REVISION OF THE 'CLINICAL TRIALS DIRECTIVE' 2001/20/EC

COMMENTS TO THE CONCEPT PAPER SUBMITTED FOR PUBLIC CONSULTATION ON 9/2/2011

The Institute of Tropical Medicine (ITM) in Antwerp, Belgium (website www.itg.be; address for correspondence rravinetto@itg.be) is a non-commercial sponsor of clinical trials carried out in partnership with research institutions in the South, for addressing public health questions relevant to developing countries. As such, we see the current revision of the Directive as an opportunity to further improve the protection of patients and the quality of the research in Europe as well as in third countries. Here below, we list our inputs and comments on specific consultation items.

- ***Consultation item no. 9, on enlarging the definition of 'non-interventional' trials***. Preliminary appraisal: "rather than limiting the scope of the Clinical Trials Directive through a wider definition of 'non-interventional trial', it would be better to come up with harmonized and proportionate requirements which would apply to all clinical trials falling within the scope of the present Clinical Trials Directive." Do you agree with this appraisal? Please comment.

  ITM input: we do agree with this preliminary appraisal. The current EU definition of a 'non-interventional trial'[1] seems adequate in terms of fair and uniform patients' protection and in view of European harmonization.

- ***Consultation item no. 10, on excluding clinical trials by 'academic/non-commercial sponsors' from the scope of the Clinical Trials Directive.*** Preliminary appraisal: "rather than limiting the scope of the Clinical Trials Directive, it would be better to come up with harmonized and proportionate requirements for clinical trials. These proportionate requirements would apply independently of the nature of the sponsor ('commercial' or 'academic/non-commercial')". Do you agree with this appraisal? Please comment.

  ITM input: We fully agree with this preliminary appraisal. Protection of the safety and rights of participants and reliability and robustness of data should be the same, irrespectively of who is the sponsor.

  In addition, specific modalities on some procedural requirements for non-commercial clinical trials (not sponsors) are drafted in the "Draft guidance on 'specific modalities' for non-commercial clinical trials referred to in Commission Directive 2005/28/EC laying down the principles and detailed guidelines for good clinical practice". Finalization of this guideline is recommended, because its long-term status of "draft" makes it difficult to assess to what extent it is applicable and binding.

- ***Consultation item no. 11, on more precise and risk-adapted rules for the content of the application dossier and for safety reporting.*** Preliminary appraisal: "often cited as examples for the need for greater harmonization and risk adaptation in the EU are the rules on the content of the clinical trials application dossier and safety reporting. To address this need, sufficiently detailed provisions on these topics could be included in Annexes to the basic legal act. The Commission could, when necessary, update them by means of delegated acts. In drawing up these Annexes, one would have to take into account: the risk to trial subject safety compared to normal clinical practice; the risk to data reliability and robustness; international harmonisation work, such as the guidelines of the ICH. The contents of the Annexes would build on work recently carried out by the Commission. This approach would help to simplify,

[1] The medicine is used within the terms of the marketing authorization, AND there is no protocol AND there is no additional intervention

clarify, and streamline the rules for conducting clinical trials in the EU by providing one single, EU-wide, risk-adapted set of rules". Do you agree with this appraisal? Please comment.

ITM input: we fully agree with this preliminary appraisal. Detailed, harmonized provisions on the rules on the content of the clinical trials application dossier and safety reporting could improve the quality of the protocols, the protection of participants and could provide guidance also for trials carried out outside the EU.

- ***Consultation item no. 14, on insurance/indemnisation***. Preliminary appraisal: "several policy options could be considered, such as: • Removing insurance/ indemnisation requirements for low-risk trials: this policy option would remove the insurance requirement for clinical trials which typically pose a low risk for trial subjects; or • Optional indemnisation by Member State: this policy option would put Member States under an obligation to provide for an indemnisation for damages incurred during clinical trials performed in their territory, taking account the national legal system for liability. In view of the damages arising today, the burden on national budgets would be minimal. Both policy options could be a viable solution." Which policy option is favourable in view of legal and practical obstacles? What other options could be considered?

  ITM input: the first option, which avoids redundant insurance policies while keeping the sponsor responsible, could be preferable.

  However, this option brings the potential risk that some studies/patients could be left uncovered, because of a wrong evaluation of the trial-related risk: therefore, we strongly recommend that, if it is adopted, the risk assessment -or at least the definition of criteria for making the risk assessment and classify trials as "low risk"- must be defined at EU level.

  We also strongly recommend that the EU provides some concrete guidance on insurance policies and fees, which is currently missing.

  The "obligation for Member States to provide for an indemnisation for damages incurred during clinical trials performed in their territory, taking account the national legal system for liability" could be left as a second-line option, to be used if a patient experiences damage and need indemnisation following participation in a trial classified as "low-risk".

- ***Consultation item no. 15, on single sponsor***. Preliminary appraisal: "the Clinical Trials Directive is based on the concept of a 'single sponsor' per trial. The single sponsor is 'responsible' for the trial vis-à-vis the national competent authority and the EC. It is a recurrent criticism that the concept of a 'single sponsor' renders multinational clinical trials more onerous. Two options could be considered: Option 1: maintaining the concept of a single sponsor; Option 2: allowing for a concept of 'multiple sponsorship'/'joint sponsorship'/'shared sponsorship'/'co-sponsorship', where each sponsor is 'responsible' for a specific task or for the conduct of the trial in a Member State. In view of the above, option 1 may be preferable, provided that it is clarified that the 'responsibility' of the sponsor is without prejudice to the (national) rules for liability; and it is ensured that the regulatory framework for clinical trials in the EU is truly harmonised." Do you agree with this appraisal? Please comment.

