Revising the legislation of Ethics Committees to ease biomedical research in humans across the world: lessons from the COVID-19 emergency

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Abstract. As a legislative domain that considerably influences implementation of biomedical research, the need to improve the legal rules surrounding the organization and functioning of Ethics Committees in public health, toxicology, and clinical medicine is widely recognized within and outside the European Union. Given the often-heard complaints by researchers about the complexity and length of both the application and the review process by Ethics Committees in the authorization of new studies, adjustments to their legislation appears to be warranted. Within the European Union this seems also all the timelier, given the upcoming new regulation of clinical trials to become effective in early 2022. For this process, valuable lessons can be gleaned from the COVID-19 pandemic and the changes in the functioning of Ethics Committees that were adopted to cope with the exceptional circumstances imposed by the health emergency. The pandemic experience clearly indicates that a more responsive and practical system of applications' review by the Ethics Committees can be squared with acceptable levels of transparency and reliability in ethical accountability. For this reason, countries like Italy should consider undertaking a significant revision of the public law rules that govern the review processes of Ethics Committees in light of the pandemic experience. (www.actabiomedica.it)

Key words: Ethics Committee; comparative public law; European Union legislation; COVID-19; public health

Introduction

Ethics Committees play a significant role in the working agendas of researchers in biomedical fields and especially of those studying human subjects in clinical, epidemiologic and toxicological settings (1). The Ethics Committee authority rests on the general and somewhat undisputed understanding that biomedical research is not an autonomous value but is instrumental to other superior goods (e.g., human life). In this respect, Ethics Committees are charged with the eminent task of verifying that the means never contrast with the ends. While the idea that ethical norms should guide and to some extent constrain scientific research is lost in the mists of time, the most influential documents are relatively recent, the first paramount example being Nuremberg Code that followed the Nuremberg Trials and the terrifying atrocities occurred in the Nazi Germany (2,3). Today, however, the Declaration of Helsinki of 1964 remains the primary reference for ethical regulations of medical research involving human subjects, including research on identifiable human material and data. Developed by the World Medical Association, both in the original version and in its first revised version of 1975 the Declaration is considered the cornerstone for ethical principles regarding human

experimentation (4). At the same time, given the open-endedness of its clauses and the fact that it is technically not binding under international law, there remain significant differences in the practice of Ethics Committees of different countries which can ultimately be explained on cultural grounds (2).

While the need of ethical constraints to scientific research lies undisputed, there is also a general and substantiated concern that the complexity of applications to the Ethics Committees for ethical approval of prospective research and the length of the respective review processes unduly delay and hamper the implementation of scientific inquiry involving humans (5-11). The grievance is somehow transnational, in that it can be found both in Western countries as well as in middle/low-income developing countries (7-15). To some extent, the complaint has not gone unnoticed as one can see in the domestic changes of countries such as Italy with Law n.3, January 11, 2018, or the European legislation about clinical trials (10,13,14,16), which is based on the European Regulation 536/2014 about human trials with medicinal products. This latter European legislation has eventually paved the way for the European Commission Clinical Trial Regulation which is to become effective on January 31, 2022 and to repeal European Directive 2001/20/EC (17): such regulation is said to fill a relevant gap that has been repeatedly highlighted by investigators (18,19).

In this paper we aimed to determine if the procedural disruptions induced by the COVID-19 pandemic allowed the public law rules regulating the institutional review activity of Ethics Committees to remain effective and cope with the emergency period, if their activity during the early, most severe COVID-19 wave could yield elements of interest to pave the way for an effective reform of the organization and procedures regulating the Ethics Committee activity. This in the interest of effectively performing scientific research but without lessening compliance with ethical standards and protection of safety of patients against toxicological endpoints and other issues of ethics relevance. We performed this assessment by carrying out a scoping review of the 2020-2021 literature, in a perspective of comparative health law. Finally, we will also conclude on some policy takeaways for the Italian case.

