions, or social networks. In science, it is neither the weight of the majority nor the argument of authority that is the law*" [8].

Moreover, the experience of the first wave of the pandemic has unfortunately discredited public confidence in experts, who have been more inclined to state their convictions or intuitions rather than scientific facts. This phenomenon could only provide fodder for the media, allowing them to highlight and value their personality, charisma, or ability to communicate to the detriment of the reliable and factual scientific analysis of data.

On the basis of the lessons learned from the problems of the clinical trials of the first wave of COVID-19, RECs must carry out a global reflection and put forward proposals to further develop their expertise and opinions in relation to the ethical principles like the question of the relevance of research.

3- Considerations for the ethical management of ongoing and future research

a- Resituating research in the overall context of general societal interest

In research involving humans, it is *a priori* difficult to prioritize research projects based on the expected results, which are, by definition, hypothetical. However, in the context of the COVID-19 pandemic, the knowledge acquired on this virus and its consequences should now make it possible to prioritize projects in a more relevant manner, according to their direct or collective therapeutic interest, with the goal of updating and improving scientific knowledge and public health data, particularly epidemiological data. In addition, the experience acquired during this pandemic imposes upon the various actors and institutions involved in research,

and specifically the RECs, an ethical responsibility to base the interest of a research project not only on the aspects and contents of the presented application, but also in the more general context of societal interest. Thus, it is not sufficient to consider only the effects of the research on the rights and interests of the participating and involved individuals. Such research, however well designed, could harm the collective interest by interfering with the implementation of another study (and its results), simply because of its competitive weight in terms of recruiting the necessary participants.

The ethical basis of biomedical research cannot be limited to mere compliance with regulations but must also be based on obtaining results in a timely manner.

Results that are obtained too late, because of the difficulties encountered in reaching the necessary number of participants to meet the set objective, will render the research useless and therefore ethically unacceptable. This is true even if it would result in publication in more-or-less prestigious and indexed journals and bring recognition to its authors and prestige and other advantages to its sponsors.

This situation is not specific to this pandemic. In many research projects, the opinion of the RECs must consider the consequences for participants and the validity of the study results, as well as incorporate the need to prohibit any possibility of simultaneous participation in other research. Indeed, this constitutes a not insignificant risk of the loss of opportunity for the participant, as well as society, by delaying the emergence of further progress. This phenomenon occurs frequently in cancer research, in which the duration of the proposed studies is increasingly merging with the life expectancy of the participants.

In particular, concerns have been raised about the possible over-solicitation of patients with a positive diagnosis of COVID-19 for their participation in research projects, which are multiplying. There is therefore a high probability that a patient will be repeatedly solicited in

his or her care pathway to participate in studies. In addition, the emergence of epidemiological studies or surveys for which patient participation can also be expected may arise. Such a risk of over-solicitation should therefore be considered in supporting an effort to move towards the coordination and prioritization of research projects on COVID-19.

b- Putting ethics back at the centre of research

As the Ethics Committee of the CNRS reminded us on April 7, 2020 concerning the emergency context, the need to resort to pragmatic reflection and potential pressure must not prevail over the respect of ethical principles, nor encourage us to free ourselves from them [9]. It should be recalled that the integrity of scientific research is based on epistemological and ethical principles, guaranteeing rigor, reliability, and honesty. Respect for these principles guarantees the credibility of research on humans and the trust that can be placed in it by society. In this respect, the Academy of Medicine stipulates that "*Although the anxiety-provoking context of the pandemic stimulates competition between research teams throughout the world, this imperative cannot justify the use of inappropriate methods, botched studies, or the greed for exclusive communication*" [8]. The first wave, by its speed and brutality, placed the organization of research in a state of emergency. Now that this wave has passed, it would be ethically unacceptable not to focus on the general consequences of competitive recruitment as we move forward.

This context of crisis and emergency, unprecedented in its scope, highlights a trend, hitherto contained and controlled, in which the greed for individual recognition, supported by the excessive quest for publications stamped "COVID", tends to supplant the collective scientific interest in the search for hypotheses and reliable data. The authoritative individualistic logic of justice, in subscribing to the professional interests it frames, neglects to consider that the only ethical justification for research lies in the collective improvement of well-being that

must result from the expected new knowledge [10]. It cannot be accepted that research efforts supported by the community - using collective resources - are of interest only to the professionals who design it, having a direct impact on the choice of research topics, in favour of the researcher's interest rather than that of the community and its needs, at the time the study is designed. Neither researchers nor ethicists assume the cost of research, but citizens and especially patients. How do we ensure that one research project is more relevant to patients than another? How can we justify the existence of multiple projects on the same topic, with similar procedures, in different centres and on a very small number of subjects?

