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Y POLÍTICA SOCIAL

COMMENTS ON THE ASSESSMENT OF THE FUNCTIONING OF THE "CLINICAL TRIALS DIRECTIVE" 2001/20/EC (ENTR/F/2/SF D(2009) 32674)

General Comments:

The Spanish Ministry of Health and Social Policy welcomes the proposal of the EU-Commission to assess the application of the Clinical Trials (CT) Directive 2001/20/EC as well as the initiative to assess possible opportunities for further improving the conduction of clinical trials with medicines in the EU.

The main benefits of the CT Directive 2001/20/EC have been, in our view, the establishment of a common standard of CT requirements with respect to guaranties and protection of CT participants, assuring at the same time reliability of the CT results, setting the basis for a systematic collaboration between National Competent Authorities (NCAs) supported by European databases and an increase in transparency. Although it is recognized that some of the procedures established with the directive may result in some complexity for the sponsors, this fact should not obscure the achievements of the Directive, that appear underrepresented in the document of the EU-Commission.

The opinion of the Spanish Ministry of Health and Social Policy is that we have to carefully assess those areas where the burden of the intervention is not proportionate – where some adaptation of the CT Directive can be considered mainly through European guidelines– and to intensify the harmonization procedures among NCAs and Ethics Committees (EC) both at a national and multinational level (where information technologies are called to play a main role).

Key Issue N°1: Multiple and Divergent Assessments of Clinical Trials

The facts show that multiple assessments of CT (by NCAs and ECs) do not normally result in divergent decisions, which are rarely taken. So the question is which of those multiple assessments are the minimum to guarantee safety and quality of CT in the place they are going to be undertaken. Although the CT Directive sets common rules for the authorisation, differences between Member States (MS) for example, in clinical practices, health systems or cultural reasons could be the basis for differences in the questions raised to the sponsor in different MS. Therefore, the issue is not divergence but multiplicity, and the discussion is to what extent multiple assessments by ECs and NCAs are justified in terms of local acceptability of a specific trial and how they convey in further improvements and guarantees to the trial.

To deal with unacceptable multiplicity in CT evaluation, the Spanish Ministry of Health and Social Policy proposes several lines of actions:

(a) Finishing the pilot phase of the voluntary harmonisation procedure (VHP) In order to reduce multiplicity of assessments and different administrative procedures between MS, there is an ongoing initiative –the voluntary harmonization procedure- established by the Heads of Medicines Agencies. This procedure initially covering initial applications is going to be expanded to also cover substantial amendments. This procedure has been supported by all NCAs at the EU, and 25 out of the 27 MS are already participating in the procedure. The experience gained during this year will be very valuable in order to assess the feasibility of applying a mutual recognition procedure to the CT assessment,. Up to now, the VHP experience can be considered a success.

The VHP is not only a very efficient procedure to reduce multiplicity of assessments but also a procedure that permits to harmonize the assessment criteria among MS. Therefore, it also enables that the assessments of only national CT performed by NCAs are consistent with the criteria agreed at the VHP assessments..

It should be taken into account that only 25% trials are performed in more than one MS and that all areas of medicine can be found in either national or multinational trials. We do not believe that this is a consequence of the CT Directive but a trend of CT development in EU. Advanced therapies could be a good example of an area where the exchange of information and collaboration between all NCAs brings scientific consistency and expertise to the assessments performed by NCAs for purely national trials, which in this field are the majority of the trials (In Spain only 1 out of 19 CT applications received in 2009 for advanced therapies was international).

