

Editorial

Are the Ethical Committees for pharmacological research bureaucratic bodies?

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Background

The question, reported in the title of this editorial, has the purpose of being intentionally a little provocative. It is obvious the Ethical Committees (CE), founded and established to approve clinical trials of new drugs that the pharmaceutical industry intends to market and, in general, biomedical research such as pharmaceutical *no profit* controlled clinical trials and observational studies, are *Bureaucratic Bodies*. Indeed, they are a group of people with various skills that work in compliance of well-defined rules and laws in order to realize the common good of health on the basis of criteria of impartiality, rationality, impersonality and, mostly relevant, independence; property, this latter, that it is not actually requested for a real Bureaucratic Body, but that is an essential requisite for an Ethical Committee. So, the answer can only be affirmative.

It is however equally obvious that the above question refers rather to the negative connotations of the term *bureaucracy*, such as an inefficient, convoluted, too inflexible structure perched on privileged positions to consider with extreme fussiness irrelevant aspects and to formulate unnecessary requests for themselves to meet absolutely non-substantial needs. Indeed, the current question arises from an e-mail sent to me by a researcher working in a hospital afferent to the CE Milan Area 3 (CEMiA-3).

The researcher's complaints and outburst were due to the fact that the CEMiA-3 did not immediately approved a study of which she/he was the Principal Investigator. Indeed a suspension judgement was expressed, requesting the clarification of several aspects and the completion of some relevant documents, among which, in the information sheet for the patients to be enrolled into the controlled clinical trial, it had to be reported the time and the place of conservation of the biological samples (*now suspended by you because there is no written as long as we keep the samples and where: at the XY or XZ hospital! and it goes next year! Was not a phone call enough?*, just for reporting the exact text). Furthermore, she/he wrote *This CE would not be able to approve the discovery of the wheel or the fire for a thousand pretexts on the experimental plane or on the danger ... in short, it lacks courage and confidence in the talented Researcher and gets entrenched in the bureaucracy.*

Obviously, the talented researcher *with capital R*, as she/he wrote, had only grasped the aspect of the conservation of the biopsy specimens which is, let me to say, a *minor flaw* compared to the shortcomings and mistakes that the CEs systematically find in the documentation of the studies submitted for their judgement.

However, it must be recognized that what the researcher wrote is a widely held opinion of the physicians/researchers who have to interact with the CEs and the aim of this Editorial is precisely that of trying to start to build a bridge of understanding and collabora-

tion; indeed, it is clear that if the ECs and the researchers remain seated on the opposite banks of a river, they may perhaps recognize who it belongs the body that passes first in the river stream, but certainly they will never actively communicate.

I have to say that first of all I asked myself how it is possible to make clinical researcher understand that the EC do not make mere vexatious requests of a bureaucratic nature. I argued that, since the physicians member of the CEs, do not share this opinion but rather take it for granted that they are absolutely legitimate, a solution could be to impose a period of mandatory participation in the work of the ethics committees to all the clinicians and researchers. However, I must say, this solution could be impractical and even counterproductive.

In addition, I also wondered if it is ever possible to establish an active relationship of mutual collaboration between the CEs and the clinical researchers, given that every time the CE tried to do it through several workshops that I have proposed and contributed to organize for this purpose, the participation of researchers was extremely scarce and practically null.

I refer to the following three workshops held at the ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy.

Workshop Il Comitato Etico di Niguarda e La Sperimentazione Clinica. 27th September 2006. [Niguarda's Ethics Committee and Clinical Trial].

Workshop del Comitato Etico dell'Azienda Ospedaliera Ospedale Niguarda Ca' Granda: Sperimentazioni Cliniche: Nuovo Decreto Ministeriale Clinical Trial Application (CTA). 29th September 2008. [Workshop of the Ethics Committee of the Hospital Agency *Hospital Niguarda Ca' Granda*: New Ministerial Decree Clinical Trial Application (CTA)].