The COVID-19 experience

A few reports from different world regions have bene recently published about the functioning and performance of Ethics Committees during COVID-19 pandemic, and particularly in the first part of 2020 (20-25), when the SARS-CoV-2 outbreak swept across many European countries, Italy first, and later on in other regions all over the world (26-28). This has been done through a direct investigation of the Ethics Committee activities, and through an assessment of the ethical issues as reported and declared by investigators in their papers. This evidence is of considerable interest, both to assess if during a pandemic or comparable conditions of extraordinary health emergency an effective institutional review of biomedical research may still be carried out, and to derive clues for a swifter and better functioning of these committees on a regular basis, still ensuring full respect of the ethical principles.

Overall, one study carried out in the Netherlands has shown that during the COVID-19 pandemic in the country it was implemented the so-called 'fast-track-review-procedure' (23). This review system was designed to enable to carry out biomedical research particularly during the COVID-19 emergency and especially the first wave of the outbreak. The authors collected in May-June 2020 through online questionnaires and interviews a comprehensive set of information about the implementation of institutional reviews of COVID-19-related studies by the 20 Dutch Ethics Committees. The survey included questions about the details of review procedure, the timelines and the 'satisfaction' by both Committee reviewers and COVID-19 investigators for such as review process. Overall, the feedback gave clear evidence of the high quality of the review process, of the swiftness of the process of Committee review (8.0 days during the emergency period, compared with the usual figure of 50 days before the pandemic), and of the satisfaction of both reviewers and investigators. Despite this short and clearly accelerated timeline, it was general opinion by all professionals involved that the review process has not affected the evaluation which was still thorough and ensured the high ethical standards, i.e. with reference to careful scrutiny of the proposals submitted

and accuracy, as compared with the pre-pandemic period. This was perceived as due to the awareness of the emergency period but also to the avoidance of useless bureaucratic procedures (such as signature leniency), and eventually to online working, thus speeding up the entire review process. As noted by the authors of the paper, these results showed full compliance by Dutch Ethics Committees with the requirements of the European Network of Research Ethics Committee: "the pressure currently being exerted on medical research must not lead to research or testing of pharmaceuticals on humans without complying with the ethical standards applicable to medical research" (29).

Within a very different geographical and social context, a group of Chinese investigators assessed the review process and timelines of the Ethics Committee of the Henan Provincial People's Hospital in an early period of the COVID-19 epidemic from February 2 to March 7, 2020 (25). Results of their assessment showed that the timeline for initial review of the submitted research proposals became extremely short, i.e. 2.13 days from request submission until an initial review decision, and 12.4 days to provide a final decision after full review of the application. Around 15% of the submitted proposals were approved as such, 75% approved after requesting some modification, and 10% rejected.

Another study sought in June 2020 detailed information from the 90 Ethics Committees of Italy, obtained a feedback from only 46 of them, about Committees' activities during the first COVID-19 wave, March-May 2020 (24). The responses showed that the workload due to the high number of submitted research proposals increased of 75% among the Committees located in areas with high COVID-19 incidence and of 53% in the low incidence regions. Ethics Committees generally moved to online activity only, or to a mix of smart working and on-site activity, the first modality representing nearly 80% of the total activity in areas with high COVID-19 incidence, and 60% in low-incidence areas. Though the increased workload and the organizational difficulties hampered an in-depth assessment of the proposals, members of the Committees perceived their assessments as being still characterized by satisfactory quality and capacity to fully ensure that patients' safety, respecting the key ethical principles of scientific research. Nevertheless, a general perception of Committees' members was that many submitted studies were characterized by a lower scientific quality compared with the antecedent period in the area where the number of proposals markedly increased.

