Presidenza del Consiglio dei Ministri

CNB

COMITATO NAZIONALE
PER LA BIOETICA

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" (17July 2012)

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This brief declaration does not intend to examine all the issues addressed in the Proposal for a Regulation, but merely to highlight certain elements which are approved and others which cause concern and problematicity in ethical terms.

1) The NBC considers the initiative to replace Directive 2001/20/EC with a Regulation to be acceptable, in order both to clarify the conduction of international, multi-centre clinical drug trials on human subjects and to streamline assessment/authorisation procedures.

2) However, in the preamble of the document an explicit reference to the *Convention on Human Rights and Biomedicine* (1997) and the *Additional Protocol concerning Biomedical Research* (2005) Council of Europe (opened to a greater number of States than those foreseen by the European Union) would have been appropriate - precisely because the regulation repeals an EU Directive already in force and operational for some time in several Member States. The definition of unified content regulations between the two European Institutions is a fundamental objective to be pursued.

The references to human dignity and fundamental rights in the Preamble (paragraphs 22, 52 and 65) do not seem sufficient. An explicit reference to the protection of human dignity should be clearly asserted at the very beginning of the Proposal for a Regulation as an essential ethical principle.

3) Concerning the designation of the "rapporteur/reporting Member State" by the sponsor (Article 5, 1) it is considered appropriate to establish some objective criteria, designed also to ensure a "rotation" of the Member States to be appointed, to prevent situations of "conflict of interest", and to avoid the risk of privileging the State that raises fewer "ethical criticalities" possibly slowing down research or not approving it.

4) The gradation of foreseeable risks and related regulations to ensure prevention and protection according to the complexity of testing procedures (Article 2) is significant, although (for reasons of consistency with the objectives of the Proposal for a Regulation) more careful and accurate determination - where possible - is desirable. In particular, three major categories of risk could be determined: high risk (e.g. the study of a new drug for marketing approval), low risk (e.g. research on the expansion of the indications of a drug); negligible risk (e.g. research on the optimisation of the use of drugs already on the market).

5) The need for simplification and centralisation of administrative procedures, the search for ways to reduce excessive bureaucratisation, in order on the one hand to ensure the interests of the patient, avoiding unnecessary delays and on the other to ensure European competitiveness internationally, are appreciated in principle.

It should be noted, however, that carrying out of the indicated procedures in a very short time (Articles 5ff) could compromise patient protection. The fixed time period for the drafting and transmission of the Report by the Member State is extremely short, even if "the group of experts" has already expressed its view, and prevents careful scientific and ethical assessment.

The Regulation in the absence of notification to the sponsor by the rapporteur/reporting Member State within the established time period adopts the concept of tacit authorisation already present in Directive 2001/20/CE (preamble 8). In consideration of the timing which characterises the procedure, the NBC disagrees with this authorisation criterion and strongly calls for the definition of procedures other than those specified.

6) The explicit reference to third parties in relation to the sponsor and the institution in the assessment of the protocol is welcomed in the Document.

It should be noted, however, that the Regulation lacks explicit reference to ethics committees as assessment bodies. Although this document rightly ascribes to individual States the internal organisation and determination of institutions that are involved in the assessment of trails in accordance with the principle of subsidiarity, the absence of a mention of ethics committees or bodies set up in accordance with the same principles introduces an unacceptable exception to the national and international regulations which have made provision for their establishment for many years and disregards well-established practice, created with the aim to better protect the patient's rights with respect to the requirements of progress in research. In (Article 9) there is a general reference to a group of people, of a reasonable number, who collectively have the necessary qualifications and experience. The Regulation only specifies that the view of at least one person, whose primary area of interest is not scientific, 'will be taken into account', without any reference to ethical competence.

The NBC considers the presence of a system of ethics committees for the scientific, clinical and ethical assessment of protocols and informed consent to be essential.

7) With regard to the recruitment of participants there is no reference to sex differences in the carrying out of studies and the participation of women in trials is not considered. Reference to vulnerable groups such as older people and detainees in particular is also missing. It is hoped that patients from developing countries, provided with adequate safeguards given their vulnerability, will also be recluted in the research.