Workshop del Comitato Etico dell'Azienda Ospedaliera Ospedale Niguarda Ca' Granda: Validità del consenso informato ed applicabilità nelle situazioni critiche. Lo stato dell'arte degli aspetti normativi e le sfide per il futuro. 27th September 2012. [Workshop of the Ethical Committee of the Hospital Agency *Hospital Niguarda Ca' Granda*: Validity of informed consent and applicability in critical situations. The state of the art of regulatory aspects and challenges for the future.]

Finally, I refer to the recent conference: *Quale prospettive per i Comitati Etici in Italia?*, 1 December 2017, Bergamo, Italy. [Conference: *What prospects for the Ethics Committees in Italy?*]

The requests of the ECs are bureaucratic acts?

First of all, it has to be considered that the ECs are not sovereign and have to answer for their work to the Agenzia Italiana del Farmaco (AIFA, established by the Law 326 of 2003)¹

to which the Law n.189 of 8 November 2012 recognizes the role of competent authority for the evaluation of clinical trials with drugs.² Therefore, it seems that the EC has to play the role of being a kind of interface between researchers and AIFA trying to prevent that AIFA does not approve their trials with drugs.

In addition, as also the so-called *Balduzzi Decree* points out,³ the ECs must take their actions and issue their judgements by inspiring to non-normative reference documents such as: i) The Helsinki Declaration, 2013;⁴ ii) The Oviedo Convention,⁵ which was ratified in Italy by the law of 28 March 2001,⁶ but this ratification has not yet been filed making it practically ineffective in Italy; indeed, it has to do a subsequent deposit of the instrument of ratification in the Council of Europe for making this ratification effective;⁷ iii) the rules of “good clinical practice (GCP);^{8,9} iv) the updated guidelines of the European Agency (EMA) such as the ICH E8,¹⁰ the ICH E9,¹¹ with its revision ICH E9(R1);¹² v) but also, and above all, the laws of the Italian State such as the Legislative Decree of 24 June 2003 n 211.¹³

The requests, such as those that have triggered the protests of the researcher, are carried out on specific current indications of the Guarantee of Privacy such as i) the authorization No. 9/2016,¹⁴ that considers the conservation of data and samples together with their security referring also to ii) the provision of 24 July 2008,¹⁵ which also takes into account the problems of the data transfer abroad and the relevant ways to inform patients; iii) the Authorization 8/2016 concerning genetic data also in the field of research,¹⁶ with the problem related to the request of a further consent ranging from the *broad consent* to the *blanket consent* for future genetic investigations also considered, together with the topic of the biobanks in the biomedical research, by relevant guidelines of the National Bioethics Committee.¹⁷ About this point, it cannot be left out the famous guideline written in 2006 by the Smith Kline foundation and the Italian Society of Human Genetics,¹⁸ even if it is aimed primarily at genetic studies that are completely different from the so-called “substudies” on genotypes of patients primarily aimed at identifying potential prognostic factors, usually proposed as a corollary in controlled clinical trials, particularly in oncology.

Then, also the request to include in the information sheet at least the details of the insurance policy is a minimum requirement compared to the requirements of the Decree July 14, 2009 on insurance (the investigator is always required to inform the participants to the trial protocol, even through the informed consent... Article 1, Point 6).¹⁹ It has to point out that, according to the Decree, the ECs judgement is null by law in the absence of an appropriate insurance policy. It has also to be reported that the ECs are so blind bureaucrats that they almost usually accept the formal commitment of the sponsors to take out an appropriate insurance once the favourable judgement has been obtained, since it seems acceptable and sensible that the sponsors face additional economic charges only if they are appropriate.

In conclusion, these requests are to be considered absolutely in line with the principles of GCP and their revision to which the ECs inspire their work,^{8,9} principles that can be extended to other types of studies in addition to the controlled clinical trials on medicinal products.

Thus, ECs demands must be considered not as the expression of a boring and dull bureaucracy, but rather as the expression of attention, consideration and respect towards a patient who is required to express informed consent consciously and freely. Indeed, it has to point out that the first mission of the ECs is the guarantee and protection of the patient, who constitutes the weakest and most suggestible link in the chain: patient, medical Researcher, AIFA, ethical committee, Pharmaceutical Industry, CRO, etc.