A scoping review assessed the 'ethical features' of studies on COVID-19 published from December 2019 until May 2020, by assessing which type of ethical approval and guidelines these studies followed in the phase of institutional protocol review and during their implementation (22). Results of this assessment, based on almost 12000 screened papers and 656 included in the final analysis, showed that preliminarily ethical approval was sought and obtained by over 80% of the studies, through review by different bodies such as institutional review boards, Ethics Committees and research ethics boards. However, an in-depth assessment of the ethical procedures followed to get the informed consent by study participants showed that only 30.6% of the studies highlighted the implementation of such ethical procedure, while 30.2 % obtained consent waivers and 39.2% did not make any mention of such ethical issue in the paper content. These features considerably differed across studies, depending on the continent, the size, the publication type and the impact factor of the relevant journal. The authors highlighted this heterogeneity, the flexibility of the ethical procedures and the large number of studies either dismissing or ignoring the key issue of participant consent. They also outlined that this overall picture raises some concern about the functioning of both biomedical research and Ethics Committees during an extremely severe emergency period such as that characterizing the first wave of COVID-19, despite acknowledging that most studies were still adhering to some kind of ethical regulations and institutional control.

Another recent review aimed at investigating the same issues of the aforementioned scoping review, i.e. which kind of compliance with ethical standards was preliminarily obtained and reported by investigators involved in COVID-19 human studies (21). This review was carried out by retrieving and scanning all the relevant articles published up to November 2020, focusing on open access and English language related to COVID-19 research in humans. The assessment

retrieved nearly one thousand papers, almost all published in journals having policies full compliant with the International Committee of Medical Editors (ICMJE) ethical standards. In these articles, reporting of ethical details such as preliminarily approval by an Ethics Committee, collection of informed written consent by study participants, and avoidance to provide individual details has not always been satisfactory particularly for studies carried out and published during the first wave of the pandemic. Such reporting was higher in trials (100% both in the early and the second waves/periods) than in observational studies (rising from 70% to 80% over time). However, few details of the ethical aspects of the study were generally reported. As far as informed consent request for inclusion in the study was considered, most case studies published in the first wave did not report any documentation of such consent (over 70%), while this figure decreased to 38% over time. Corresponding figures for observational studies were 92% and 36%. Finally, for case series the percentage of studies with no detail about informed consent by participants remained quite high over time with little difference, i.e. 71.1% in the first wave and 75% in the second one. About patient confidentiality, in case studies a progressive decrease over time was noted (from 37% in April to 4% in November) for variables characterizing individual patients, which could have allowed identification of the subject. In case series, aggregate data were generally used thus preventing patient identification, though some studies reporting initials of participants also emerged. Overall, these findings highlight that the COVID-19 pandemic has impacted the quality of the ethical scrutiny of the biomedical research on COVID-19, but this to a limited extent and in addition with a clearly decreasing trend over time, reaching a satisfactory picture after the first, most acute period of the health emergency.

Finally, a study by a group of American investigators showed that, following a survey across 14 US Human Research Protection Programs, among 194 COVID-19 specific research protocol, only one study was assessed with a possibly inadequate procedure and care, raising some ethical concerns (30). In addition to this excellent finding, the authors noted that usual time for the convened and expedited protocol review was 15 days, much improving compared to the average of 40 days generally required for these committees, and even faster if compared to figures of 70-180 days characterizing other teams of Ethics Committees. As expected, protocols that were not subject to ethical review and rules as strict as those characterizing the toxicological, clinical and public health projects, i.e. the social/behavioral studies, required even less time for review, on average 11 days from submission to final approval.

Discussion and conclusions

The need to adequately address the ethical issues to increase the credibility of biomedical research has been largely recognized, and this also includes the consideration and disclosure or commercial interests that may affect the freedom of scientific research, and the reporting of the toxicological outcomes in both non-experimental and experimental human studies, i.e. observational studies and trials, generally in the form of randomized controlled trials (13,16,31). This is crucial not only for a correct implementation of human (and non-human) studies in the field of public health, toxicology and human medicine, but also for the credibility of their results, i.e. the capacity of these studies to be interpreted by both the scientific community and the general population as unbiased and independent. The activity of the Ethics Committees in charge of scrutinizing biomedical research projects has been extensively outlined and regulated during the last years, based on legal (public law) and non-legal (professional) regulations and principles (1,32).

