European Review for Medical and Pharmacological Sciences 2015; 19: 481-485

Research Ethics Committees and clinical research in Italy: where are we going?

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Abstract. **Italian Ethics Committees (ECs) have entered a new phase because of the recent Law no. 189 of November 8 2012 and the Ministry of Health Decree of February 8 2013. The new norms have introduced important changes. In fact, ECs are now established not to serve a single hospital or research institution but to serve even Regions. Moreover, they are established on the basis of the number of inhabitants, research sites and expected amount of clinical trials.**

The implementation of the news norms into practice have produced a drastic reduction in the number of ECs. This fact could raise some issues but it could obtain some benefits.

The paper explains the main steps of ECs and clinical research development in Italy. Special attention will be paid to recent trends. Moreover, the new norms will be illustrated, showing possible issues and benefits connected to their implementation.

Key words:
Research Ethics Committee, Clinical research, Pharmacological research, Clinical trials, Clinical research regulation.

ECs in Italy: a historical recall

Due to the recent Law no. 189 of November 8 2012 and the Ministry of Health Decree of February 8 2013, Italian Ethics committees (ECs) have entered a new phase.

In Italy, the origins and the diffusion of ECs occurred with several years of delay behind other nations, particularly USA, where ECs have risen in 1974[1].

Within a decade, from the mid-80s to mid-90s, there has been a rapid proliferation of Italian ECs (perhaps not always justified), up to a probably excessive number (248 in 2011). This period could be considered as a "start-up phase", to define members' skills, standard operative procedures and aims[2].

Early ECs were founded mostly through local initiatives of some universities and research medical centers. The fundamental reason for setting up them was to apply and to promote ethical principles into medical practice and research. In other words, ECs were particularly intended to make more clear the mission of the hospital/research center, even though it is doubtful if every Italian EC had developed own statutes referred to ethical principles and values.

This issue is relevant: in fact, at that time in Italy no specific law on ECs was in force and the only reference was the World Medical Association "Declaration of Helsinki". Instead, a great contribution was soon given by the simultaneous increasing spread of bioethics, beyond academics.

Afterwards, ECs were established in hospitals, local health units, research institutes, assuming importance and credibility above all for the evaluation of clinical trials rather than representing a place for a wider ethical reflection. This aspect was decisive for the improvement of clinical research in the country.

All the laws produced by the mid-90s up to now highlight the transformation of ECs into Research Ethics Committees (RECs). However, these regulations have created a complex situation transforming RECs in more bureaucratic rather than ethical bodies[3]. In 2001, the Italian National Bioethics Committee (NBC) raised some issues such as the adequate qualification of the members, the aim of the ethical reflection and the persistent risk of bureaucratization. NBC also stressed the role of the REC on trial monitoring at the research site[4].

From 2000, Italian pharmacological clinical trials are collected through an online national database by the Italian Medicines Agency (AIFA). This database is called "National Monitoring Centre for Clinical Trials" ("Osservatorio Nazionale per la Sperimentazione Clinica" – Os-SC), that ensures the monitoring of all clinical

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trials conducted in Italy and approved by the ECs. Moreover, this observatory is open and accessible to the ECs, the Regional Authorities and the sponsors and it publishes an annual report on clinical research.

Before the OsSC implementation, data on RECs activity and on clinical research were few and fragmentary. For example, Venturini et al[5] presented data from 20 RECs (about 10% of the total amount) of 9 Italian regions, describing the characteristics of clinical trials, which were mainly pharmacological, sponsored, multicenter studies. Even if RECs sample was limited, data already showed a quantitative and qualitative improvement of pharmacological research in Italy than in the past.

