

COMMENTARY

Ethics committees and research in Italy: seeking new regulatory frameworks (with a look at the past)

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Abstract

The legislation of Italy and the European Union requires a shift in terms of the organisation and national regulation of ethics committees and clinical trials. More generally, this affects the entire sphere of biomedical research. The first part of this contribution provides a brief review of the history of ethics committees in Italy. We then discuss the current situation and formulate proposals. There is a vital need for rules that promote efficiency of ethics committees, to guarantee that Italy's position remains competitive and attractive within the European Union.

Key words

- biomedical research
- ethics committees
- human experimentation
- legislation

A LOOK AT THE PAST

The story of ethics committees (ECs) in Italy is at a watershed point, because of a number of factors.

Certain factors result from new technical and scientific advances, others from new legislative requirements.

In terms of new technical and scientific advances, these include a range of possibilities, including digital therapies, the increasing interconnections between devices and medicines, and advanced therapies. Technical and scientific advances are also reflected in new methods and new designs for clinical trials, such as adaptive studies or decentralised clinical trials.

New technical and scientific advances are not the subject of this commentary, which relates, rather, to a discussion of certain considerations associated with the regulatory environment, and in particular in terms of the organisation and functioning of ECs.

The regulatory picture is changing both within the European Union and domestically.

In the European Union, a new era began with the application of Regulation (EU) No 536/2014 on clinical trials on medicinal products [1] and Regulation (EU) No 2017/745 on medical devices [2]. Both will be in force from 2020: Regulation (EU) No 536/2014, as established in Article 99, will apply from six months after the publication of a notice (referred to in Article 82(3)) regarding the full functionality of a portal and a database containing the data and the information about the trials, while Regulation (EU) No 2017/745, as estab-

lished in Article 123, will apply from 26 May 2020.

In Italy, Articles 1 and 2 of Law No 3 of 11 January 2018 [3] introduce important changes in the procedures for the authorisation of clinical trials on medicinal products for human use.

To view the problem appropriately, a brief historical review of the organisation of ECs in Italy might be valuable.

In the 1980s, there were few bodies in Italy that could be classified as ECs (regionally, in public bodies and in universities).

The first legislative text took the form of the Ministerial Decree of 27 April 1992, *Provisions on the technical documentation to be submitted in support of applications for marketing authorisations for proprietary medicinal products for human use, in implementation of Directive 91/507/EEC* [4]. Article 2 of that text stipulates as follows: "Where they are created in Italy, ethics committees, which must comply in all cases with the requirements of good clinical practice (...), must be established within medical or scientific bodies of proven reliability".

A more precise physiognomy was laid down in 1997, with the Decree of 15 July 1997, *Transposition of the EC good clinical practice guidelines for clinical trials on medicinal products* [5]. In Article 4 ("Establishment of ethics committees and reference committees"), paragraph 1 establishes that "Independent ethics committees for the evaluation of the clinical trials on medicinal products shall be established according to the information

laid down and in compliance with the minimum requirements stated in paragraph 3 of Annex 1 to this Decree". Various operating requirements are listed in that Annex.

However, a precise framework for the establishment of ECs was only enacted in 1998, in the Decree of 18 March 1998, *Reference guidelines for the establishment and functioning of ethics committees* [6]. Article 1(1)(1) of Annex 1 to that Decree defines an EC as "an independent body, created within a medical or scientific research institution according to interdisciplinary criteria".

The following year, Legislative Decree No 299 of 19 June 1999, *Provisions intended to rationalise the Italian national health service, in accordance with Article 1 of Law No 419 of 30 November 1998* [7], created an "Ethics Committee for Research and Clinical Trials" nationally, with the composition of that body governed by the Decree of 23 November 1999, *Composition and determination of the functions of the National Ethics Committee for Clinical Trials on Medicinal Products, in accordance with Legislative Decree No 299 of 19 June 1999* [8]. However, that national committee never became operational.

A fundamental step for clinical regulation in Italy was achieved, following the adoption of Directive 2001/20/EC [9], through Legislative Decree No 211 of 24 June 2003, *Implementation of Directive 2001/20/EC on the implementation of good clinical practice in the conduct of clinical trials on medicinal products for clinical use* [10]. Article 2(1)(m) establishes that an EC is "an independent body consisting of healthcare professionals and non-medical members, whose responsibility it is to protect the rights, safety and wellbeing of human subjects involved in a trial and to provide public assurance of that protection [...]".

In the last two years of the previous century and the first two years of the current one, ECs were therefore created in each Italian region within hospitals, university polyclinics and biomedical research bodies and institutions.