The VHP offers significant advantages for small and intermediate size companies and for non-commercial sponsors

(b) To establish mutual recognition procedure rather than centralized procedures for evaluation of CT. A true mutual recognition procedure (as proposed in 3.3.2.1.a) of the commission consultation paper) could be the natural evolution of the VHP. Taking into account that only 25% trials are performed in more than one MS (only 10% in more than 4 MS), and the fact that assessments of a CT are not only required for initial applications but also for substantial amendments, and safety monitoring data a centralised procedure as proposed in 3.3.2.1.b) is considered not practicable and is not supported by Spain. In addition to the unjustified complexities and costs of such a procedure, it would not get the collateral benefits of harmonizing criteria an practises among MS obtained by the VHP (mutual recognition procedure) and therefore it would not provide the best scientific and technical supervision of clinical trials in the Community .

(c) To support the proposed one-stop shop assessment for submission with regard to the options for Competent Authority and Ethics Committees assessment. In fact, in Spain there is a Clinical Trials Portal at the Ministry of Health and Social Policy which enable sponsors to submit an electronic CT application to both the NCA (Spanish Agency for Medicines and Medical Devices, AEMPS) and the EC. It is in place since May 2008 for applications to the AEMPS and since June 2009 for applications to ECs. All ECs have access to the documentation through a specific application maintained by the Ministry of Health. During 2009, 63% of all initial applications submitted to the AEMPS have been received through this Portal (no paper documents are needed).

(d) To support harmonization in the set of data required for CT applications to both Competent Authorities and Ethics Committees and development of an standard for electronic applications

(e) The improvement of common EU databases in order to simplify their use

This is also considered a relevant instrument to facilitate CT in the EU.

(f) Clarification of the scope of EC and NCA assessments is necessary as well as to foster cooperation between NCA and EC at a national level. Efforts to further clarify the different tasks of assessments by ECs and NCAs are endorsed as well as initiatives to improve common standards and networking between ECs. Common training, exchange of best practices and common EU accreditation criteria for Ethics Committees are some of the good basis for building mutual trust between ethics committees and paving the way for reducing multiplicity of assessments in the future. It is unrealistic to decide that single opinions could be forced by regulation without previously covering the ECs networks needs. Therefore, EU initiatives to foster networking of ethics committees and common training strategies are needed.

Key Issue N°2: Inconsistent Implementation of the Clinical Trials Directive

Legislation on CT in the EU is very extensive and complex to read. It involves not only Directive 2001/20/EC, but 2 Commission Directives and many guidance documents included in volume 10 Eudralex. We consider that there are possible different interpretations of some of the Directive definitions and requirements. Therefore an effort should be done in order to refine the guidelines according to the principle of ensuring a proportionate intervention and a risk based approach. In this sense, identified best practices at MS could be of help. Some examples are:

(a) Definitions of clinical trial and of non interventional trial- "Clinical trial" and "non interventional (observational) trial" are classical epidemiological terms linked to specific methodological designs, being the main characteristic of the second ones that the investigator has no intervention in the assignment of the factor which is the objective of the clinical research (in our case a medicinal product). Case-control and cohort studies are typically non interventional studies according to a simply methodological point of view.

Among the conditions that a non-interventional study should fulfil, according to the Directive definition, is the requirement that *"No additional diagnostic or monitoring procedures shall be applied to the patients*" *(it is understood that "additional" means different from the ones used in current clinical practice")*. Although this requirement is easily fulfilled by retrospective studies, this may not be the case for many non-interventional prospective studies because they may include some procedures which in some member States are interpreted that fall within "current practice" while in others are considered that fall outside.

On the one hand, this requirement implies that clinical practice is homogenous across different countries of the EEA which is certainly not the case (even within the same country clinical practice may differ across different clinical settings); on the other hand, such criterion may convert a typically non interventional study such as a case-control or a cohort study into a clinical trial if some procedures, not required by the usual clinical practice, are adopted just to improve the accurateness of what is being observed, for instance, a thorough questionnaire on the disease and potential exposures, a test to assess the quality of life, the extraction of additional blood samples to explore disease features or individual traits, the performance of additional EKG etc. Neither of these procedures would have an impact or discernible risk for patients and may be of great importance to assess and follow-up the effects of medicinal products in an non-interventional study. The protection of patients from the use of procedures which may pose them to an additional risk without the appropriate ethical review and other legal safeguards (e.g. the need for insurance can be obtained by developing an EU guidance for non-interventional studies without forcing true observational studies to be considered administratively as clinical trials