8) Possible dissension by the rapporteur/reporting Member State to the trials should be justified in detail on the basis of "scientific and socio-economic arguments", without any explicit reference to ethical issues (Article 8, 2 (b); Article 14, 4 (b); Article 23, 2). But the same analysis of the study and design of trials does not only regard scientific and socio-economic aspects but it must contain at the same time elements of ethical consideration for the protection of participants from unnecessary risk and damage.

A specific reference to an ethical assessment is present only when vulnerable populations, children and incapable adults are mentioned (Article 10, 1 and 2). This highlights, as other parts of the Regulation, the minor importance given to the ethical dimension in the overall assessment of clinical trials.

9) To ensure the right of the participant in the study to be duly and clearly informed as regards consent is essential and cannot be deferred. The clear

regulation of informed consent in the Document (Articles 28-29) is welcomed. However, particular attention should be paid to understanding the characteristics of the proposed clinical trial, such as the use of placebo, non-inferiority design, the use of the reference drug, and the use of surrogate or therapeutic parameters. An integration in the formulation should be introduced with the indications included also in the *Oviedo Convention* and the *Additional Protocol* (particularly with respect to the specific provisions on information given to the participant prior to consent and the absence of negative consequences for those who withdraw from clinical trials).

10) The requirement of no financial incentives with reference only to incapacitated subjects and minors is made explicit in the Document (Articles 30-31), leaving open to interpretation that they may be possible in other cases. Direct or indirect compensation for participation in trials is a delicate bioethical and biojuridical problem which requires a clearer position on the part of the Regulation, also taking into account what has already been expressed in preceding regulations (the *Convention* and *Protocol*). A single payment, intended as reimbursement of expenses, can be expected regardless of the risk of a trial. A limit to the number of participations in trials must be indicated for healthy participants.

11) It is appreciated that provision has been made in the Regulation for assistance in emergency situations (Article 32), where it is not possible to obtain consent directly from the person concerned as a result of clinical circumstances (e.g. cranial trauma) or from the legal representative, in the time frame needed to make use of the medicinal product under investigation (the so-called "therapeutic window"). However, the justifiable reasons (deduced by preclinical testing methods or sporadic observation) for the effectiveness of the new medicinal product compared to the current treatment, must be supplied.

12) The mandatory publication of adverse events and negative results (Article 37) and transparency to improve and facilitate access to data and international scientific communication (even in order to avoid duplication) is welcomed.

13) Lastly, the possibility offered to every Member State to have partial autonomy in regulating the practical arrangements for acquisition of consent and use of the medicinal product under investigation even in relation to the unique characteristics of the subject participating in the research (vulnerability, disability, protected categories etc.) is appreciated.

The text was drawn up on the initiative of Prof. Adriano Bompiani, member of the Steering Committee on Bioethics of the Council of Europe (DH-BIO), in a select group composed of Profs. Lorenzo d'Avack, Silvio Garattini, Laura Palazzani.

The NBC believes it is important and urgent to issue pronouncement on a national and international level on the general aspects of the Proposal for a Regulation of the European Parliament on clinical trials, highlighting the elements which are approved and those causing problematicity in ethical terms.

The text, discussed in the plenary session, was voted and approved unanimously by those present, Profs. Salvatore Amato, Luisella Battaglia, Adriano Bompiani, Cinzia Caporale, Antonio Da Re, Bruno Dallapiccola, Lorenzo d'Avack, Riccardo Di Segni, Romano Forleo, Marianna Gensabella, Laura Guidoni, Assunta Morresi, Demetrio Neri, Andrea Nicolussi, Laura Palazzani, Vittorio Possenti, Lucetta Scaraffia, Monica Toraldo Di Francia, Giancarlo Umani Ronchi, Maria Grazia Zuffa.

Profs. Stefano Canestrari, Francesco D'Agostino, Silvio Garattini, Aldo Isidori, Alberto Piazza, and Rodolfo Proietti absent from the session subsequently expressed their adherence.