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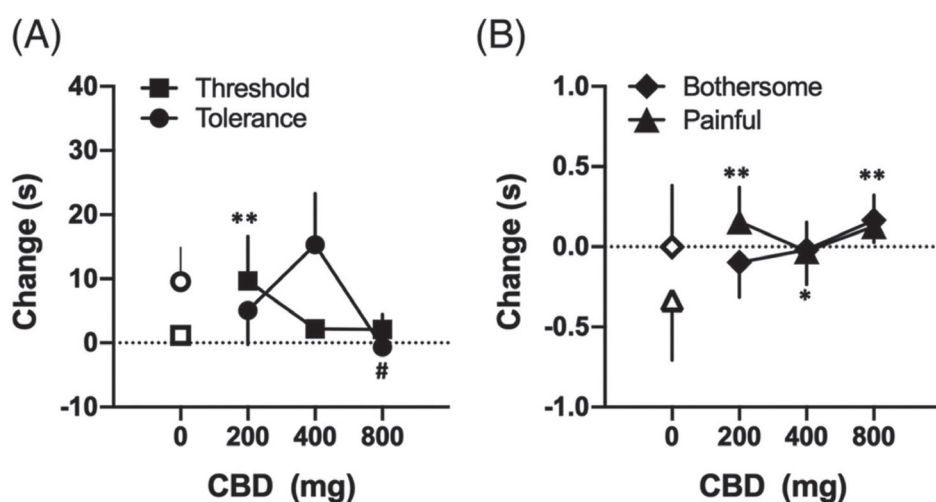
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Rethinking the role of Research Ethics Committees in the light of Regulation (EU) No 536/2014 on clinical trials and the COVID-19 pandemic

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Research Ethics Committees (RECs)—or Institutional Review Boards (IRBs), as they are known in the US—were created about 50 years ago to independently assess the ethical acceptability of research projects involving human subjects, their fundamental role being the protection of the dignity and rights of research participants. In this paper we develop some critical reflections about the current situation of RECs. Our starting point is the definition of the role they should ideally play, a role that should necessarily include a collaborative approach and the focus on the ethics component of the review. This ideal is unfortunately quite far from reality: inadequacies in the functioning of RECs have been discussed for decades, along with reform proposals. Both in the US and in the European Union (EU), reforms that aim at the centralization of the review process were recently approved. Even though these reforms were needed, they nonetheless raise concerns. We focus on two such concerns, related in particular to Regulation (EU) No 536/2014: the risk of narrowing the scope of the ethics review and that of disregarding the local context. We argue that the COVID-19 pandemic paved the way for the transition towards the centralized model and that an analysis of its impact on the research review process could provide some interesting insights into possible shortcomings of this new model. We conclude by identifying three objectives that define the role of a REC, objectives that any reform should preserve.

KEYWORDS

Research Ethics Committees, Institutional Review Boards, research ethics, Regulation (EU) No 536/2014, COVID-19

1 | INTRODUCTION

One of the fundamental ethical requirements of research involving human subjects is that every research project must undergo an independent assessment of its ethical acceptability.^{1–4} The awareness of the need for such independent review developed in the 1960s in the US as a consequence of a series of infamous scandals related to research with human subjects.⁵ Ethical violations of different kinds

seemed to be ordinary rather than exceptional⁶ and this fact made clear that investigators' judgment was not sufficient to “protect the dignity, rights, safety and well-being of research participants”.² Hence the need for independent review bodies whose approval started to be compulsory before any study could be undertaken: in the US the National Research Act⁷ of 1974 established Institutional Review Boards (IRBs), in Europe in 1991, Directive 91/507/CEE⁸ established Ethics Committees, now more correctly called Research Ethics

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Committees (RECs)⁹ to distinguish them from Healthcare Ethics Committees (HECs). In this paper we will use just the denomination “RECs”, which we prefer because it highlights the ethical focus of the committee review, a focus we deem essential.

The ultimate goal of RECs is to ensure that research conforms to ethical and legal standards and, in particular, that participants' rights are protected. Due to their role, RECs find themselves in the unique position of being at the intersection of the main stakeholders involved in research: participants, healthcare professionals, investigators, research institutions, contract research organizations (CROs), sponsors, regulatory agencies. However, if we look at how they actually operate, the enormous potential of RECs is often not met, and the risk that they end up being merely bureaucratic boards is real.