Therefore, we consider that this requirement leads to inconsistencies in the interpretation of the definition and the development of a specific EU guidance on non interventional studies is proposed. This guidance could include an agreed list of procedures that are acceptable within a non-interventional study such as those representing minimal risk (e.g. mere blood sampling, certain diagnostic measures, etc) and would help to smoth differences in the interpretation and to reduce unnecessary burden of intervention.

(b) Definition of Investigational medicinal product The Directive establishes requirements for IMPs such as the need for a specific labelling even in cases where the medicinal product is authorised in the EEA or the need to be made available free of charge by the sponsor.

As a consequence sponsors try to avoid the categorization of IMPs for medicinal products which are indispensable for the conduction of the clinical trials (background or combination therapies, comparators) and discrepancies have been identified.

(c) Substantial amendments. Definition of substantial amendment in the Directive 2001/20/EC leaves room for different interpretation. Although it is the sponsor's responsibility to differentiate between substantial and non-substantial amendment and to decide what to submit, inclusion of more examples, as planned in updated guidance, of what is/what is not a substantial amendment and who should assess the amendment (CA, EC or both) will help to avoid over reporting.

(d) SUSARs. The introduction of a Community Database for SUSARs for CT and electronically reporting is endorsed. However, the functionality needs to be simplified in order to allow reporting to Eudravigilance-CT by non-commercial sponsors. Whenever a fully functional version of this Community Database for SUSARs from CT complies with the needs of the MS to ensure the protection of the Clinical trials' participants, the national systems might be changed or abolished.

Over reporting of SUSARs by the sponsors of clinical trials might reflect the complexity of the reporting criteria which could support the sponsor tendency to report everything, just "to comply in the worst case". An update and further clarification of the Guideline to the Directive 2001/20/EC Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use might reduce the numbers.

SUSAR reporting in the Directive is only defined with respect to IMPs and there are no clear criteria with respect to how SUSARs associated to non-IMPs o to concomitant treatment taken by the CT participants should be handled.

Key Issue N°3: Regulatory Framework not Always Adapted to the Practical Requirements

It is agreed that the intervention is not always risk-commensurate and adapted to practical requirements. The review of current guidances can be of much help provided the revision is guided by the principle of proportionate intervention and following a risk based approach.

At the level of the network of medicines agencies, the Clinical Trials Facilitation Group is working together with the EU inspectors group in this risk based approach and a useful categorisation of risk is expected.

In the light of a possibly fast revision of guidelines, changing of the Directive would not be considered an urgent need.

The exclusion of "academic" sponsors from the scope of the Directive is not supported. There is no justification to establish different standards of protection of participants and authorities supervision based on the characteristics of the sponsor, being in addition rather difficult to decide which trials are "academic" trials. The decrease of the regulatory burden to trials with low added risk is a preferred option that may also facilitate the non commercial clinical trials that could be hindered by the regulatory requirements.

Key Issue N°4: Adaptation to Peculiarities in Trial Participants and Trial Design

Clinical trials in the paediatric population and in emergency situations need specific regulatory provisions in order to permit clinical trials. Best regulatory practices in MS could be identified and serve as common guidance to the Community.

Key Issue N°5: Ensuring Compliance with Good Clinical Practices ("GCP") in Clinical Trials Performed in Third Countries

The Spanish Ministry of Health and Social Policy considers unacceptable that subjects anywhere in the world are recruited into clinical trials lacking adequate control to protect patient safety and data integrity and therefore, it is fully supported that demonstration of GCP compliance is mandatory for any study which is to be submitted as part of an application within the EU. Further initiatives to ensure a global standard may be achieved by voluntary collaborative action between regulators and we are ready to cooperate with any initiative in this area.