Presidenza del Consiglio dei Ministri

MOTION

ON THE IMPLEMENTATION OF REGULATION (E.U.) NO.536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL OF 16 APRIL 2014 ON CLINICAL TRIALS ON MEDICINAL PRODUCTS FOR HUMAN USE, AND REPEALING DIRECTIVE 2001/20/EC.

25 September 2015

The European Union has approved a new regulation to streamline the rules for the authorisation and carrying out of clinical trials in the Member States.

- The NBC puts forward a number of considerations with regard to this[1].

The Regulation sets down in Art. 4 that "a clinical trial shall be subject to scientific and ethical review" and that "the ethical review" shall be performed by an ethics committee in accordance with the law of the Member State concerned, and may encompass, according to the cases, aspects addressed in Part I of the assessment report for the authorisation of a clinical trial as referred to in Article 6 and in Part II of that assessment report as referred to in Article 7

It must be considered that in Part I there are not only scientific aspects but also aspects of an ethical nature (therapeutic benefits, the importance of clinical trials, the reliability and robustness of the data generated in the clinical trial, the risks and inconveniences for the subject, etc.) and in Part II aspects linked to the protection of subjects and the requirements for informed consent, as established in Ch. V of the Regulation and in relation to the territory of the Member State in question

Nevertheless, the combined provisions of such norms is not so explicit and an interpretation of the Regulation can also be made that is in favour of the choice on the part of the State of a separation between the scientific and ethical aspects to be allocated separately, the former to scientific committees and the latter to ethical ones.

The NBC highlights the risks of this possible separation and recommends that the single national committee or ethics committees for clinical trials deal with the review of both the aspects concerning Art. 6 (Part I) and those related to Art. 7 (Part II).

In this motion we set out to stress the reasons for this recommendation.

Undoubtedly there are aspects that must be considered strictly ethical: that the controlled clinical trial is carried out in such a way as to defend the interests of the patients balancing the foreseeable risks and benefits, that the patient gives his/her informed consent, that the patients are insured against any possible harm, that there are no conflicts of interest, etc.. Moreover, as generally happens in research, such interests shall be essentially defended by making sure that the protocol satisfies significant requirements for which the trial is worth carrying out and that the modalities whereby the study is conducted makes it possible to achieve valid conclusions.

More in general the ethics committees must ascertain that the interests of industry, science and society do not prevail over the wellbeing of the subject[2]. It is also just as important to verify that the methodology of the study is in line with ethical principles. Special attention must be paid to what is stated as a general principle in Art. 3 of the Regulation: a clinical trial may be conducted only if the rights, safety, dignity and well-

[1] The NBC has already expressed its opinion on the regulation in the Motion *NBC Declaration on the document "Proposal for a Regulation of the European Parliament and of the Council on Clinical Trials on Medicinal Products for Human Use, and Repealing Directive 2001/20/EC" (17 July 2012)",* of 31 October 2012. It also gave its opinion on clinical trials in previous opinions. Among these in particular: *Clinical trials in adult or minor patients who are unable to give informed consent in emergency situations,* 28 September 2012; *Pharmacological trials in developing countries*, 27 May 2011; *The improper use of placebo,* 29 October 2010; *Bioethical problems in clinical trials with non-inferiority design*, 24 April 2009; *Pharmacological trials on women*, 28 November 2008.

[2] Among the many documents on this *Convention on Human Rights and Biomedicine*, 1997, Art. 2 *and Declaration of Helsink*i, October 2013, Arts. 3-4.

being of subjects are protected and prevail over all other interests, as well as being designed to generate reliable and robust data. And again it stresses the importance of monitoring and inspections foreseen by the Regulation in arts. 48 and 78.

For this reason the NBC strongly reaffirms the inseparability of the scientific aspects from the ethical principles. Science and Ethics are closely connected and cannot be separated, without the risk of the revival of a dichotomy that was overcome decades ago both at a theoretical and operational level by the ethics committees present in the research institutes and healthcare facilities all over the world, Italy included.