As a further comment, it is curious that the researchers do not complain so wildly about the strict rules, such as the fixed number of words, when they fill the application forms for obtaining funds for their research from some Agencies such as Telethon, Cariplo, Regione Lombardia, AIFA, International Agency For Research on Cancer (IARC), Horizon 2020, European Funds, Progetti di Ricerca di Interesse Nazionale (PRIN), etc.

The adherence to the laws of the country can be considered a bureaucratic act?

In addition to *bureaucrats only able to put the sticks in the wheels*, the ECs are also considered cowards when they do not authorize the so-called *deferred consent* in the case of an adult unable to express her/his informed consent and without a legal representative. In particular the EC, established by the Decree of 15 July 1997, Article 4,²⁰ were regulated by the Decree of March 8, 1998 which,²¹ at point 3.7.8 considered the so-called *deferred consent* to be acceptable following the ICH E6 GCP.⁸ Indeed, the ICH E6 guideline defines the informed consent at the point 1.28,⁸ devoting to this topic a large space compared to the randomization, for example, which is considered only in a short five lines paragraph, and, finally, consider the *deferred consent* at the point 4.8.15. However, in the subsequent Decree 211 of 24 June 2003,²² the *deferred consent* is no longer considered acceptable as can be seen in Article 3 where only the legal representative of the person who is not able to providing informed consent is entitled to provide it in its place and also with particular limitations considered in the following Article 5.

How much and where the problems, misunderstandings and conflicts between the ECs and the researchers are more relevant?

I have to point out that the requests of the ECs are particularly relevant and numerous in the context of the research on medicinal products so-called *no profit* (characteristics that the CEs must carefully verify) that, according to the 15th AIFA Report on Clinical Trials in Italy,²³ constitutes just a little less than a third of all the studies. In addition, this kind of research is particularly supported by the legislator with the Decree 17 December 2004²⁴ and also with the recent Law Lorenzin.²⁵

Indeed, the research *no profit* or *independent* presents the greatest criticality as researchers have to face a series of obligations that require specific skills, adequate equipment and the necessary funds: perhaps, the funds given by the pharmaceutical industry, as occurs in various circumstances, should be intended for the involvement of an *Organizzazione di Ricerca a Contratto (CRO)*²⁶ to support all the aspects of the planning and conducting a research.

I am convinced and I want to support the thesis that in reality the researchers *R capital with or without talent* do not necessarily have to be aware of all the specific and detailed aspects that are associated with the drafting of documents to be set up for the request of the CEs judgement. In fact the researchers have to be fully supported in the path that runs from the conception of an idea (more or less spontaneously matured) to the presentation of the appropriate documentation to the ECs.

To this regard, I want to remember the *Fondazione per la Ricerca Ospedale Maggiore di Bergamo (FROM)* a non-university foundation at the ASST Papa Giovanni XXIII, and the recently

founded *Dipartimento di formazione e ricerca* at the ASST Grande Ospedale Metropolitano Niguarda having precisely the aforementioned tasks and purposes.

In addition, I like to particularly mention the AIFA project of a few years ago, called the *quality in non-profit clinical experimentation*,²⁷ in which the characteristics necessary for the establishment of a Clinical Trial Quality Team (CTQT) were identified, defining its composition, operational details and skills, and also the timing of activation and implementation of its activities.

I firmly believe that these structures of which there is a list dating back to 2010 of a dozen centres, especially placed in *Istituti di Ricovero e Cura a Carattere Scientifico* (IRCCS) and Universities with characteristics similar to the Clinical Trials Unit set up abroad, almost exclusively at University level and gathered in a specific network ([website: http://www.ukcrc-ctu.org.uk/](http://www.ukcrc-ctu.org.uk/)), constitute the only way to overcome problems of misunderstandings and conflicts, to relieve the EC from an activity of mere control that diminishes its mission and its work and to win the challenge of independent and effectively *no profit* research that researchers cannot face alone as a trans-oceanic solitaire.

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