Annals of Research in Oncology
Vol. 2(3), 202-08, 2022

OPINION PAPER

EUROPEAN CLINICAL TRIALS REGULATION 536/2014: CONCERNS AND PERSPECTIVES OF A MEMBER STATE

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ABSTRACT: The European Regulation 536/2014, entered into force on June 16, 2014 and not effective for several years for a delay in the development of a fully functional European portal, has represented a turning point in the legislation regarding clinical trials on medicinal products. Unlike other countries, Italy was unable to translate the multitude of decrees regulating clinical trials in one legislative act. The first step towards the alignment with Regulation 536/2014 was the Law 3/2018 that recognized the necessary changes that had to be made, the simplification of the submission and evaluation process by the Ethics Committees, the importance of infrastructure and support personnel in the conduct of clinical trials, among others. So far only three implementing decrees have been circulated one introducing the Coordination Center of Territorial Ethics Committees (CNCCE), one establishing two national ECs and a decree regarding observational and no profit studies. Certainly, further legislative measures will be needed to complete the implementation framework. There is a great deal of expectation with respect to the measure that will define the minimum requirements of clinical centers authorized for the conduct of clinical trials, as well as any other decrees necessary to address the critical issues described above.

Doi: 10.48286/aro.2022.53

Impact statement: The paper provides an overview of the actions taken in a Member State to implement the European Regulation, some of which took a long time and continue to present multiple criticalities.

Key words: *Clinical trial regulation; European Regulation; European Portal; Ethics Committees; research infrastructures.*

Received: July 22, 2022/**Accepted**: August 30, 2022/
Published: September 8, 2022

INTRODUCTION

The European Regulation 536/2014 (1), entered into force on June 16, 2014 but not effective for several years for a delay in the development of a fully functional European Portal (CTIS), has represented a turning point in the legislation regarding clinical trials on medicinal products.

The previous legislation (2), in fact, despite being the first to include Good Clinical Practices in the European Law and having represented the first attempt to harmonize the local legislations of the different member states, had led to an increase in costs and lengthy timelines for study activation. Over the years, this has led to a reduction in trial authorization requests and notable disparities among Member States (3, 4).

The Regulation introduces novelties aimed at optimizing the process of regulatory approval for Clinical Trials, first and foremost the new authorization process, that sees the introduction of one authorization at European level (Part I) and leaves at each Member State the possibility of accepting or not accepting this decision. The new process, tackled the issue of high costs from the previous legislation, drastically cutting down timelines, and was meant to represent an opportunity for Member States like Italy, for a long time restrained by the complex bureaucracy and the need to undergo multiple evaluations by the competent authority and the various Ethics Committees (ECs), to increase their performance (5, 6).

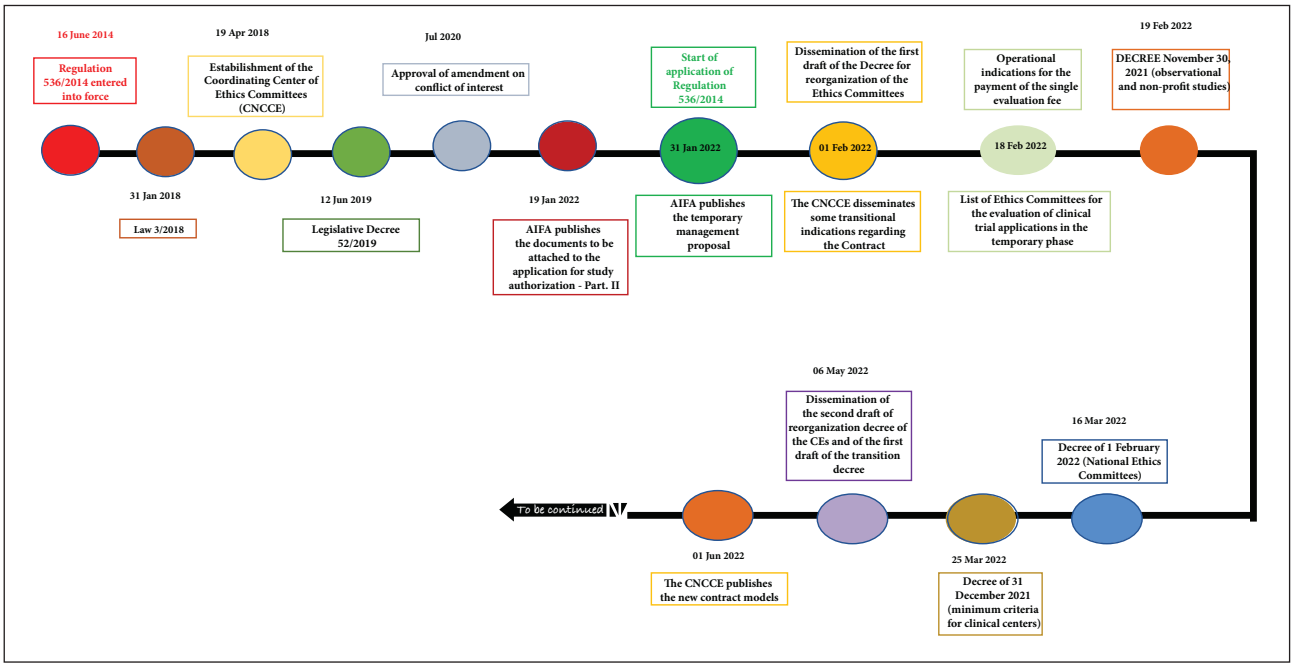
The delays portal go-live date, initially foreseen for May 2016, have led to a continuous postponing of the date of the applicability of the Regulation, ultimately fixed for the January 31, 2022. In these 6 years of halt Member States have had the opportunity to gain knowledge on and prepare for all changes that would be implemented with the enforcement of the new Regulation.