In this paper we develop some critical reflections about the current situation of RECs. We first present two fundamental elements that in our view should define the role RECs have to play if they want to fulfil their ethical task. Then we briefly discuss some of the main critiques and complaints raised against them in the past decades: such critiques and complaints explain the recurrent calls for reforming the ethics review system. Indeed, both in the US and in the EU some reforms have recently been approved. However, these reforms raise serious concerns because, despite tackling some of the limitations of the current situation, they could increase the gap between the reality of RECs and the role they should ideally play. Interestingly, the COVID-19 pandemic has given us a glimpse of what the future could be like: by presenting an example of how the ethics review system of research protocols has changed during the emergency, we aim to identify some pros and cons of a centralized review mechanism. We conclude by proposing three objectives that essentially define the role of a REC and that any reform should preserve.

2 | THE AIMS OF A RESEARCH ETHICS COMMITTEE

The fact that REC approval is necessary to conduct research and the great amount of paperwork related to the review procedure are probably the main factors contributing to the widespread image of RECs as “research courts” delivering sentences and fulfilling a merely bureaucratic task.¹⁰ However, this is not the role RECs should play in the research field. We argue that, if they want to be faithful to their original mandate, RECs should necessarily aim at realizing two objectives in particular: practising a collaborative approach and focusing on the ethics component of the review.

Firstly, notwithstanding its independence, the REC should be considered more as a partner and a supporter in the research process rather than a judge and an obstacle.¹¹ As stated by the Declaration of Helsinki (Art. 23), the purpose of the review process is to offer “comment” and “guidance”, in addition to approval. The same view on the desirability of cooperation between investigators and RECs is shared by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (henceforth, “National Commission”) that, in its report on IRBs, describes their role as that of

sharing with investigators the responsibility of determining whether research projects fulfil ethical standards and of “working closely with investigators to assure that the rights and welfare of human subjects are protected and, at the same time, that the application of policies is fair to the investigators”.^{12(pp1-2)} Moreover, the National Commission suggests that IRBs can play an important educational role, both by becoming resource centres for information regarding ethical and legal requirements, and by engaging in research ethics education activities for the research community and the public. This description of the functions of a REC is consistent with the idea that such committees should encourage clinical studies that are relevant and scientifically sound and should provide support in identifying and tackling the related ethical issues.

The second crucial element is the focus on the ethics component of the review. Even if it is undeniable that RECs have to fulfil many regulatory obligations and verify that research protocols are compliant with legal norms, the core of each review should be the evaluation of the *ethical* requirements. It is worth pointing out that the ethical requirements should by no means be considered as related mainly (or even only) to the informed consent procedures, nor to just some specific details of the research project: almost every aspect of research with human beings could be ethically sensitive. On the one hand, this is because clinical research is a complex activity that can raise a lot of ethical issues,⁹ that depend on the kind of research, the design, the target population, the local context, etc. On the other hand, the ubiquitous risk of ethical quandaries is related to the very nature of the practice of clinical research, a practice in which participants “are used for the benefit of others and are at risk of being exploited”.^{13(p125)} It is precisely because of the intrinsically morally problematic nature of research involving human subjects that RECs should focus on the ethical acceptability of the protocols they review. This explains also why some guidelines⁹ and scholars¹³ highlight the importance of assessing first and foremost the social value of research: without the potential of improving health care, a research project lacks the basic ground for ethical justification. As the National Commission states: “The ethical conduct of research involving human subjects requires a balancing of society's interests in protecting the rights of the subjects and in developing knowledge that can benefit the subjects or society as a whole”.^{12(p1)} This balance should be the ultimate purpose of the work of RECs: a task that clearly goes far beyond a purely formal check that legal requirements are met.

