NATIONAL COUNCIL OF ETHICS FOR THE LIFE SCIENCES

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Opinion on the Draft bill No. 146/XII (2nd) – Approves the Law of Clinical Investigation

(September 2013)

INTRODUCTION

The reflection of the National Council of Ethics for the Life Sciences (CNECV) has been suggested by the presentation of the Draft Bill No. 146/XII (2nd) in the Portuguese Parliament, which "Approves the Law of Clinical Investigation", on which CNECV was asked to issue an opinion.

As the CNECV had the opportunity to notice in its Opinion No. 74/CNECV/2013 on the Additional Protocol to the Convention on Human Rights and Biomedicine with regard to Biomedical Research, in July 2012 the European Commission has presented a Proposal of Regulation regarding clinical trials of medicines for human use, which aims at the revocation of Directive 2001/20/CE - on which the European Parliament has presented its opinion. Being a legal instrument of direct application in the legal orders of the Member States, the Proposal of Regulation is currently in discussion and the process is expected to be approved until the end of 2013, which must be taken into consideration in the current discussion at a national level.

The CNECV had the opportunity of recently issuing an Opinion on this problematic – See Opinion No. 66/CNECV/2012 about Draft Bills No. 266/2012 and No. 323/2012 in terms of clinical research and clinical trials, referring the general ethical considerations and principles mentioned in the above.

The Draft Bill No.146/XII differs from the (previous) Draft Bill No.266/2012, integrating in one single document the content of Draft Bill No. 266/2012 and of Draft Bill No. 323/2012. This aimed to proceed the second change to Law No. 46/2004, of 19 August, which transfers to the national legal order Directive No. 2001/20/CE, of the European Parliament and of the Council, of 4 of April, concerning the proximity of the legal, regulatory and administrative provisions of the Member States regarding the application of good clinical practices during clinical trials of medicines for human use, and establishing the legal framework for conducting clinical trials in human beings using medicines for human use.

Being more comprehensive, the current legal proposal revokes Law No.46/2004 and partially revokes Decree-Law No.145/2009, of 17 June – Establishes the rules to which the research, production, commercialization, commissioning, surveillance and the publicity of medical devices and respective accessories must obey; and transfers to the internal legal order Directive No.007/47/CE, from the European Parliament and of the Council, of 5 September.

This harmonization in one sole text has very positive consequences, considering that the possibility of coexisting documents on correlative matters might mislead, and frequently does lead, to internal contradictions. In the writing of Draft Bill No. 146/XII these anomalies no longer exist, which is commendable.

On the basis of the comparative table regarding the texts of Draft Bills No. 266/2013 and No. 146/XII – table elaborated by CNECV's Secretariat – it becomes easier to point out which suggestions of CNECV's Opinion No. 66 were taken into consideration in Draft Bill No.146/XII currently in discussion. Therefore, we can verify that many of the most important suggestions were accepted in the new Draft Bill.

Looking back to this Council's previous Opinions in terms of clinical trials, namely Opinion on the Clinical Evaluation of Drugs (4/CNECV/93) and Document Analysis and Comparison between Legislation related to Clinical Trials and the Ethical Committees and the Doctrine issued by CNECV (13/CNECV/95), both available in www.cnecv.pt., the current Opinion proposes, strictly according to the requested, a double task: insisting in certain suggestions not accepted but which pertinence would justify its inclusion; and commenting some aspects or expressions only present in the new Draft Bill.

ASSESSMENT OF THE DRAFT BILL'S TEXT

1. At the end of the eighth paragraph of the «Explanatory Memorandum», it would be convenient to indicate the actual average or frequent length of the «term for review of the clinical trials and the studies with intervention of medical devices», in order to justify the laudable intention of reducing this same term («reducing the review term», etc.).

2. A clearer wording on No.1 of Article1 is recommended, namely to what concerns the definition of "Clinical Investigation". Still in No.1 of Article 1 and subsection p) of Article 2, the definitions of "clinical investigation" and of "clinical study" use the expression "health factors", which sense is not clear. It probably refers to "health indicators", expression we think more appropriate in this context.

One can notice that regarding Law No. 46/2004, the Draft Bill considerably enlarges the aim of its action[1].