The update of the legislation was done in the form of a Regulation instead of a new Directive purposely to avoid more disparities among States; in fact, the Regulation, unlike the Directive, does not require further legislative steps by the single nations and can be enforced directly in single Member State. Some nations managed to prepare for the new regulation through a thorough revision and simplification of their regulatory apparatus; Spain is exemplary of this, implementing only one Decree that includes all aspects of interventional clinical trial with medicinal product (7). This could not be easily done in Italy, where the previous Directive had triggered the implementation of multiple ministerial decrees and other legislative measures that, unlike in Spain, could not be easily translated into one legislative act. The reorganization process was thus initiated in 2017 with the decree known as "*Decreto Lorenzin*" but is still far from being completed. A never-ending story (8) (**figure 1**), that is based on a management proposal made by the Competent Authority (9). This process that should have been an opportunity for simplification and harmonization leaves us, instead, completely unprepared despite six months have gone by since the go-live date of the new Regulation. This unpreparedness was foreseeable years ago when the majority of the personnel involved was oblivious of the imminent changes ahead (10).

LAW 3/2018 E LEGISLATIVE DECREE 52/2019

Italy made its first attempt towards adapting to Regulation 536/2014 with Law 3/2018, known as "*Lorenzin Law*" (11). The law provided for important changes (**table I**), introducing the need for a simplification of the articulated process of submission and evaluation of new Clinical Trials by the Ethics Committee, necessary in light of the very stringent deadlines introduced with the Regulation for this process. Another important novelty was the need for a drastic reduction in the number of ECs active throughout the country, in line with the hypothesis that the evaluation performed by one designated Committee would be valid for all clinical centers on the national territory. Moreover, this law recognized for the first time the importance of research infrastructures, currently absent in many of the Italian clinical centers (12, 13), providing that clinical trials on medicinal products be conducted through the support of specific professionals in the field of data management and research coordination.

The Legislative Decree 52/2019 (14) was the natural evolution and a mere implementation of Law 3/2018, aimed at establishing areas of competence



Figures 1. *Timeline of the European Regulation's implementation in Italy.*

Area	Novelty
Requirements clinica centers	Identification of requirements of centers authorized for the conduct of clinical trials for phase I studies and other phase studies.
Requirements clinica centers	Presence in the trial centers of professional profiles specialized in data management and coordination of clinical trials.
Requirements clinica centers	Mechanisms of evaluation of results of clinical trials within public hospitals.
Legislation	Simplification of the bureaucratic process regarding the request for evaluation by the Ethics Committee and the conduct and evaluation of studies.
Legislation	Identification of the tasks and objectives of the local Ethics Committees (maximum 40) and introduction of the Coordination Center of Territorial Ethics Committees (CNCCE).
Legislation	Provision mechanisms of compensation or participation in any profits deriving from the marketing of research results or in public research centers.
Legislation	Reformulation and rationalization of the administrative sanctioning apparatus for the violation of current regulations.
Legislation	Establishment, at the Istituto Superiore di Sanità, of a national list of qualified individuals with adequate experience, selected through public notices, on the basis of criteria and requirements predefined.
Legislation	Simplification of procedures for the use for research purposes of remaining biologic or clinical material remaining from previous diagnostic or therapeutic activities.
Training	Identification of general criteria to define specific course programs on clinical research methodology, management and conduct of clinical trials on medicinal products.