A new regulatory framework was then introduced through Law No 189 of 8 November 2012, *Conversion into law, with amendments, of Decree-Law No 158 of 13 September 2012, on urgent provisions to promote the development of the country by providing a higher degree of health protection* [11]. In Article 12 ("Procedure concerning medicinal products"), paragraph 10 establishes that "by 30 June 2013, each of the regions and the autonomous provinces of Trento and Bolzano shall restructure the ethics committees existing within its territory" and states, under subparagraph c, that "The jurisdiction of each committee may extend, in addition to clinical trials on medicinal products, to any other question relating to the use of medicinal products and medical devices, the use of surgical and clinical procedures or the study of food products on humans generally referred, per international practice, for assessment by such committees".

On the basis of that law, the Decree of 8 February 2013, *Criteria governing the composition and functioning of ethics committees* [12], was then enacted. In Article 1 of that Decree ("Definitions and functions of ethics committees"), paragraph 1 states that "Ethics committees (...) shall be independent bodies (...) that have the responsibility of guaranteeing the protection of the rights,

safety and wellbeing of persons involved in trials and of providing public assurance of that protection" and paragraph 2 states that "Where these are not already attributed to specific bodies, ethics committees may also perform consultative functions in relation to ethical questions associated with scientific and healthcare activities, in order to protect and promote the dignity of the individual. Ethics committees may also propose initiatives for training of healthcare professionals in relation to the sphere of bioethics". This Decree resulted in a substantial reduction in the number of ECs in Italy: from 243 in 2012, this figure fell to 91 in 2014 and is currently 90 [13]).

The following year saw the adoption of the above-mentioned Regulation (EU) No 536/2014 [1]. The principal implications of that Regulation have already been discussed in this journal [14].

Article 8 of the Regulation ("Decision on the clinical trial") states that "Each Member State concerned shall notify the sponsor through the EU portal as to whether the clinical trial is authorised, whether it is authorised subject to conditions, or whether authorisation is refused. Notification shall be done by way of one single decision". The need to express a "single decision" nationally stimulated the debate on the reduction in the number of ECs. There were numerous suggestions: there were those who proposed that all assessments of clinical trials conducted in Italy be centralised in a single National Ethics Committee, those who proposed the creation of a national institution subdivided into sections corresponding to therapeutic areas, those who suggested establishing a dozen committees, those who proposed assigning a committee to each region, and those with other ideas [15, 16].

THE PRESENT AND THE FUTURE

Law No 3 of 11 January 2018 [3] provides for a further reduction in the number of ECs: indeed, on the basis of Article 2(7), within 60 days following the entry into force of the Law (15 February 2018), a decree enacted by the Minister of Health was to (...) "identify a maximum of 40 local ethics committees" and, on the basis of paragraph 9, a decree enacted by the Minister of Health within the same period "[was to identify] a maximum of three national ethics committees, with one reserved for trials in a paediatric environment". The difficulty inherent in implementing this reform of Italian ECs is demonstrated by the fact that the decrees creating the local ECs and the national ECs have still not been enacted.

Legislative Decree No 52 of 14 May 2019, *Implementation of the delegated powers to review and reform the regulatory provisions in relation to clinical trials on medicinal products for human use, under Article 1(1) and (2) of Law No 3 of 11 January 2018* [17], implemented certain of the delegated powers for the Government established under Article 1 of Law No 3 of 11 January 2018. Certain provisions contained in the Decree could have a significant impact. In particular, in order to gain value from non-profit clinical trials, even those with limited intervention, sponsors are permitted to transfer the corresponding data and results of the trial for regis-

tration purposes. Until now, the use of data obtained from non-profit trials for registration purposes was not permitted. With the new text, in the case that these data and results are used for registration purposes, the sponsor or transferee is required to pay and reimburse the direct and indirect costs associated with the trial, and, following potential reclassification of the study as profit-making, to pay the corresponding charges, including any revenues resulting from the exploitation of intellectual property. On this point, a Decree of the Minister of Health to be enacted by 31 October 2019 is required to stipulate measures intended to facilitate and support the performance of non-profit clinical trials and observational studies and to identify the methods for coordination between public and private sponsors in the same clinical trial or clinical study, including for the purpose of acquiring information following market introduction of the medicinal products. That Decree also introduced criteria for identifying the types of and requirements for non-profit trials and trials with cooperation between public and private sponsors, and for governing the methods for transferring data relating to trials to the sponsor and the use of those data for registration purposes. The Decree also establishes that an order enacted by the AIFA will identify the appropriate methods for protecting the independence of the clinical trial and guaranteeing the absence of conflicts of interest in assessment of corresponding requests.