3 | RECS BETWEEN PAST AND FUTURE: LONG-KNOWN INADEQUACIES AND RECENT REFORMS

Inadequacies and failures in the functioning of RECs have been discussed for decades, along with reform proposals.¹⁴ The debated issues are countless. At one level, the discussion revolves around concrete obstacles to RECs' good performance, like the fact that they are often understaffed and overworked and lack training in research ethics.¹⁵ These are real problems that seriously undermine the capability of

RECs to adequately perform their tasks, which include not only the review of research proposals, but also the monitoring of approved studies and the ongoing ethics education of their members. At another level, the focus is on the shortcomings of the actual review system, in particular the slowness of the review process and the inconsistencies in the evaluations by different RECs, with regard both to the number and the type of revisions they require.^{16–20} These inefficiencies explain the perception, widespread among researchers, of the overview system as a barrier to scientific progress rather than a constructive process necessary to protect participants' rights and well-being.²¹

A further matter of concern is the lack of structured and systematic evaluation of the REC system and the absence of data to perform an adequate assessment of the performance of RECs.^{16,22,23} Moreover, many contributions underline the importance of considering how changes in clinical research affect the ethics review system and how this system should change as well to remain effective even in the most recent research scenarios: can the local REC model appraised by the National Commission still work for studies that are increasingly sponsor-driven and carried out in many research sites at the national and international level?^{14,24} What consequences will big-data-related research have on the ethics review of studies, given the shift in the way research is designed and carried out?^{25,26}

This situation led to the reform of clinical trials regulation, that has recently occurred both in the US and in the EU. In the US the revised version of the “Federal policy for the protection of human subjects”²⁷ (known as the Common Rule) was published in the *Federal Register* on 19 January 2017, and has become effective starting 21 January 2019 (or 20 January 2020, with regard to the cooperative research provision, sec. 114). One of the main changes²⁸ pertains to the review procedure for multisite clinical trials that now relies on a single IRB (§46.114 [b]).

In the EU, the Clinical Trials Regulation (Regulation (EU) No 536/2014)²⁹ entered into force on 16 June 2014. However, the timing of its application depends on the development of a fully functional EU Clinical Trials Information System (CTIS): on 21 April 2021 European Medicines Agency's (EMA) Management Board confirmed that the CTIS is fully functional and should go live on 31 January 2022.³⁰ The new Regulation explicitly aims at simplifying and harmonizing both the application and the evaluation procedures for clinical trials, in order to ensure “that the Union remains an attractive place for conducting clinical trials” (whereas no. 8). The sponsors shall submit only one application—regardless of how many member states will be included in the trial—which is divided into two parts. Part I (Art. 6) concerns the so-called “technical-scientific aspects”, including the evaluation of the methodology, the clinical relevance, the risk/benefit ratio, and will be reviewed by one reporting member state that will prepare an assessment report in agreement with the other member states involved. Part II (Art. 7) concerns aspects that each member state should assess for its own territory (like informed consent procedures, subject compensations, participants selection), by means of a single decision. How this single decision shall be reached is left to the deliberation of each member state (whereas no. 18) and is a matter of dispute.³¹

Both reforms aim at addressing some of the inadequacies discussed above, especially the uncertainty about the time lag between the submission of a research project and the final REC decision, and the scarce coordination among RECs, that often leads to a great variety in the decisions they reach and in the revisions they demand. Even if there is agreement that these were serious shortcomings that needed to be tackled,^{32–34} many commentators are doubtful that the centralization of the review process, besides being more efficient, will allow RECs to guarantee the protection of research participants.^{33,35,36}

The concern is particularly serious in the EU³⁷ because the decision of splitting the application into two parts determines two different reviews, one of the “technical-scientific aspects”, the other of the local aspects of ethical relevance, without any guarantee that RECs will be involved in the evaluation of Part I. It is up to each member state “to determine the appropriate body or bodies to be involved in the assessment of the application to conduct a clinical trial and to organize the involvement of ethics committees” (whereas no. 18) and some member states have already opted for narrowing the scope of the ethics review performed by RECs to Part II.³⁸ For this reason commentators wrote that the new Regulation “defeats the role of ethics committees”^{39(p504)} that are gravely marginalized.³⁶ The idea that basic aspects of clinical trials—like its methodology, clinical relevance, objectives, the admissibility of placebo and the risk/benefit ratio—do not require an ethics review is clearly incoherent with the role of RECs as described above and is in contrast with the main international documents relevant to the ethics of research with human subjects.³⁸ CIOMS Guideline 23 is very clear in this regard: “research ethics committees must always have the opportunity to combine scientific and ethical review in order to ensure the social value of the research [...] The *ethical* review must consider, among other aspects: the study design; provisions for minimizing risk; an appropriate balance of risks in relation to potential individual benefits for participants and the social value of the research; safety of the study site, medical interventions, and monitoring safety during the study; and the feasibility of the research”.^{9(p88)} That in some European countries this could soon not be the case anymore is indeed very worrisome.