When many rules on clinical research was added and changed, both ethics committees and researchers had to overcome difficulties regarding clinical research protocol assessment and approval. On the matter, Mosconi et al[6] interviewed 83 oncologists of 67 Italian hospitals (and 60 RECs) on the relationship and the satisfaction level with REC that have been consulted for their studies. The survey shows a high degree of satisfaction of most oncologists with regard to the ethical/scientific protocol, but a low satisfaction and critical judgments on the bureaucratic aspects, on the relations with the REC secretary office and on the training activities of the committees. Therefore, the authors highlighted the need for much training and for a wider collaboration between researchers and RECs.

In another study, Porcu et al[7] examined some issues concerning RECs review activity and the timing spent for providing the opinions. It has been analyzed the impact of two fundamental laws: the national law no. 211/2003 (which implemented the EC Directive 2001/20) and the Italian Ministerial Decree of December 17, 2004 (concerning the "no profit" clinical trials) on the timing and operating procedure required from the protocol submission until its authorization. In this survey conducted with 134 RECs data showed that many of them did not meet the time required (60 days) by Directive 2001/20, while the median was significantly higher (72 days). In addition, this study found a lack of communication and coordination among the surveyed RECs: the authors highlighted the need of more uniformity in the protocols submission procedures.

Great improvement in the procedures timing and organization was obtained through the OsSC, particularly through the on line mandatory submission of the Clinical Trial Application (CTA) form. De Feo et al[8] showed the main effects of these news, analyzing 5 multi-centre clinical trials presented to 107 RECs. They found a significant reduction in the time to give the opinions. Nevertheless, an unsolved issue was represented by the long time for obtaining the authorization from competent authority.

Recent trends of pharmacological clinical research in Italy

OsSC data show a positive trend with a gradual increase in the number of pharmacological clinical trials (557 in 2000 *versus* 880 in 2008). Since 2009 there has been a decline (676 in 2011). This decrease could be explained by three factors: (1) The global economic crisis which has also affected the pharmaceutical sector; (2) The shift of much pharmacological research in some Developing Countries, where costs and times are lower[9]; (3) The promulgation of the Decree on insurance coverage in the clinical studies (in force since 2010), which has increased costs and budgets[10].

However, if Italian situation is compared with others EU Countries, it can be noted that the decrease has been relative: in fact, the percentage of the Italy/EU ratio shows that in 2010-11, Italian pharmacological research has had a satisfactory trend (16.4% in 2011 compared to 15.8% in 2007)[11].

OsSC data support others considerations. Firstly, it is clear that the majority of drugs clinical trials in Italy were conducted at University hospitals, general hospitals, and Scientific Institutes for Research, Hospitalization and Health Care (Istituti di Ricovero e Cura a Carattere Scientifico – IRCCS), while a much lower number of them was carried out at the local health units. Secondly, the majority of them was concentrated in the regions with the highest number of inhabitants (Lombardy, Lazio, Sicily, Campania), with the exception of Veneto, Emilia Romagna and Piedmont, that had the highest inhabitants/EC ratio. Thirdly, comparing data from 2007 to 2011, there has been a progressive and significant reduction of the median time (from 45 to 31 days) to provide the single opinion from the EC of the coordinator centre of multi-centre studies. On the contrary, the median time to provide the acceptance/refusal from the ECs of the other participating centers remained substantially unchanged. Finally, a negative factor that emerged was red tape for competent authority deliberation (in Italy, competent au-

thorities are, for example, general manager of local health units, rector of university, president of IRCCS).

Excessive number of ECs, increasing costs and time were challenging issues. Anyway, these critical points concern not only Italy, but also other EU Countries. Druml et al[12] highlight the "tribulations" that promoters and researchers has to overcome to start a study in several EU Countries. These authors also show the several differences among RECs in Europe, such as their total number for a single nation, members training and selection, protocol review requirements, fee payment and attention to conflict of interest.

The last Italian regulation on ECs and clinical research

The recent Law no. 189 of November 8 2012 and the Ministry of Health Decree of February 8 2013 have introduced important changes for ECs and clinical research in Italy.

