UZ/KULeuven Reply to Public Consultation Paper 'Assessment of the functioning of the "Clinical Trials Directive" 2001/20/EC
Entr/F/2/SF D(2009) 32674

General remarks

- In the 'background' section it is stated that "about 64% of clinical trials is sponsored by the pharmaceutical industry and 36% are sponsored by others", whereas, on the other hand, "it is a fair assumption that approximately 60-80% of all clinical trials performed in the EU are intended to be subsequently used in the framework of marketing authorization applications in the EU".
  Does this mean that up to 20% of the trials, not sponsored by the pharmaceutical industry, deal with non-registered medicinal products, developed by academic institutions or that the pharmaceutical industry provides grants outside the scope of a commercial trial but with the intention to obtain data which are suitable for registration purposes? We come back to this point below.
- Under current practice, the pharmaceutical industry exerts absolute ownership and control over raw data resulting from clinical trials. This remains so even though public agencies grant a market authorisation based on these data and social security systems eventually pay the larger part of the cost of treatment. We consider that more transparency regarding raw data gathered by trials, independently from the sponsor, would allow a more open and scientifically relevant discussion and would thus increase the level of confidence of academic hospitals and investigators towards the pharmaceutical industry[1]. In our Belgian situation (with a summa divisio commercial / non-commercial experiment), this would redirect the focus when setting up a trial towards risk and scientific value, which should actually be the major concerns.

Consultation item n°1

We have no clear answer to this item since we haven't been actively involved in the close follow-up of protocols and contracts long enough to compare our specific situation before and after the implementation of the Clinical Trials Directive.

Consultation item n°2 and 3

This items seem very much directed towards the pharmaceutical industry involved in multicenter and international clinical trials.

Consultation item n°4

Concerning option b (one-stop shop) we wonder which 'body' would be responsible for the assessment of the trials. We suppose a new expert group would be organized at the level of the European Medicines Agency. If this group would be able to deliver advice within a limited timeframe, we consider this the best option. The scope though should be limited to certain trials, like larger international trials or those trials in which an Investigational Medicinal Product (IMP) not yet registered is investigated. The 'FDA system' in which the same expert group follows the entire development process of the same IMP seems interesting from a scientific point of view.

[1] This becomes in fact mandatory when one considers the –rightful- expectations of medical journals, e.g. "Scientists have an ethical obligation to submit creditable research results for publication. Moreover, as the persons directly responsible for their work, researchers should not enter into agreements that interfere with their access to the data and their ability to analyze it independently, to prepare manuscripts, and to publish them." (on http://www.icmje.org/2005_urm.pdf).

Consultation item n°5

We have some considerations concerning the option of a 'one-stop shop' for the assessment of all possible clinical trials:

- We believe that each university or (university) hospital should keep the possibility to apply its own ethical/scientific values when deciding whether or not to approve a trial protocol. How to reflect these sometimes very different viewpoints in one single assessment procedure? This problem holds more specifically for academic national (monocentric) research.
- The quality/availabilities of the hospital or research environment and the competence of the Principal Investigator are crucial when considering whether a trial could take place in a given center. Evaluating this at European Level requires Quality Assurance / Quality Control assessment on a case by case basis, which requires specific knowledge about these local situation and thus seems complicated to perform. Of course, this is more important in trials implicating a higher risk to the participants.
- As already mentioned in our answer to consultation item n°4, we wonder how this huge amount of extra assessment work for the European Medicines Agency would be organized in a way which also guarantees an assessment within reasonable timelines.
- We believe that the current Clinical Trials Directive relies profoundly on the Ethics Committees of the Member States, since their assessment represents a very important and responsible step in the final approval or non-approval of a trial protocol. In this scope, we would advice that the quality standards for these committees and the procedural requirements[2] would be more precisely described by the European Commission. Moreover, we believe that the European Commission should provide tools to control how these committees comply with this legislation (by implementing an obligated accreditation, by performing audits,…) in order to assure that their assessments are performed in a more or less consistent way.

Consultation item n°6 and 7

- The non-interventional trials should be classified more precisely (for example: registries, cohorts, randomized trials but using standard procedures, or non-interventional diagnostic procedures, …).
- To our opinion, the 'borderline' between an interventional and an observational trial is insufficiently defined in the Clinical Trials Directive.
- The situation in which a trial is considered "non-interventional" in one Member Sate while it is considered "interventional" in another Member State also has important implications on the insurance of the participants.
- This insurance item is a matter of eternal debate in Belgium. The Belgian Law of May 7, 2004 is the result of the implementation of the Clinical Trials Directive into Belgian law. According to Article 29 of this Belgian law the sponsor is, even if faultless, liable for the damage which the subject or, in the case of death, his rightful claimants sustained and which shows either a direct or an indirect connection with the experiments; every contractual provision aiming at limiting this liability is considered null. Before commencing the experiment, the sponsor shall enter into an insurance contract which covers this liability, and the liability of every individual intervening in the experiment, irrespective of the nature of the affiliation between the intervening individual, the sponsor and the subject.