4 | RECS ROLE DURING THE COVID-19 PANDEMIC: POSSIBLE PITFALLS OF A CENTRALIZED REVIEW SYSTEM

A reflection on the role of RECs today cannot leave out of consideration the impact of the COVID-19 pandemic on the ethics review of research. Among the different actions undertaken worldwide to contain the pandemic, one of the most urgent was the creation of a fast track for the development and testing of effective and safe means (drugs, vaccines, tests) for the treatment, prevention and diagnosis of SARS-CoV-2 infections. Most European countries have put in place accelerated procedures for the evaluation and authorization of clinical trials related to the management of the pandemic⁴⁰ covering also the REC review process, with the prevalent tendency to centralize decisions. Indeed, the international health emergency related to the

pandemic had a huge impact on the process of review and authorization of research.⁴¹ This would surely deserve an in-depth analysis, which is, however, outside the scope of this paper. Therefore, we will just offer some preliminary considerations.

On the one hand, it is clear that the urgency related to the pandemic made a strong case for expediting the timing of the review process of research protocols: this experience made clear that, if we want to be prepared for the health challenges of a global world, streamlining and centralizing the review process are goals we must attain.

On the other hand, the pandemic experience can offer important elements to reflect on the pitfalls of an expedited and centralized review process. There are already data suggesting that many studies related to COVID-19 had serious methodological limitations⁴²⁻⁴⁴: it would be quite useful to understand what went wrong in the review process in order to adjust the way we are reforming RECs.

A quick look at what happened in Italy, to offer one example, can give a clearer idea of some of the different issues that the transition from an ethics review system with strong local roots⁴⁵ to a centralized one can raise. It is worth noting that Italy is already undergoing a reform of the REC network⁴⁶ along the following provisions^{47,48}: the reorganization and reduction of existing RECs (from about 90 to a maximum of 40); the creation of three national RECs and of a National Coordination Centre of local ethics committees for clinical trials on medicinal products for human use and medical devices.^{48,49} The COVID-19 pandemic paved the way for the transition towards the centralized model. From March 2020, a series of law decrees^{50,51} established that the evaluation of all clinical trials of medicinal products was delegated to a preliminary assessment by the AIFA Technical Scientific Committee (CTS), followed by the authorization of the AIFA Clinical Trial Office as national competent authority, while the Ethics Committee of the National Institute for Infectious Diseases Lazzaro Spallanzani (INMI Spallanzani) in Rome, performed the ethics review (acting as Single National Ethics Committee in charge of expressing the single opinion valid as authorization for all Italian sites). It is important to point out that this temporary centralized review system did not include either the evaluation of clinical trials for other diseases, clinical trials on medical devices and retrospective observational studies or nominal compassionate use and off-label use of drugs, which was nevertheless very important given the rapid spread of SARS-CoV-2, the serious clinical conditions of some patients, the absence of resolute care. RECs at regional-local level continued to evaluate these kinds of studies.

A partial assessment of this centralized organization can be performed by analysing the nineteenth Report on Clinical Trials in Italy, published in December 2020.⁵² According to this report, from March 2020 to September 2020, out of the 252 clinical trial protocols on COVID-19 submitted, 130 (51.6%) were not approved. Most of the proposed clinical trial protocols (65.9% of the approved ones and the vast majority of the not-approved) were submitted by academic or non-profit sponsors from institutions without adequate infrastructures and facilities to conduct a clinical trial. Due to lack of consideration of the local context and of a feasibility plan, in most cases these clinical

trials have failed to enrol the number of patients initially expected and in many cases they had not even started enrolment.