Justice therefore refers not only to the selection of participants, but also to the resources allocated to research. The tools of economic analysis provide the means today to combine the multiple dimensions of advantages and disadvantages and to order the proposed solutions towards more justice [10].

It is important to recall the terms of the World Medical Association's Declaration of Helsinki: *"Even the best proven interventions must be continuously evaluated by research into their safety, efficacy, appropriateness, accessibility, and quality... Medical research is subject to ethical standards that promote and ensure respect for all human beings and protect their health and rights"* [2]. The ethical principle of respect for dignity, according to which all research involving humans has the patient as its end, through the prism of his pathology, his disorder and therapies for the preservation of his health or the improvement of it, must remain unequivocal in the face of the tendency to subordinate the welfare of research subjects to the objectives of the research. As sometimes explicitly invoked, does the main ethical issue reside only in obtaining a rapid and unambiguous response to the objectives of the study? There would then be a great risk of deviating from the principle that human subjects should not be treated as a means to an end [11]. In other words, it is not acceptable to instrumentalize patients to satisfy the narcissistic stakes of researchers. It is therefore a question of dignity, as

an intangible dimension of man and for man, as "*a requirement which is in itself its own end and which cannot be a means to an end other than itself*" [11]. Human dignity, in its moral and legal sense, is not a trait, but the embodiment of intangibility; it comes from interpersonal relationships of mutual gratefulness and symmetry [12].

In addition to these considerations, the high level of technicality and high degree of specialization in clinical research, which implies a high level of expertise from the involved actors, can lead to confusion between the progress of knowledge for its own sake and that of those who bear it, and the relevance of such progress for improving the lot of patients or the health of populations [13].

By including their opinions in an in-depth ethical reflection, both for the continuation of COVID research projects, as well as future projects, RECs have the duty to contribute to restoring public opinion to the essential importance of the value of clinical research and, in this way, to facilitating public support for and participation in these studies.

4- Inputs for the reflections of RECs on requests for COVID-19 study extensions

RECs are now receiving requests to extend studies that did not achieve their inclusion objectives during the first wave. In addition to the administrative aspects often put forward by the sponsor in such a request, the RECs may consider the following points, in particular:

- Are the scientific bases of the project still valid and do they integrate the entire progress of knowledge acquired since the initial submission of the project?
- Is the requested extension period adapted to the objective of the study in terms of recruitment capacity, as well as the possible obsolescence of the project due to results that are obtained too late or by another protocol that is more likely to yield results and individual and/or collective benefits?

- Has the project presented been included in all of the research projects of the participating research organization(s)?

The RECs do not have the means to carry out such a feasibility analysis. Indeed, each of the 39 Committees only receives the research protocols that it has to evaluate. They do not have any information on other projects in progress. It is therefore impossible for them to carry out an analysis of the overall situation in terms of patient recruitment. Consequently, it would be highly desirable for such regulation of the prioritization and ranking of research projects to be entrusted to an independent national authority. Pending the implementation of such coordination, it is up to the sponsor to provide the RECs with the following information with its request for an extension:

- Circumstantial elements enabling the removal of all obstacles that have prevented the sponsor from fulfilling their commitments for the submitted project
- An inventory of the inclusions already made, including a precise and relevant analysis of the corrective measures put in place to reach the study's target population
- A table of all COVID-19 research projects underway in their structure, with the inclusion curve for each project, to demonstrate the true possibility of non-competitive inclusion.

CONCLUSION

As a result of the errors of research during the first half of the 20th century and following substantial reflection, our society has built the ethical foundations of research on humans, largely based on the validity and reliability of the scientific basis of data and hypotheses.

The recent experience of the emergency phase of the first wave of the Covid-19 epidemic has enabled the RECs to more advantageously support the ethical basis for the formulation of

their opinions concerning "COVID" research projects. These can be based not only on the acquisition of new knowledge to be included in a request for an extension of inclusions, but also the risk to other more innovative or promising projects that arises from the pursuit of uncontrolled competitive recruitment between research projects.

Issuing a favourable or unfavourable opinion on the extension of a project or new research project on COVID-19 forces the RECs to make complex ethical choices. They cannot be limited to the administrative analysis of the presented research protocol application but must place it in the general context of all projects. Such positioning will allow not only sufficient ethical validation, but also a successful outcome of the projects and, thus, better acceptance and adhesion of the participants to research, as well as society as a whole.

Conflict of interest: none.

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