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Ten years after Regulation 536/2014: ethical reflection on the role of Ethics Committees in Italy

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Abstract

Since their institution, Ethics Committees (ECs) dedicated to the ethical evaluation of research protocols have been traditionally entrusted with the role of finding a delicate balance between protecting research participants' rights and avoiding the hampering of scientific progress. In Europe, these bodies have evolved significantly over time, shaped by a dynamic regulatory framework culminating in Regulation (EU) 536/2014, which has been fully applied since 2022. Focusing on the Italian scenario, a decade after the adoption of the Regulation (2014-2024), this paper is aimed at shedding light on the extent to which the evolution of the pertinent normative framework has affected ECs' space for reflection within the ethics review process of clinical trials, essential to protect the rights of research participants. Although focused on the Italian scenario, the analysis holds relevance for the broader European context, since the Regulation is unique and developments in a single Member State may impact the others.

Key words

- ethics
- bioethics
- ethics committees
- Regulation (EU) 536/2014
- clinical trials

INTRODUCTION

Throughout history, the scientific discoveries that laid the foundations of modern and contemporary medicine often relied on processes that, by today's ethical and scientific standards, would be deemed unacceptable. One notable example is the efforts to combat smallpox, a devastating disease that once posed a severe threat to public health. In 1717, Sir Hans Sloane studied the technique of "variolation", namely using pus from blisters obtained from patients with smallpox [1]. This technique was also approached by Lady Mary Worley Montagu in 1718 [1]. In the effort to eradicate smallpox, the most notable example involves Edward Jenner's research. He observed that persons (typically dairymaids) who had suffered from the cowpox did not contract smallpox. On these grounds, he started a series of experiments. In 1796, Jenner inoculated, among others, an eight-year-old boy with cowpox and, after his recovery, with smallpox. The boy did not contract smallpox (https://biotech.law.lsu.edu/cphl/history/articles/jenner.htm) [2]. While Jenner's experiments provided a relevant contribution to the history of medicine, at that time no one questioned the involvement of vulnerable people in medical research.

It has been a long time since Jenner's experiments and, following numerous instances of abuse, particularly involving vulnerable individuals, strict ethical requirements have been established to safeguard the rights of those involved in research. As a result, even though Jenner's work significantly contributed to the eradication of a disease that is estimated to have killed more than 300 million people in the 20th century [3], his experiments would not be authorized today [2]. Should we regret, then, the times in which freedom for any method of scientific research was granted? Certainly not: criteria for research ethics and scientific rigor are needed. Research with humans, in fact, can be detrimental to the rights and wellbeing of participants. Yet, while safeguarding rights of persons involved, at the same time ethics should not hamper the scientific progress we all rely on as a society.

Such a delicate, yet essential, role of finding a balance between these two dimensions in the evaluation of research protocols has been conferred to specific bodies with different names depending on the countries in which they are located – some examples are Research Ethics Committees (RECs) or Institutional Review Boards (IRBs). Since this paper focuses on the Italian context, the expression "Ethics Committee (EC)" will be used in compliance with the Italian context. Though ECs in Italy are in charge of different tasks, this analysis will take mainly into consideration the ethical clearance of clinical studies involving humans.

2024 was the tenth anniversary of the adoption of Regulation (EU) 536/2014 (hereafter "the Regulation") of the European Parliament and of the Council of 16 April

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2014 on clinical trials on medicinal products for human use [4] which revolutionized the whole research field in European countries and is fully applied since 2022. Drawing upon the Italian scenario, this paper aims at exploring whether changes in the normative framework regulating research – with specific focus on the last 10 years – has been affecting the quality and the space for the independent ethical reflection. This aspect is crucial as EC's independent ethical reflection underpins the extremely delicate role of protecting the rights of research participants, traditionally assigned to these bodies.

Although focused on Italy, the analysis is of interest for the entire European context, since the community Regulation is the common regulatory reference and what happens in a single Member State has repercussions for all the others.

ADVENT OF REGULATION (EU) 536/2014: STRENGTHS AND WEAKNESSES

The adoption of the Regulation constituted a breakthrough for ECs in Italy and for the whole medical research field.

The Regulation, aimed at speeding up and harmonizing the extremely fragmented evaluation system across Europe, introduced two main changes to the clinical trials' assessment procedure. First, each Member State involved in a research protocol is required to convey a unique decision uploaded through the EU portal as to whether the clinical trial is authorized, authorized under specific conditions, or whether authorization is denied within strict deadlines. The second innovation concerns the rethinking of the whole procedure of clinical trials' assessment. The Regulation divides clinical trials' assessment reports into two different sections. Part I, described by article 6 of the Regulation, involves verification of: requirements for low-intervention trials where applicable; the anticipated therapeutic and public health benefits; the risks and inconveniences for the subject; compliance with the requirements concerning the manufacturing and import of investigational medicinal products; compliance with labelling requirements; and completeness and adequateness of the investigator's brochure.