  ITM input: we fully agree with this preliminary appraisal. A given person or a given institution should remain ultimately responsible for the clinical trial. This does not prevent the sponsor to "delegate" the execution of specific activities to members of a research consortium.

- ***Consultation item no. 17, on compliance with GCP in clinical trials performed in third countries***. Preliminary appraisal: "in view of the jurisdictional limits, particular consideration should be paid to clinical trials in third countries where the data is submitted in the EU in the framework of the authorization process of Clinical trials; and Medicinal products. Regarding the authorization process for a clinical trial, this is currently addressed in point 2.7.2.4. of the detailed guidance CT-1,14 which provides that: 'All studies [submitted in the authorization process of a clinical trial] should have been conducted in accordance with the principles of Good Clinical Practice (GCP). To this end, the applicant should submit the following:

  - a statement of the GCP compliance of the clinical trials referred to,

  - where a clinical trial referred to has been performed in third countries, a reference to the entry of this clinical trial in a public register, if available. Where a clinical trial is not published in a register, this should be explained and justified.'….." Do you agree with this appraisal? Please comment.

  ITM input: we agree in general with the preliminary appraisal, but we have some major comments:

  - A "statement of the GCP compliance of the clinical trials": the formulation seems to be too vague. The actual significance of such statement depends on whether it has been released by a stringent regulatory body. Self-statements may have a very limited value.
  - A clinical trial should <u>always</u> be published in a public registry, and there should not be any exceptions for trials performed in third countries. This is also explicitly required by the most recent version of the Helsinki Declaration (Seoul, 2008).
  - In general, we consider that it of paramount importance that the EU remains highly committed to promoting universal standards in clinical research, in particular by ensuring that there is no double standard in clinical trials carried out in third countries. Here below, we attach the comments we already sent to EMA in 2010, and that may apply also to the present framework:

  COMMENTS TO THE REFLECTION PAPER "ETHICAL AND GCP ASPECTS OF CLINICAL TRIALS OF MEDICINAL PRODUCTS FOR HUMAN USE CONDUCTED IN THIRD COUNRIES AND SUBMITTED IN MARKETING AUTHORISATION APPLICATIONS TO THE EMA"

  When a clinical trial is carried out, coordinated or funded by a European entity in a non-European country, it is fundamental that any double standard practices are avoided. This constitutes a strong moral requirement, especially in those resource-poor settings with a weak regulatory framework.

  However, simply applying the European regulations and procedures may be not sufficient for ensuring an equivalent level of protection for the study subjects in resource-poor settings: their effectiveness in the host country should always be verified. For instance, it is likely that the "no fault policy insurance", as it is used in Europe, is not effective in protecting study subjects in developing countries, because of the geographical, linguistic and cultural barriers between the patients and the insurer. The EMA could cooperate with regulatory agencies in the third country(ies) to adapt such tools depending on the context, to the benefit of study subjects.

  In the same spirit of international partnership, we recommend that each international collaborative clinical trial (with or without registration purpose) should undergo a double ethical review, in the sponsor's country and in the host country. This recommendation responds to the need of complementarity of opinions (from an ethics committee close to the sponsor and one close to the study population) and should not be primarily seen as a "compensatory mechanism" in case of weakness of the ethical review in the host

country. While the opinion of the ethical committee of the host country should take precedence, regulatory guidance is needed about how to deal with cases of conflicting opinions.

Clinical research in vulnerable populations is only justified if the research is socially relevant to that population and if they will have access to any beneficial intervention resulting from it. Article 17 of the Helsinki Declaration states that "medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research". Clinical trials of products for registration purpose in Europe should not be allowed to be carried out in non-EU countries UNLESS they fulfill these two requirements.

Vulnerability exists both at individual and group level. We recommend that the document considers vulnerability at group level as well as individual level, by identifying "categories of vulnerability" and by putting special emphasis on ethical standards when trials are performed in "vulnerable groups" (including the socio-economical disadvantaged and those lacking free access to quality health care, who may be more prone to exploitation and for whom more precautions are needed).

Post-trial access should be considered at individual and population level. Even if sponsors and researchers cannot be expected to solve the problem of access to care in resource-poor countries, a realistic plan for future access should always be proposed, based on the model developed by some Product Development Partnership (e.g. DNDi): prior dialogue with national and international health authorities, commitment to submit the study drugs for registration in the host country(ies), "access" plan (e.g. preferential prices, IPR-measures…).

Very serious non-compliance with internationally agreed ethical requirements should lead to exclusion of an individual trial from the submission package to EMA, even if in itself they do not put at stake the reliability of data. In addition, findings of serious non-compliance should prompt regulatory inspections on other trials belonging to the same development plan.

The EMA mandate concerns trials submitted in marketing authorization applications. However, in the long term, the rules and regulations described in this reflection paper should also be applied more generally by European national regulatory authorities, when trials carried out in third countries are included in national applications for marketing authorisation.

In addition, appropriate standards, as defined in internationally agreed guidelines, should be strongly recommended for all trials carried out, funded or coordinated by European entities in third countries (irrespectively of the registration purposes), and for clinical trials which are part of a development program for which the scientific opinion of EMA is asked under Article 58.

Thought should be given to allowing, and even requiring, European legal sponsors of clinical trials in non-European countries without adequate regulatory authorities, to have the trial formally registered and certified by national and /or European regulatory agencies. While such registration would have no explicit value in the country of countries where the trial takes place, it would provide moral protection to the population, the investigators and the sponsor.