New criteria have produced a drastic reduction in the number of RECs. At the moment, except Le Marche, all Italian Regions have established new RECs. Their actual number is far 92 (Figure 1).

Figure 1. RECs number established by Italian Regions.

RECs are now established not to serve a single hospital or research institution but to serve even Regions. More, they are established on the basis of the number of inhabitants, research sites and expected amount of clinical trials. So, each REC will assess not only trials related to its institution but also those related to other search sites of territorial competence. The RECs have been selected taking into account the amount of opinions provided in the last three years.

Further changes have been introduced about RECs function and composition[13]. RECs will be composed of experts in different disciplines (Table I), with the possibility to consult external experts for specific areas[14,15]. The term of office is three years and the members may be renewed consecutively only once. The composition must ensure expertise and experience to assess ethical, scientific and methodological issues. The members must have documented knowledge and experience in clinical trials of drugs, medical devices and other health technologies.

The independence of REC must be guaranteed by a series of measures and at least: (1) lack of hierarchical subordination to the institution in which the REC works; (2) adequate presence of external members; (3) absence of any conflict of interest (members must also sign a declaration stating that they do not participate in the evaluation of clinical trials in which they are directly or indirectly involved).

Table I. REC composition according to the Ministry of Health Decree of 8 February 2013.

a) Three medical doctors;
b) A general practitioner;
c) A pediatrician;
d) A biostatistician;
e) A pharmacologist;
f) A pharmacist of the regional health service;
g) The medical director or his/her deputy and – in the case of IRCCS – the scientific director;
h) A n expert in law and insurance, or a forensic doctor;
i) A n expert in bioethics;
l) A representative of the health professions involved in the trial;
m) A representative of the voluntary associations or the association for patients' rights;
n) A n expert in medical devices;
o) In the case of medical device, a clinical engineer or other qualified professional;
p) In the case of food studies, a nutrition expert;
q) In the case of new technical procedures, an expert in the field;
r) An expert in genetics in the case of genetic studies.

Critical points

New norms could raise some issues. Firstly, drastic reduction in RECs number, and the fact that they will assess not just trials related to a single institution could cause a challenging workload. Consequently, RECs, and particularly their organizational structure, could not be able to face with the large amount of clinical trials to be assessed.

Secondly, since RECs will assess trials that will be carried out in other search sites, they could not know all the elements needed for evaluating the local feasibility of these trials. How could this inconvenience be avoided? Some RECs are involving one representative from each local search site. Will this presence be enough?

A third question: could these "overloaded" Committees – that are also pressed to give opinions quickly – be able to monitor the great amount of trials? A relevant REC task is also to follow trials from the approval until their end. On this regard, a possible solution could be to set up an operating section of RECs aimed at monitoring or, in alternative, search sites local commissions that follow trials under the responsibility of the regional REC.

A fourth question: in the previous setting, multicenter trial review was under the control of more RECs and, therefore, of many experts (coordinator center and local ones). Now, review is under the control of few RECs and few experts. Will actual reviews be effective?

Fifthly, RECs risk to became simple "technical" bodies, losing their original ethical mission, including the challenge of new way of communication[16,17]. In others words, the discussion on ethical aspects risks to be reduced in favor of reviewing technical-procedural aspects.

Finally, further elements to be clarified are: RECs members selection and payment criteria (at the moment they are not uniformly defined) and requirements for avoiding conflicts of interest.

On the other hand, positive elements of new norms are: firstly, reduction in RECs number will decrease trial review costs. Secondly, a fewer number of RECs could facilitate communication and collaboration among them. Thirdly, this new setting could favour a better professionalization of REC activity. Finally, new norms will reduce administrative time for the authorization: in fact, operative procedures must guarantee the possibility to draw up contracts by three day after RECs' approval, so allowing to start the trials.

Anyway, this new phase represents a period of adjustment that needs to be monitored and assessed in the short-mid term.

Conflict of interest

The Authors have no conflict of interests to declare.

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