  Although obliging the Member States to provide insurance to cover the liability of the investigator and sponsor is clearly an improvement for the protection of clinical trial subjects, the practical application is very complex. The main reason for this complexity is the different implementation of the Clinical Trials Directive by the Member States into national law. Another reason is the absence of an insurance system for trials involving several Member States or third countries.
- Moreover and very specifically for Belgium a distinction should be made between commercial and non-commercial clinical trials. In commercial trials the obligation of an insurance to cover the no

[2] Clear decision taking, written motivation of decisions, clear conflict of interest policies, … (as they are a.o. described in the ICH Guidelines for Good Clinical Practice, page 11-12).

fault liability is the responsibility of the company. This situation rarely causes problems in terms of insurance. In non-commercial trials the sponsor of the study is either a university, a hospital or a research fund (Article 2, 15° Belgian law). In these non-commercial trials this ambiguity and the lack of a coherent insurance system is even more pronounced.

- The following questions arise: who is responsible for insurance coverage in a multicenter international trial initiated by a Belgian university or hospital? Is this Belgian university or hospital obliged to ensure the insurance of all participating sites? What is the scope of the insurance coverage: only the participating sites in Belgium or also those in other EU Member States? Who is legally required to provide insurance coverage for Belgian trial subjects when the sponsor of the trial is a hospital, university or research fund vested in an EU Member State or a third country?

Consultation item n°8

We undoubtedly prefer the legal from of a Regulation, providing that the definitions are clearly outlined and no longer possible subjects to many possible and sometimes very different interpretations. Other points needing clarification such as the insurance, the task of the Ethics Committee, the use of data, should also be addressed in such a Regulation.

Consultation item n°9

- In the list of risk factors we would add “the proposed hospital and Principal Investigator”. The assessment of this risk factor legally lies with the Ethics Committee.
- In the same list, bullet 1, 3 and 4 all refer to the IMP/medicine involved risk factors.
- The risk of non-interventional trials should be addressed here as well. Is there a risk for the participants? If not, is there a need to insure them? If so, for which kind of non-interventional trials?
- We believe it could be dangerous to implement less stringent rules for trials which are considered ‘of lower risk’. The rules for some of the examples given (such as labeling of the IMP, reporting of SUSARs) should to our opinion be equal for all trials, regardless of the estimated risk for the participants (example: testing a registered medicinal product in a new indication).

Consultation item n°10

The idea of one single sponsor seems difficult to implement given our Belgian Law context since the distinction between a commercial and a non-commercial trial has very explicitly been made in our law. We refer to our answer on consultation item n°8 and 9: a Regulation with clear definitions and in which a no-fault insurance obligation is imposed to the sponsor could solve this ambiguity.

Consultation item n°11, 12 and 13

We were surprised by the statement that ‘clinical trials sponsored by academic/non-commercial sponsors are not necessarily performed with the intention to generate data to support an application for a marketing authorization of a medicinal product’. We would rather say that these trials ‘are only very exceptionally performed’ to generate data for a marketing authorization, based on the following:

- We refer to the ‘Draft Guidance on Specific Modalities for non-commercial clinical trials referred to in the Commission Directive 2005/28/EC laying down the principles and detailed guidelines for good clinical practice’. Although we realize that this is only a draft guidance which has never been transposed in a final document, the 3th bullet of the ‘characteristics of the sponsor’ states that ‘no agreements between the sponsor and third parties allowing them to use the data for regulatory or marketing purposes should be in place’.
- Moreover, under title 5.4.3., this document refers to a Community legislation in which it is stated that ‘the results of clinical trials performed by academic sponsors cannot be referred to in the framework of an application for a marketing authorization in the EU’. We believe this is in

contradiction with what is stated under 5.3. and we wonder what legislation is referred to since a clear statement of the European Commission regarding this item of complicated debate, namely the use of data collected in non-commercial trials, would be of major help to the Belgian non-commercial sponsors.

Consultation item n°14

In Belgium, we have no major problems because these specifications are very specifically outlined in our national law. Nevertheless, we do believe that a European Regulation would solve the uncertainties that exist in other Member States, moreover since the obligation of submitting a Pediatric Investigation Plan for each new application for a Marketing Authorization now exists within the European Medicines Agency.