The overview of what happened in reviewing and approving the research protocols by Ethics Committees during the acute health emergency represented by the COVID-19 pandemic is of extreme interest, clearly showing that the procedures and legislation controlling their procedures could undergo a sweeping overhaul and substantial changes. This seems particularly necessary to decrease the bureaucratic delays hampering scientific research, i.e. shorten the timeline between submission of the research proposals and their review and final assessment, without any reduction in the adherence to the key ethical principles. Such goal could be achieved through organizational changes in the Eth-

ics Committee handling of submissions or by a more substantial, long-term change of the laws and regulations concerning these committees. For instance, Pan American Health Organization has identified some of these possible changes, in order to ensure a much higher speed of their activity still maintaining an high standard of review (20). These measures include a shift to online procedures from physical work and meetings, as occurring before the COVID-19 pandemic, a tighter interaction between Ethics Committees to streamline multicenter proposals, the lessening avoidable procedures such as non-electronic signatures, the addition of *ad hoc* experts to the Committees for a swifter review of highly specific applications, the institution of sub-committees with highly specific review, the shift from regional committees to a review model based on centralization at a single national center, a better training of the Committee members, a full digital handling of the documents and the procedures, establishment of tight internal deadlines for all phases of the review process. Interestingly, all these choices appear to be feasible still ensuring full adherence to national and international research standards of the research activity involving human subjects, either experimental (e.g. clinical trials) or nonexperimental (otherwise named observational, such as case-control and cross-sectional studies) (33). Furthermore, they are fully consistent with the implementation of the digitization process as envisaged in the by the digital innovation promoted by the recent National National Recovery and Resilience Plan (34).

In addition to the aforementioned organizational changes, some modifications of the legislations and the rules concerning the Ethics Committee activities appear to be needed in an effort to improve the swiftness of their procedures. Such changes should be made aiming at streamlining the process, but still fully ensuring safety and protection of study participants, either during a health emergency such as COVID-19 or on a regular basis. For instance, providing informed consent by participants to a study, either experimental or not, should be possible also through digital techniques and devices, such as emails, SMS or other techniques through the use of mobile phones. Some authors have also considered the possibility to dismiss the collection of informed consent or its signature for studies carried out during an emergency period, or of delaying the informed consent to a subsequent period (35), though such as choice has also been challenged as not compliant with ethical guidelines even in situation of duress (24). In order to fulfill respect of all key ethical guidelines, collection of participant informed consent should always be guaranteed, and any disclosure of individual information leading to the identification of the study participant must be avoided, even more during emergency periods. This has been adequately highlighted by the European Network of Research Ethics Committees, that in 2020 has acknowledged the potential for much improved and swifter procedures for the review of research projects, but still maintaining a satisfactory degree of 'ethical safety' of those studies (29).

Other regulatory choices made during the COVID-19 emergency period that can also be envisaged on a regular basis, there is the possible centralization of the review process in one single center at the national level (33,36), though this could not always work as a better solution in case of specific local characteristics (6,16). The reduction of the quorum needed to take the final decisions about the submitted protocol, or the use of staggered review and decision-making by the Committees particularly when members are overwhelmed, and finally the mandatory adoption of tight deadlines for the review process. The past point is of particular relevance, since as it has been shown by a review of the Ethics Committee behaviors during COVID-19, the usual timeline of the review process could be easily streamlined and shortened without substantial loss to its quality. This is of key relevance in order to carry out innovative and potentially most beneficial clinical and epidemiologic studies, in the interest of patients and the general population, as well as to address toxicological endpoints of major relevance when testing the safety and effectiveness of new drugs.

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