Table I. *Main novelties introduced by Law 3/2018.*

and application timelines, for the issue of subsequent implementing decrees, the final acts necessary to obtain what is established by the law. A series of tasks entrusted to the Italian Medicines Agency (AIFA) and the Ministry of Health, the least "urgent" of which had to be carried out within 120 days after the publishing of decree 52.

Between these two legislative acts, the first (and for a long time only) implementing decree arrived, with which the Ministry of Health established the Coordination Center of Territorial Ethics Committees (CNCCE) (15). A body, based at AIFA, which has been assigned tasks of coordinating, directing and monitoring the process of ethical evaluation of clinical trials on medicinal products for human use and medical devices entrusted to the territorial ethics committees that should have been established shortly thereafter.

THE MAIN ISSUE: ETHICS COMMITTEES

In Italy, the arrival of the Regulation has led to a revolution in the authorization and ethical evaluation process, not so much for Part I, which is conducted through a coordinated process between Member States, but especially for Part II. Historically, in fact, the request for an opinion was made not only to an Ethics Committee but to all those representing the centers involved in the trial (16, 17). A Coordinating Ethics Committee, with the power to request changes to the entire document package from the promoter, provided a "single opinion" that Satellite Committees were called to accept or not accept, with the possibility of requesting changes solely to the documentation for the patient.

The tight deadlines granted by the new European legislation impose a single opinion at national level (9), as already experienced in the pandemic era for Covid-19 studies (18). To implement this new process, a drastic cut in the number of Ethics Committees operating on the national territory, which exceeded 90 units is crucial.

Law 3/2018 decreed that 40 local and 3 national ECs would be adequate, all under the supervision of the CNCCE. National committees have been established; two, at AIFA, will evaluate pediatric trials and trials with advanced therapies, respectively; the third, under the Italian Institute for health (ISS), will deal with national clinical trials carried out in public research centers (19). So far, there is no mention of which will be the territorial ethics committees, despite the first two proposals of the final implementing decree on the reorganization of ethics committees have been circulated.

What seems certain is that members will be appointed by the single regions and that these committees will be in charge of evaluating interventional studies with medicinal products and medical devices and any end-of-life requests; there might be the intention of involving these ECs in Part I of the evaluation. Numerous issues remain unattended, first of all the definition of the areas of competence and possible strategies to avoid overlapping of areas of expertise between national and territorial committees. It will also be necessary to clarify who will be in charge of evaluating all the research of the national and territorial committees that is not applicable to the Regulation, such as the evaluation of observational and / or interventional studies of other nature and requests for compassionate use drugs. At the moment the role of the territorial committees is carried out by a fairly high number who, following a self-nomination, have been charged with managing the temporary phase. Costs and the economic aspect still need to be defined. It is certain that the promoters will pay a single fee to cover the evaluation but there is no specific decree that clarifies specific payment methods, amounts and their division between the various actors involved.

CURRENT MANAGEMENT OF STUDIES ACCORDING TO REGULATION

The temporary management proposal released by AIFA, is buffering the situation in view of the completion of the regulatory review process.

Clinical centers that in the past had participated in clinical trials have been registered on the single portal directly by AIFA while the CNCCE has published all the documents required for Part II: curriculum template and public declaration on conflict of interest for the principal investigators, specific site eligibility form, eligibility model for participants' reimbursement, as well as guidelines for the preparation of informed consent forms and contract templates.

The ethics committee that will evaluate the specific site feasibilities cannot currently count on a list of minimum requirements established by law, except for phase I studies, for which, for years now, a self-certification is required as confirmation of compliance to the minimum standards set out by the competent Authority (20). Law 3/2018 introduces the obligation of requirements extended also to the other phases, confirmed by a specific decree (21), although to date the specific requirements identified by AIFA, remain unknown.

It will be interesting to understand, and perhaps the delay in identification is also due this issue, which requirements will be able to guarantee an adequate quality for clinical studies in profoundly different therapeutic areas, without excluding any bodies that might have an important role in scientific advancements in specific fields. It will perhaps be important not to repeat some mistakes made with phase I studies, which in fact in many cases have required considerable efforts greater than the actual needs for the conduct of clinical trials and a large investment both in economic and non-economic terms, perhaps also incompatible with the current possibilities of the National Health System (22, 23).