It is equally important to refer that the new Proposal for the Regulation of the European Parliament and of the Council regarding clinical trials of medicines for human use defines and distinguishes clinical study from clinical trial. Thus, the Proposal of Regulation will not be applicable to studies without intervention, contrarily to Draft Bill No. 146.

[1] Law No. 46/2004 in force defines Trial or clinical trial as "any investigation conducted on a human being, destined to find out or verify the clinical, pharmacological or other pharmacodynamics effects, of one or more experimental medicines, or identify the undesirable effects of one or more experimental medicines, or analyzing the absorption, distribution, metabolism and elimination of one or more experimental medicines, in order to determine the respective safety or efficiency;"

3. In subsection n) of Article 2, one can read "pharmacological… effects or other pharmacodynamics effects", which is erroneous: pharmacology includes pharmacodynamics which is precisely incumbent to study the drugs' actions. It should then be read "pharmacological… effects" with no reference to pharmacodynamics, a subdivision of pharmacology.

4. Still in subsection gg) of the same Article 2, the definition of «adverse reaction» must mention "harmful and/or undesirable manifestation" (for it may be undesirable, useless or uncomfortable but not harmful). The reference to "adverse reaction" and "adverse effect" is frequently used separately, when both express the same – as already mentioned in Opinion No. 64 of this Council.

5. The definition of "conflict of interests" should be added to the glossary contained in article 2, according to Opinion No. 72/2013 of this Council about Declaration of Interest and Conflict of Interests in Health and Biomedical Research.

6. In the subsection d) of No. 1 of Article 6, as well as subsection a) of No.1 of Article 7, subsection a) of No. 2 of Article 8 and subsection b) of Article10, when mentioning the need of obtaining the «informed consent», it is important to explain that this consent must be obtained in written format.

Above all, it is paramount to clarify that consent implies a process according to which the trial participant voluntarily confirms his or her will of participating in a specific study, once informed in a clear, adequate and sufficient manner of all the relevant aspects for his or her decision, including the rights he or she is entitled in case consent is withdrawn.

7. Articles 7 and 8 of the Draft Bill in assessment are not clear regarding the situations of studies without intervention in which minors or incapable persons may not receive adequate information, or give their assent. This exception seems to contend with Articles 16 and 17 of the already mentioned Convention on Human Rights and Biomedicine, (integrated in the Portuguese legal order since 2001).

In any case, the investigation cannot take place if minors and other individuals incapable to consent have opposed, according to No. 5 of Article 17 of the same Convention. In this sense, No. 3 of Article 7 and No. 4 of Article 8 must be suppressed.

8. In Article 12 (Clinical Study Center), it is important to mention, among the Center's competences, the possibility to accept or refuse the execution of the proposed study; if that was not the case, the Center would be compelled to allow the execution of every kind of study proposed and approved by the Competent Commission of Ethics (CEC), which does not make sense.

9. In subsection g) of No. 5 of Article 16, which refers the «Participant Recruitment Methods», we recommend this expression to be replaced for "recruitment criteria".

In substantial terms, it is convenient to add that who actually recruits cannot be the person who conducts the respective trial, according to the Principle of separation.

10. In subsection h) of No. 5 of Article 16, it should be added to the proposed text («Situations of conflict of interests by the promoter or the investigator involved in the clinical study»): «as well as every professional who direct or immediately intervene in the clinical study». In the same sense, subsection d) of No. 2 of Article 40 should be completed.

11. No. 2 of Article 23 might cause the reader two qualms: «After the conclusion of the clinical study with intervention, the treatments mentioned in the previous number should, *until its introduction in the market*, be provided to the participant for free by the promoter, as long as the investigator finds it indispensable for the participant and as long as *there are no therapeutically alternatives of comparable efficiency and safety*».

First of all, what happens if, after the new treatment reaches the market, the trial participant does not have enough financial resources to purchase it? Such possibility does not seem to be foreseen in the draft bill. Therefore, its consideration is recommended.

Secondly, the wording of No. 2 shows, in any case, a great ambiguity: in fact, if the new treatment, object of clinical study, seems superior, then it stands to reason that there are not «therapeutically alternatives of comparable efficiency and safety»; in reverse, if there are «therapeutically alternatives of comparable efficiency and safety», then won't the new treatment be relatively useless? In other words, in the end of the clinical study it would only be refused to the participant «to continue» the new treatment for free if this didn't add any «efficiency or safety» comparable to the ones obtained in already existing treatments. The acknowledgement of this absence of improvement stated by the new treatment would also have to be recognized, both by the experimenter and the pharmaceutical firm that produces it, in case the participant didn't continue to freely benefit from the treatment after the study's conclusion, with reference to the Declaration of Helsinki, in its most recent version of 2008.

