Festina lente

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ABSTRACT

The provisions adopted in Italy for clinical trials on medicinal products and medical devices for the epidemiological emergency caused by COVID-19 had an impact also on the functioning of Ethics Committees (ECs). All COVID-19 clinical trials are evaluated preliminarily by the Technical Scientific Committee of the Italian Medicines Agency (AIFA). They are then evaluated by the Clinical Trial Office of the Competent Authority (AIFA) and by the EC of the Lazzaro Spallanzani National Institute for Infectious Diseases. On the basis of this experience, several parties have recommended the adoption of a new structure that envisages the involvement of a single EC for the activation of new studies, similar to the system put in place for studies on COVID-19.

Rather than a single EC with jurisdiction over the entire country, we could envisage the accreditation of a certain number of ECs, possibly subdivided by therapeutic fields, with the trials to be evaluated distributed among them, so that each is authorised to issue an opinion that is valid nationally.

The entire world is waiting for vaccines (effective also against new SARS-CoV-2 variants) and treatments to deal with the COVID-19 pandemic. Everywhere, measures have been advocated to reduce the period of time required to get these vaccines and treatments from clinical research to the patient’s bedside.

Many countries have adopted simplified procedures.

For example, the European Commission has issued specific guidelines aimed at the performance of clinical trials during the COVID-19 pandemic [1].

Given the pandemic situation and the need to have access as quickly as possible to effective products for prevention and treatment that are not yet available, we need to find a way to optimise the periods of time involved. However, this must not undermine the rigour of the scientific method or the observance of ethical requirements: we need to relax - where possible - and optimise the procedures but it is not acceptable to give up any degree of scientific quality or rigour in compliance with ethical criteria.

One crucial step is the beginning of the process, when the clinical trial is authorised. This is the point when the Ethics Committees (ECs) are involved.

The benefits and limitations of procedures introduced to accelerate authorisations for initiating clinical trials vary depending on the characteristics of the procedures concerned. The provisions adopted in Italy for “trials on medicinal products and medical devices for the epidemiological emergency caused by COVID” are significant in particular in terms of the crucial role played by the ECs. On the basis of those provisions, and only for the emergency period [2,3], clinical trials, prospective observational drug studies (namely “studies on drugs used in normal clinical practice in line with the authorised indications” [4]), and compassionate therapeutic use programmes (namely “programmes presented, by a pharmaceutical company, for use of medicinal products for compassionate use in more than one patient, on the basis of a pre-established clinical protocol identical for all patients” [4]) are evaluated on a preliminary basis by the Technical Scientific Committee of the Italian Medicines Agency (AIFA). They are then evaluated by the competent AIFA authority (Clinical Trial Office) and by the EC of the Lazzaro Spallanzani National Institute for Infectious Diseases [5,6] in Rome, as the single national EC for evaluation of clinical trials on medicinal products for human use for patients with COVID-19. Projects are approved if they have favourable opinions from the Technical Scientific Committee, the AIFA and the EC of the Lazzaro Spallanzani Institute. Centres other than the Lazzaro Spallanzani Institute in Rome that are involved in the study are included as satellite centres and the corresponding reference ECs, although not formally required to issue an opinion, must accept the single opinion issued by the national EC. This has made it possible to obtain approval from the EC within a very short period, often within 24 h.

On the basis of this experience, several parties have recommended the adoption of a new structure that envisages the involvement of a single one of the existing ECs for the activation of new studies, similar to

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the system put in place for studies on COVID-19. On that issue, it is worth mentioning that Regulation (EU) No 536/2014 [7], which is on the verge of being implemented, provides for a “single national opinion” but does not contain any information about the process used to obtain that opinion: each Member State may organise its own network of ECs through specific national provisions. The adoption of a procedure that channels any trial to a single national EC using methods similar to those adopted for trials on COVID-19 is impractical for a number of reasons, two of which are particularly important. The first is the fact that the EC would be burdened with an unsustainable workload. The second is that, in the case of COVID-19, the single EC has been able provide opinions very quickly because a scientific review has already been carried out by the AIFA’s Technical Scientific Committee, which has only selected projects with scientific value and validity. Under ordinary conditions, however, the ECs are required to carefully evaluate every aspect of the project, and that process cannot be cursory: an adequate evaluation requires a commensurate period of time.

Rather than a single EC with jurisdiction over the entire country, we could envisage the accreditation of a certain number of ECs, with the trials to be evaluated distributed among them, so that each is authorised to issue an opinion that is valid nationally. This orientation is also consistent with the provisions of law No 3 of 11 January 2018 (which provides for the establishment of forty “territorial” ECs authorized to evaluate clinical trials of medicines) [8] and with European Regulation (EU) No 536/2014 [7]. Centralization undoubtedly favors efficiency. Inevitably, however, it also entails the risk of not adequately considering local specificities and real feasibility. In this perspective, the involvement of the local EC next to the structure that will participate in the experiment could also be desirable. Alternatively, the local feasibility could be assessed by the General Management of the structure involved: most likely this would have the advantage of a more streamlined procedure than the involvement of the EC, giving equal guarantees of reliability.

In Italy, centralization in a single national assessment, with a multisites and nation-wide validity, has also been recommended by numerous scientific societies and institutions both for clinical trials [9] and for observational studies [10]. For this purpose, the establishment of a list of ECs certified by the Ministry of Health and authorized to provide the nationwide assessment was also recommended.

We could also envisage single national ECs subdivided by therapeutic fields (e.g.: oncology, cardiovascular diseases, neuropsychiatry, metabolic diseases and musculoskeletal disorders, among others). Although this possibility has been proposed and discussed in Italy, it seems difficult to implement. In fact, it would entail a radical change from the traditional subdivision of ECs based on the territory (and not the therapeutic areas), also confirmed by law No. 3 of 11 January 2018 [8].

In conclusion, the fact that the Italian experience has been very good in terms of evaluations carried out by the single EC for COVID-19 studies within an extremely tight time-frame, through electronic consultation, should not create the illusion that this can be the standard procedure: ECs must be efficient in evaluating and must not cause delays in initiating trials but high-quality evaluations require an adequate period of time to enable a careful, in-depth analysis of all documents. There is a need to optimise procedures and avoid unnecessary delays, but any lessening of rigour in relation to compliance with the scientific and ethical requirements is unacceptable because this will cause harm to patient. The best time to slow down is when you are in a hurry: “festa lente” (hasten slowly).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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