Part II, described by article 7, involves compliance requirements: for informed consent; of arrangements for rewarding or compensating subjects and investigators; of arrangements for recruitment of subjects; with Regulation 2016/679 on General Data Protection (GDPR); with Article 49, regarding the suitability of individuals involved in conducting the clinical trial; with Article 50, involving the suitability of clinical trial sites; and with Article 76, regulating Damage compensation.

In this scenario, the Regulation does not provide Member States with guidance and indications aimed at meeting the newly introduced requirements. In relation to the role of RECs, Regulation (EU) 536/2014 requires Member States to organize the involvement of these bodies in the evaluation process at the national level, but does not impose any binding modality for the organization of this process. As a result, each Member State is free to decide how to set the national network in order to reach the required "single decision" and how to distribute the tasks described in assessment report Part I or Part II, provided the strict deadlines imposed by the Regulation are met. This choice grants Member States a certain discretion in choosing and adopting the organizational model each one deems best for their national background. Nevertheless, such a lack of centralization leads to a significant heterogeneity and often Member States do not know what happens "behind the scenes" of the single decision reached by confining countries participating in the same study. The rigor of a Member State's decision, however, does impact the overall evaluation' quality of the European system.

APPLICATION OF REGULATION (EU) 536/2014. THE ITALIAN CASE

The procedural revolution introduced by the Regulation deeply impacted each Member State's research apparatus. Italy, with its extensively articulated network of ECs, was no exception [5]. As in other European countries, it took several years for the rearrangement to be implemented.

Law n.3/2018 [6] intervened to regulate the Italian framework by rethinking the arrangement of ECs. In particular, the network for ethical clearance of medicinal products, considerably reduced, is outlined as follows: 40 Territorial Ethics Committees (TECs), distributed throughout the national territory and chosen among the already existing ECs, in charge to provide a single evaluation for clinical trials with medicinal products, medical devices, and observational studies with medicinal products; and 3 National Ethics Committees (NECs) in charge of the ethical clearance of clinical trials pertaining to specific research areas (pediatrics; advanced therapies; and clinical trials conducted by public research bodies, EPR, and other national public institutions). The already existing ECs that were not incorporated into the structure envisaged by Law n. 3/2018 have been allowed to continue their work subject to regional resolution, for matters not covered by the newly established ECs.

On January 31st, 2022, after 8 years from its publication and entry into force, the Regulation was applied in European Member States.

In Italy, TECs and NECs (henceforth referred to with the expression "ECs") are in charge of completing Part II of the assessment report. They may express observations on Part I as well, yet the Competent Authority (CA), i.e., the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA), is in charge of completing this first part. Abiding by the law, AIFA may hypothetically refuse to endorse observations raised by ethics committees if deemed inadequate, which is controversial given the ethical relevance of Part I.

Also, observations on Part II may have an impact on the evaluation of Part I and vice versa.

The introduction of the Regulation has profoundly influenced how Italian ECs conduct their ethical evaluations. Before its application, in Italy the authorization of AIFA together with that of one or more independent EC(s) was required to start a clinical trial. In this scenario, at least in theory, the opinion of the EC(s) was binding and covered all aspects of the study under review. The situation changed radically within the Regu-

lation: the authorization of both AIFA and EC is still required, but ECs can express their binding evaluation only on some aspects of ethical relevance.

2024 has marked ten years since the adoption of the Regulation in 2014. This anniversary is particularly significant as it calls for a reflection on the evolution of these bodies focused on clinical trials' evaluations.

Has this evolution maintained the quality and scope of ethical analysis – crucial for fulfilling the delicate role of encouraging research advances, while safeguarding participants' rights – that ECs have traditionally been entrusted with?

ITALIAN ETHICS COMMITTEES AND REGULATION: A QUANTITATIVE AND QUALITATIVE ETHICAL FLATTENING?

Ethics has been gaining growing relevance and significance in the global healthcare scenario and, in particular, within the research field (https://www.weforum.org/stories/2024/01/trust-ethics-economics-governance/; https://www.who.int/activities/ensuring-ethical-standards-and-procedures-for-research-with-human-beings). Surprisingly, Italian ECs do not appear to have benefited from this change. The general impression is that, over time, there has been a gradual flattening of the value placed on the ethical reflection that ECs have had the opportunity to contribute to within the Italian medical research field.

Despite such a flattening has been affecting the whole research field in Italy[a], this analysis will focus on changes regarding clinical research. Already in the '90s the huge number of trials to be evaluated by Italian ECs reportedly "poisoned" these bodies and their space for ethical reflection [7].