11. In the Draft Bill No. 146/XII, the term «placebo» is only present in subsection bb) of Article 2. The use of placebo in clinical studies raises ethical questions. Thus, mentioning exceptional use of placebo should be included in the Draft Bill; the ethical rule is to privilege the comparative trial between therapeutics that are clearly effective or useful and the new therapy in study.

When, during the clinical trial against placebo, it clearly shows the efficiency of the product in study, the trial should be reformulated, so that the group that had placebo starts receiving the active pharmaceutical ingredient (API).

In any case, the clinical study cannot cause harm to the participants by not providing them the «best» treatment already known and proven.

12. It is also convenient to mention that the multicenter studies that are performed in countries which legislation slightly differs from the Portuguese legal framework must respect the content of Article 29 of the Additional Protocol to the Convention for the Protection of Human Rights and Dignity of the Human Being considering the Applications of Biology and Medicine: Convention on Human Rights and Biomedicine, concerning Biomedical Research «*Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research*»[2].

13. Article 37 of Draft Bill No. 146/XII founds RNCES (National Network for the Commissions of Health Ethics), formed by CEIC and by the CES. This establishment lies however in a great ambiguity, which the Legislator must clarify. In fact, the Draft Bill's objective is the clinical investigation and clinical studies and trials. Yet, the competence of the CES comprises a multiplicity of problematics and matters that do not concern the clinical investigations. Thereby, how is it possible to create a RNCES from a Draft Bill that is limited to clinical investigation? Despite many subsections of the abovementioned Article that do not ignore this situation, the creation of a RNCES, according to the content of the Draft Bill in which it is shaped, implies that clinical investigation is the central matter of the CES; the presence of CEIC in this RNCES, assuming a centralizing role regarding clinical investigation, reinforces this presumption, which shouldn't be the case. In fact, this normative changes CEIC's competences and its relation with the CES. On the other hand, if the Legislator wishes to create a RNCES which job is limited to clinical investigation and effectively incorporates the CES, the name RNCES is not appropriate and must be altered in a more strict way in order to exclusively aim clinical investigation.

14. In Chapter VIII «Publication of clinical studies», it is convenient to explicitly mention that clinical studies, methodological aspects and primary and secondary results ought to be published in a specialized journal. Moreover, the scientific community, individual investigators and/or institutions should be able to access all the respective information.

[2] "CHAPTER IX – Research in States not parties to this Protocol. Article 29 – Research in States not parties to this Protocol - Sponsors or researchers within the jurisdiction of a Party to this Protocol that plan to undertake or direct a research project in a State not party to this Protocol shall ensure that, without prejudice to the provisions applicable in that State, the research project complies with the principles on which the provisions of this Protocol are based. Where necessary, the Party shall take appropriate measures to that end."

CONCLUSION AND OPINION

- Considering expectable the approval of the Regulation of the European Parliament and of the Council regarding clinical trials with medicines for human use until the end of 2013, the CNECV draws the attention to the fact that this Regulation's entry into force will bring consequences to the ongoing legal process in Portugal.

- Notwithstanding, and trying to respond to the request issued by the Parliamentary Committee of Health, considering the reflection already stated, the CNECV considers that the document in question might and should be revised and improved taking into consideration the various aspects abovementioned.

Lisbon, 20 September 2013.

The President, Miguel Oliveira da Silva.

Rapporteurs: Counsellors Michel Renaud, Miguel Oliveira da Silva and the Council's Executive Secretary, Cíntia Águas.

This Opinion was approved in the plenary meeting on 20 September 2013.

Besides the President, the following Counsellors were present:

Ana Sofia Carvalho; Carolino Monteiro; Francisco Carvalho Guerra; Isabel Santos; João Ramalho-Santos; Lígia Amâncio: Lucília Nunes; Maria do Céu Patrão Neves; Michel Renaud; Rita Lobo Xavier; Rosalvo Almeida.

NOTE – This reflection has benefited from Professor Walter Osswald's comment.