A NEW SOURCE FOR ACADEMIC RESEARCH

The biggest novelty introduced by the regulatory revolution, after the need for a single national opinion, is certainly the breakthrough in data transfer for registration purposes in non-profit studies (24), previously prohibited in Italy. A possibility that involves a fairly complex process, which perhaps will require further clarification and perfecting, but which in fact could represent the first real opportunity to give an economic value to the intellectual property of academic research. A significant advancement especially in a nation populated by brilliant minds but penalized by the limited interest, also and above all in terms of investments, of the institutions (25). The possibility of including data of the non-profit trials in the dossier for application for authorization naturally translate into the need for a considerable increase in the standards of conducting such studies, especially with respect to data management, as well as in the increased exposure of centers and promoters to possible audits, previously very rare in academia. So far it is unclear how all this will be compatible with an environment that is notably weak in research support staff (26) and infrastructures, the real Achilles' heel of the Italian research system (5, 6). While pharmaceutical companies will manage, albeit with some initial difficulties, to perform the necessary reorganization in order to face the increased quality standards in compliance with the new Regulation,

it is highly improbable that academic Sponsors will succeed in this endeavor, given the already critical situation in terms of lack of resources. This situation, as described by Gehering *et al*., places Italy in a state of disadvantage compared to other Member States, also where the quality system, considered to be the most affected area in terms of time and personnel required, is managed by external Promoters. The enormous workload and responsibility that come with promoting a new clinical trial is hardly tackled with the available resources in a system that lies in a political reality not inclined to granting public investments.

POTENTIAL FURTHER HURDLES

The first criticality is that the current state of implementation of the regulation contrasts with the intentions of the European legislation and above all of the Law 3/2018, which called for a "simplification of the purely formal obligations pertaining the modalities of submission of the request for evaluation to the ethics committee and for conduct and evaluation clinical trials". Moreover, there are many other areas where the current national legislation is discordant with what is dictated by regulation 536/2014. This is the case, for example, of the reimbursement of expenses to patients: the European Regulation greatly widens, compared to the past, the areas of applicability of reimbursements, while in Italy a rule is still in force that restricts these benefits only to rare diseases within selected recognized hospitals (17). Same goes for the use of secondary data; while the European trend, both in accordance with the provisions of Regulation 536/2014 and the premises of the General Data Protection Regulation, GDPR (27), would allow for the patient to provide an extended informed consent, and the secondary use (always for research purposes) of data previously collected, without the need to re-contact the patient again. Possibility in fact prohibited, or at least hindered, by the recent Italian legislation in the field of privacy (28) which always requires, with very rare exceptions and with the need for prior authorization from the privacy officer, the collection of a new consent, with serious negative consequences with respect to the secondary use of data (29, 30). Furthermore, it will be necessary to clarify to the Sponsors what their obligations are with respect to the free supply of the drugs used in the trial, given that the classification of some comparator drugs as "analogous Investigational Medical Products" only for regulatory purposes (with consequent obligation for the promoter to provide them free of charge to the centers) is only contemplated by national legislation (17), and would create a first discrepancy with other Member States.

These are the three most obvious examples, but not the only ones, of the work that needs to be done in terms of revision and adjustment of the regulatory apparatus in Italy.

FUTURE PROSPECTS

Certainly, further legislative measures will be needed to complete the implementation framework. In addition to the decree for the reorganization of the ethics committees and the one to define the single fee, there is a great deal of expectation with respect to the measure that will define the minimum requirements of clinical centers authorized for the conduct of clinical trials. This is true also for any other decrees necessary to address the critical issues described above.

One point of reflection is without a doubt the great missed opportunity, even if it does not fall directly into the sphere of 536/2014, for observational research. Given the overflow of decrees, it could have been a good time to regulate an area that has always been inexplicably gray (31), while once again the scientific appropriateness is recognized only for observational studies on medicinal products.

There remain three priorities for the immediate future: having interlocutors defined within the institutions, so that technicians can help avoid further errors and delays; seek a channel of dialogue with the national privacy officer; dignify the work of research infrastructures and support personnel.

Now the kick-off will be simultaneous for all member states; not being last depends solely on us.

ETHICS

Fundings

There were no institutional or private fundings for this article.

Conflict of interests

The authors have declared no conflict of interests.

Availability of data and materials

N/A.

Authors' contributions

Conceptualization: CC; literature review: MB, CC; writing: CC, RC, MB, FF; final revision: CC, FF.

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