- The organisational aspect of the ethics committee, referred by the Regulation to the single States in the respect of a number of very precise requirements (e.g. for the persons charged with assessing and validating the application in Art. 9, with the obligation to respect a strict timing and to express one single decision), can lead to different solutions: a single national ethics committee; national ethics committees in a limited number for specialised subject areas; ethics committee of national/ international reference and coordination for the territorial and/or sectorial ethics committees.

Among the various above mentioned solutions which all present problematic profiles that translate into advantages and disadvantages, for the formulation of the 'single opinion' the NBC proposes the setting up of an ethics committee for clinical trials – with appropriate facilities – with the function of reference for Italy at international level and coordination of a limited number of territorial and/or sectorial ethics committees with competences for therapeutic areas for the assessment of national and international trials[3].

Wherever relevant, such committee can take the assessment upon itself also availing of external experts.

Among the advantages of this option:

a) The presence of a national ethics committee of reference at European level and of reference for the territorial and/or sectorial ethics committees for clinical trials, and should it be necessary, able to assess and validate the application;

b) The ethical review can each time be entrusted to the territorial and/or sectorial ethics committee presenting the best competences for the proposed research, without having to continuously gather experts;

c) The experiences of the territorial and/or sectorial ethics committees for clinical trials are preserved and its further specialisation is promoted;

d) Italy could enter the network that – at European level – unites the States that have already achieved the coordination of their ethics committees.

For the purpose of guaranteeing the respect of the deadlines established by the Regulation, the NBC recommends that the number of territorial and/or sectorial ethics committees for clinical trials be reviewed and limited.

In such way the ethics committee of reference and coordination for clinical trials could easily take on the role of an efficient, authoritative observatory, able to communicate with the other ethics committees. It must be taken into account that in

[3] In this context the territorial and/or sectorial committees refer to the committees only for clinical trials and not to the committees for the assessment of clinical cases.

the respect of the Regulation it is not just a question of examining the traditional bioethical (and bio-juridical) profiles posed by the single clinical trials, but it is necessary to search for the origin of the bioethical issues and, therefore, to have the competence to seek possible solutions, even the most complex ones or those most difficult to identify.

The close connection between the scientific and ethical dimensions advocated above must be confirmed by the necessarily interdisciplinary composition of the ethics committee of reference and coordination and the territorial and/or sectorial ethics committees whose members, taking into account gender differences, must have ethical, scientific and juridical competences. It is necessary that the members of these committees, as foreseen in the Regulation (Art. 9) are guaranteed the requirements of independence and transparency, do not have conflicts of interest, are independent of the sponsor, as well as free of any other undue influence. They must be appointed according to the principle of “impartiality” according to transparent criteria. The assessment report cannot be made by anyone who must then use the data of the controlled studies for regulatory reasons or to assess reimbursement by the National Health Service (NHS).

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The text was drafted by profs. Lorenzo d'Avack and Silvio Garattini.

The debated text was voted on and unanimously approved by those present in plenary sitting: profs. Salvatore Amato, Luisella Battaglia, Stefano Canestrari, Lorenzo d'Avack, Antonio Da Re, Riccardo Di Segni, Paola Frati, Silvio Garattini, Assuntina Morresi, Demetrio Neri, Andrea Nicolussi, Laura Palazzani, Rodolfo Proietti, Monica Toraldo di Francia, Giancarlo Umani Ronchi.

The members without the right to vote expressed their approval: Dr. Maurizio Benato (Federazione Nazionale degli Ordini dei Medici Chirurgi e degli Odontoiatri) and Dr. Carlo Petrini (Istituto Superiore Sanità).

Profs. Carlo Caltagirone, Cinzia Caporale, Carlo Casonato, Bruno Dallapiccola, Francesco D'Agostino, Mario De Curtis, Carlo Flamigni, Marianna Gensabella, Massimo Sargiacomo, Lucetta Scaraffia and Grazia Zuffa were absent in the plenary session but endorsed the motion at a later date.

The motion was also endorsed by Dr. Carla Bernasconi (Federazione Nazionale Ordine Veterinari Italiani), Dr. Rosaria Conte (Consiglio Nazionale delle Ricerche) and Dr. Annateresa Palamara (Consiglio Superiore Sanità).