More recently, this concern has become particularly perceptible in the role the Italian application of the Regulation has attributed to ECs. Such a flattening might be traced back to two main concerns, one regarding *quantity*, and the second one regarding *quality* of the evaluation Italian ECs find themselves in the position to provide within the ethical clearance of clinical trials.

The first concern involves the *quantitative* limitation of the competences currently assigned to Italian ECs in the framework of the Regulation. Such a consideration does not mainly apply to the number of trials assigned to each EC – the number has decreased, but the amount of work and the bureaucratic procedures needed to meet the requirements has increased[b]. Rather, concerns pertain the limitation of aspects of ethical relevance ECs can evaluate within a study. Aspects related to Part I of the assessment report, like the evaluation of anticipated therapeutic and public health benefits associated with the clinical trial or potential risks and inconveniences for the subject enrolled in the study, are matters of concern from an ethical perspective and are deeply intertwined to the aspects ECs are required to evaluate in Part II. To this end, the evaluation of all these elements, particularly relevant from many different points of view, should benefit from an ethical and interdisciplinary perspective, such as the one provided by an EC. Nevertheless, in Italy such aspects are formally reviewed by the CA, whose perspective differs in skills and training from members of an EC. ECs may express their opinion, but in the event of divergent views the CA has the last word. Therefore, this leads to a quantitative limitation of the aspects ECs can express their binding evaluation on. This is a relevant element to consider as, before the adoption of the Regulation, the binding opinion of the EC covered all aspects of the study under review. Such a limitation runs counter to the ethical relevance of these aspects within the clinical trial and affects the chances for ethical contribution ECs may provide within the research scenario.

The second concern regards the *quality* of the evaluation ECs in Italy are in the position to provide. Elements relating to Part II of the assessment report are of marked ethical relevance. However, to promote procedural standardization, the ethical evaluation elaborated by the EC must be expressed within a specific (and tightened) window of time through bulletproof forms, which partly pauperize the significance of the ethical reflection underpinning the evaluation itself. Such an approach has significant benefits: evaluations are now faster and standardized, thus more easily comparable among countries participating to the same protocol. Yet, the ethical pondering, that has characterized the growth and evolution of ECs, must now be squeezed to fit the non-editable grids and be expressed through options to be flagged [8]. The risk of this procedure is to lead to a fragmentation and a debasement of the ethical reflection elaborated by ECs. Moreover, this trend implies a progressive bureaucratization of ECs by monopolizing their activity in order to meet the requirements of the Regulation. In other terms, ECs risk becoming bureaucratic machines whose main occupation is to fill out the forms pertaining Part II[c] without having an overall vision of the ethical implications regarding the protocol under evaluation, precisely because ECs are only responsible for the evaluation of Part II.

ECs' REORGANIZATION AND CHANCES FOR ETHICAL REFLECTION

As described above, ECs in Italy have gone through a profound transformation to meet the requirements of an evolving normative framework. In the last 10 years, since the adoption of the Regulation, their role has sig-

[a]For instance, there is a persistent lack of legislation and of standardized procedures regarding the ethical clearance of research involving humans that does not pertain to medicinal products or medical devices in Italy. Such a normative and procedural blur represents a barrier to the evaluation of these kinds of studies by making it arduous for ECs to express their assessments regarding a huge and heterogeneous research area that offers great opportunities for patients' care.

[b]Moreover, ECs in Italy evaluate many other kinds of study not falling under the Regulation.

[c]Although the Regulation in Italy has had significant direct consequences on the role of ECs in the evaluation of protocols with medicinal products, its application has indirectly influenced the role of ECs in the evaluation of all other types of research as well. The significant focus on the Regulation has had a knock-on effect in the whole field of research. In this framework, the evaluation of studies that do not fall within the umbrella of Regulation 536 could be perceived as of secondary relevance. In any case, these studies float in a persistent regulatory gap with enormous ethical implications.

nificantly changed. Yet, the overall impression is that this evolution has seldom constituted a fertile ground for a flourishing of the ethical depth of ECs' contribution to the research scenario. Such a trend unfolded in contrast to the awareness that ethics is gaining globally in the healthcare field and, in particular, in the research one, and was ultimately ratified, in Italy, by the role assigned to ECs within the application of the Regulation. It is worth highlighting that the present analysis does not intend, in any way, to attribute direct responsibility to the Regulation for such an impoverishment. The European harmonization introduced by the Regulation was necessary to coordinate and to streamline the protocols' evaluation procedures at a communitarian level to make Europe more attractive and competitive in the research field. Rather, the present analysis underlines that, unfortunately, it was the depth of the ethical analysis reserved to ECs, depleted from both a qualitative and quantitative point of view, that paid the price for the Italian strategy.