Such data, even if limited to a local reality, suggest that in the transition towards a centralized review model, problems can occur that deserve attention and further critical analysis. At least three such problems are worth mentioning. Significantly, all of them have to do with the relationship with local RECs and the role they play. Firstly, the EU reform concerns clinical trials with pharmaceutical products, but a huge part of health-related research does not fall into this category. The fact that in Italy local RECs continued to cover different kinds of research suggests the importance of being cautious in abruptly reducing their number without taking adequately into account that biomedical research involves much more than clinical trials.³⁷ Secondly, even with regard to clinical trials, a centralized review can be problematic as long as it fails to consider the local context and the presence of the actual preconditions for conducting the trial. The fact that many studies never took place, or failed to enrol enough participants, is a serious flaw with ethical implications. Arguably, local RECs offer an important contribution on this matter, because they can better assess the local feasibility of a study and, at the same time, offer support to the investigators. Thirdly, we need to pay attention to ensure the survival of spontaneous clinical research promoted by academic investigators: a centralized REC cannot support, educate, and provide ethics consultation to local researchers, but these activities are crucial to promote research of high quality, both from the scientific and the ethical points of view.

5 | CONCLUSIONS

The first RECs were created about 50 years ago to help achieve the difficult balance between promoting health-related research with human beings and protecting participants from the risk of exploitation. Over the years their task became increasingly complex due to deep changes in biomedical research: for instance, multi-site, sponsor-driven studies, genetic research and research biobanking pose difficult challenges for a review system that had shown some limitations from the very beginning. The old shortcomings in the functioning of RECs and the present challenges fully justify reforms that aim at accelerating and simplifying the administrative processes for reviewing research protocols: the COVID-19 pandemic has been a stark reminder of the need to go in that direction. Moreover, centralization could offer some benefits also because, on the one hand, it could help in developing guidelines relating to emerging issues in a timely manner, in applying them evenly across countries and in enforcing them efficiently; on the other hand, it could allow dealing with the difficult but crucial issue of establishing research priorities—an issue that cannot be dealt with locally. However, in moving towards a future standard of ethics review, we should not forget the role that RECs were created to play and we need to be sure that the accelerated and more efficient procedures we put in place are not at the expense of the safety of research participants, especially those who are most vulnerable.

To avoid this unwanted side effect, we propose two warnings and a plea.

The focus of the regulations on pharmaceutical clinical trials must not make us forget other kinds of research, that can be equally relevant. We need to think of biomedical research as a whole and work to harmonize (and give clear indications on) the procedures and paths each kind of research should follow. We also need to protect and promote non-sponsored research, that usually has local roots that should be preserved.

One of the ethical requirements of research with human participants that has emerged recently is that of collaborative partnership.^{5,13} Collaborative partnership supports the idea that “the community in which research is conducted should collaborate in the research endeavor”^{13(p125)} and that we should find a way to involve the community through its representatives to ask for their input and opinion about any research. Even if it did not mention community participation, the National Commission had underlined something similar: “In its deliberations, it is desirable that the IRB show awareness and appreciation of the various qualities, values and needs of the diverse elements of the community served by the institution in which it is located”.^{12(p14)} The related suggestion was to assure a diverse membership in order to be able to be sensitive to the concerns of different stakeholders, especially potential research participants and vulnerable subjects. How a centralized REC can create collaborative partnership with local communities is a question that should be considered carefully.

In conclusion, we suggest that the role of RECs we described above is still a goal we should try to attain. We discussed two crucial elements that should characterize RECs: a collaborative approach and the focus on the ethics component of the review.

As to the latter, we have seen that the EU Clinical Trials Regulation, by splitting the evaluation of clinical trials into two parts, seriously endangers the possibility of maintaining this focus and risks offering insufficient protections to research participants. This is unacceptable and goes against a central tenet that has been guiding REC members for decades: the acknowledgement of the intrinsic ethical relevance of the scientific aspects of research protocols.

As to the former, we argue that it is necessary to find ways to preserve it. Even if we decide that local RECs are no longer an option, given the way the research endeavour has evolved, we cannot but recognize that, if we delete them, we close “moral spaces”⁵³ that we actually need to keep open. A good ethics review is a poor protection for research participants if we lack a widespread awareness of the ethical implications of research with human subjects. RECs represented an attempt to bring ethical reflection inside research institutions and to nourish the culture of research ethics through three different functions: deliberating about the ethics acceptability of each research project, promoting bioethics education, and offering consultation and support to local researchers. They have not always fully accomplished these goals, and maybe it was about time for a change. But these objectives are still crucial: a reform that aims at improving the way we review, approve, monitor and conduct clinical research with human subjects must find a way to preserve and promote them.

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