We can see from the above that this moment is crucial. And it is important to consider some factors that are relevant for the choices and decisions that the legislators and the Italian Government will need to make:

- the full implementation of Regulation (EU) No 536/2014 [1] requires that the organisation of ECs and the methods used to assess requests for authorisation of new clinical trials must be efficient: if Italy is not attractive in this sector, it will remain marginalised;
- the identification of 40 local ECs is particularly difficult because this would involve a halving of the current number. The decision was made to reduce the number [3] in order to optimise the sector and improve efficiency. However, the elimination of approximately 50% of ECs would also involve a loss of valuable expertise, and a substantial workload for the 40 recognised ECs. If there is still an intention to reduce the number of ECs, the committees that will not be authorised for assessment of clinical trials under Regulation (EU) No 536/2014 [1] could still be used to assess studies other than clinical trials (such as observational studies, studies on biological material of human origin, compassionate use, etc.). The ECs authorised to assess clinical trials will in fact be overworked, and will find it difficult to find the time for studies other than clinical trials;
- the National Centre for Coordination of Ethics Committees (“National Centre for the Coordination of Regional Ethics Committees for Clinical Trials of Medicines and Medical Devices for Human Use”), created [18] under Article 2 of Law No 3 of 11 January 2018 [3] must be structured appropriately (in terms of allocated resources, location, composition) to enable it to perform its role. This fact was recognised by the Ministry of Health in the “Document on pharmaceutical governance” [19]. A bill on reforming the Coordination Centre has been tabled before the Chamber of Deputies [20];
- non-profit clinical trials must be promoted and appropriately supported, including in financial terms;
- the legal requirements governing observational studies (which currently cover only studies involving the administration of medicinal products [21-23]) must be amended, establishing streamlined, efficient authorisation processes for the many types of observational studies in which no medicinal products are administered;
- the management of conflicts of interest must be subject to rules that are rigorous but do not suffocate relationships (including in the form of public-private partnerships), which are essential for the efficiency of research. Article 6(4) of Legislative Decree No 52 of 14 May 2019 [17] establishes that “in order to protect the independence and impartiality of the clinical trial, the investigator shall declare in advance to the institution within which the clinical study is being performed that, in relation to the proposed study, there are no financial interests held by his/her spouse or partner or relations up to the second degree in the capital of the pharmaceutical company owning the drug covered by the study, and he/she has no employment, consultancy or cooperative relationships, for any purpose, with the sponsor”. It is clear that this provision is excessively restrictive: research is developed through cooperation (including private-public partnerships). Requiring “no employment, consultancy or cooperative relationships, for any purpose” imposes a serious obstacle to the development of research. That obstacle should be removed, and it is to be hoped that the measure to be adopted by the AIFA, under Article 6(1) of that Legislative Decree [17], in accordance with paragraph 4, will identify criteria that not only do not suffocate but actually promote research;
- biological material of human origin is a resource with enormous potential for biomedical research, and we need rules that enable its efficient use. Legislative Decree No 52 of 14 May 2019 [17] has entrusted the Italian National Institute of Health (Istituto Superiore di Sanità) (“with the support of the European Biobanking and Biomolecular Resources Research Infrastructure (BBMRI)”) with the task of drafting address lines “for the use for research purposes of biological or clinical material remaining from previous diagnostic or therapeutic activities or held for any other purpose”. The Italian National Institute of Health has created a corresponding working group made up of representatives of the Research Coordination and Support Centre and the Bioethics Unit from that body. This group is tasked with developing address lines to promote a sector that has seen considerable development and is destined to play a crucial role in biomedical research in the coming years;
- to make Italy attractive for companies performing clinical trials, we need to adopt a system of charges for ECs that is competitive with other Member

States of the European Union. Article 2 of Law No 3 of 11 January 2018 [3] envisages the adoption of a decree by the Minister of Health, in conjunction with the Minister of Economic Affairs and Finance, for the “determination of a single fee for clinical trials”. That decree has not yet been adopted. Currently, the charges for ECs are established by regional decisions. In multicentre studies, a payment must be made to the EC for each participating centre (each of which has, *inter alia*, at least partially, specific rules for submission of requests). Innovative choices have been made within the European Union. For example, in France the charges for ECs have been abolished (by the Financial Law No 1425/2008 [24]) and Spain established an effective network of ECs since 2015 [25]. Italy cannot allow itself to remain marginalised in a sector that, if appropriately promoted, is a source of a great deal of investment.

Italy has a long and competitive history in biomedical research. ECs' role is crucial for this process and all ef-

forts to provide clear rules and efficiency should be put in place. Nevertheless, ECs are part of the challenge and a comprehensive global approach to biomedical research should be considered a national priority. This includes both privacy issues, administrative rules, supply chain contracts, researcher status, etc. Setting up standard processes where rules and timing are clearly defined and guaranteed is a crucial challenge for the future of the biomedical research in Italy.

Conflict of interest statement

Carlo Petrini is Chair of the Ethics Committee of the Italian National Institute of Health (Istituto Superiore di Sanità) and Vice-Chair of the National Centre for the Coordination of Regional Ethics Committees for Clinical Trials of Medicines and Medical Devices for Human Use.

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