Reducing the role of ECs to a technical and bureaucratic control is a short-sighted strategy. The delicate role of finding the right balance between subjects' protection and scientific progress ECs have been traditionally entrusted with, requires space and circumstances to be both developed and exercised. Given the relevance of the role of ECs and their value in the delicate mission of safeguarding the rights of trial participants, it is crucial to find solutions for their ethical reflection to be treasured through time, rather than progressively constrained and eroded [9].

Although the role assigned to Italian ECs in the evaluation of clinical trials in the context of the Regulation is only a part of the tasks assigned to these bodies, this shift affects the role ECs play in the evaluation of research not falling under the umbrella of the Regulation, as discussed above. To this end, rethinking the Italian mechanism in order to leave more room for ECs ethical reflection to unravel seems not only desirable, but necessary. Such a call is not only relevant at a national level but, rather, at a European level since a potential flattening of the quality of the ethical reflection produced by a single Member State may affect the overall quality of the system.

To this end, without jeopardizing the effort to harmonize and streamline the evaluation procedures at European level introduced by the Regulation, a possible solution could be to reconsider the role assigned to ECs in Italy, by granting them the chance to express binding considerations also on specific aspects of ethical relevance contained in Part I of the assessment, deeply intertwined to ECs responsibility. The rationale for this proposal has to do with the importance that the assessment of research issues requiring an ethical clearance, such as, indeed, specific aspects of Part I, be effectively validated by the interdisciplinary and professional background typical of an EC. Expertise in ethics allows no improvisation and the uniqueness of the ethics committee is inherent in bringing together professionals of different backgrounds who have, as a common denominator, training in ethics. All these points of view provide a rich perspective to the analysis that cannot be replaced and that must be protected and cherished for the quality of the clearance and the safeguard of research participants. The time has come to reflect on the room we want to leave for ECs, precious institutions that have long been guardians of research participants' rights.

The lack of centralization for some procedural aspects in the application of the Regulation was extremely facilitating in order for each Member State to find autonomously the solution that best suited and valued its own pre-existent national structure. However, now that the Regulation has been finally applied and, after more than 10 years, each Member State has started the gear, a constructive dialogue between Member States concerning the solutions adopted to fulfil the requirements posed by the Regulation should be strongly encouraged. Exposing Member States to the chance to acknowledge different solutions adopted to comply with the Regulation and, possibly, to be inspired by neighbour's ones might improve and enrich the quality, the ethical perspective, and the overall accountability of the European Union research system.

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REFERENCES

1. Gallin JI, Ognibene FP, Lee Johnson L. Principles and practice of clinical research. 4th ed. London: Academic Press Elsevier; 2018.
2. Davies H. Ethical reflections on Edward Jenner's experimental treatment. J Med Ethics. 2007;33(3):174-6. doi: 10.1136/jme.2005.015339
3. Desmond A, Offit PA. On the shoulders of giants - From Jenner's Cowpox to mRNA Covid vaccines. N Engl J Med. 2021;384:1081-3. doi: 10.1056/NEJMp2034334
4. European Parliament. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials in medicinal products for human use and repealing Directive 2001/20/EC. Official Journal of European Union, 27 May 2014.
5. Petrini C, Brusaferro S. Ethics committees and research in Italy: seeking new regulatory frameworks (with a look

at the past). Ann Ist Super Sanità. 2019;55(4):314-8. doi: 10.4415/ANN_19_04_02

6. Italia. Legge 11 gennaio 2018. n. 3. Delega al Governo in materia di sperimentazione clinica di medicinali nonché disposizioni per il riordino delle professioni sanitarie e per la dirigenza sanitaria del Ministero della salute. Gazzetta Ufficiale – Serie Generale, n. 25, 31 gennaio 2018.
7. Barni M. I comitati etici. In: Comitato Nazionale per la Bioetica. Il Comitato Nazionale per la Bioetica: 1990-2005. Quindici anni di impegno. Atti del Convegno. Roma 30 novembre - 3 dicembre 2005. Presidenza del Consiglio dei Ministri, Dipartimento per l'informazione e l'editoria; 2005.
8. Centro di Coordinamento Nazionale dei Comitati Etici. Guidance on evaluating under art. 7 of Regulation (EU) no 536/2014, by the Territorial Ethics Committees. CCNCE; 2024. Available from: https://www.aifa.gov.it/documents/20142/2198424/guida_valutazione_documenti_parte-2_CCN_22.05.2024_EN.pdf.
9. Lukaseviciene V, Hasford J, Lanzerath D, Gefenas E. Implementation of the EU clinical trial regulation transforms the ethics committee systems and endangers ethical standards. J Med Ethics. 2021;47:e82. doi:10.1136/medethics-2020-106757