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COMMENTS ON CONSULTATION PAPER
REVISION OF THE 'CLINICAL TRIALS DIRECTIVE' 2001/20/EC
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A. INTRODUCTION

Revision of the directive should facilitate non-commercial research. Academic researchers are usually clinical experts, spending most of their time in clinical work. They have difficulties in understanding the requirements presented in numerous guidelines and in the application form. In contrast, large commercial companies have employees familiar with this bureaucracy, as it is their daily execise. Consequently, the number of applications for non-commercial trials in Finland has fallen from approximately ninety to fifty per year during the five year period from 2005 to 2009 (http://www.fimea.fi/). Excessive regulations are regarded as a real threat to clinical research also in other member states (Stewart et al 2008). The bias in results of commercial drug trials is well documented, lately in a recent study of trials registred in the US clinical trials database (Bourgeois et al 2010), in a classical study by Gøtzsche (1989) and in trials in psychiatry (Perlis et al 2005). Results of non-commercial research are thus essential in making correct regulatory decisions. The consultation paper includes only few elements which can facilitate non-commercial research. In contrast, some of the proposed revisions would increase the size of directive, application form and guidelines, lenghten assessment time and result in increase in administrative work.

B. CONSULTATION TOPICS

1. COOPERATION IN ASSESSING AND FOLLOWING UP APPLICATIONS FOR CLINICAL TRIALS

1.1. Single submission

It is proposed, that sponsor would send the necessary documentation to all Member States concerned through a single 'EU portal' ('single submission'), administered by

the European Medicines Agency ('the Agency', EMA). The 'EU portal' would subsequently distribute the information to the Member States concerned. More time would be spent becase of this additional distribution procedure. The distribution, at present performed by drug companies, would increase the workload of the Agency.

Single submission is in fact close to the present procedure. The EudraCT electronic application form needs only modifications in different member states. Contact information, information on study centres and investigators etc must in any case take into account the situation in each member state. These modifications can be easily made in the electronic application form by the employees of companies performing large multinational trials.

Consultation item no 1. The undersigned disagrees with the appraisal.

The *assessment* of the information would be done independently by each Member State, as at present.

Consultation item no 2. The undersigned agrees with the appraisal, separate assessment.

1.2. Single submission with subsequent central assessment

Central assessment would have the disadvantages mentioned in the concept paper.

Consultation item no. 3 The undersigned agrees with the appraisal.

1.3 Coordinated assessment procedure

This procedure has similar disadvantages than those mentioned in previous section. Increased administrative work: choosing reporting member state, writing initial reports, submitting them to concerned member states, exhange of opinions, organisation of meetings, travelling to them, increased secretarial work etc. It would increase time and costs of the assesment. It offers no significant advantages compared with the present situation. In Finland, the National Agency for Medicines (now Fimea) has rarely needed information from other member states in the assessment of clinical trial applications. If necessary, other agencies were contacted by phone or e-mail and topics of interest were discussed in an informal manner.

The undersigned was involved in the assessment of clinical trias submitted to National Agency for Medicines (now Fimea) during fifteen years. There was never any need to have a 'Reporting Member State' to lead the assessment of the application.

The suggested CAP would only address certain aspects of the assessment of an application. National authorites must always make a total, not partial assessment, considering all the aspects mentioned in catalogues a), b) and c). The characteristics of the intervention compared to normal clinical practice in infectious diseases, for example, depends on the local antimicrobial drug policy and microbial resistance.

There are also important differences in the genetics in the populations in EU, which are difficult to consider in CAP. Increased incidence of narcolepsy in the children after H1N1 vaccination was only detected in Finland and Sweden (Zarkostas 2011). There is no scientific justification for the idea of partial assessment

It is suggested, that the procedure should lead to a 'single decision' per Member State, which would include the aspects assessed in the CAP, as well as the ethical/local aspects of a clinical trial assessment. In Finland this is the present situation, when the decisions of national authority and and ethics committee are available.

Instead of CAP, when necessary, the competent authorities can contact their colleagues in other member states and discuss the topics of interest in informal manner, without participation of commission or EMA.

Consultation items 4. and 5. The undersigned disagrees with the appraisal. CAP offers no advantage, but it would increase bureaucracy.

1.3.2. Disagreement with the assessment report

The suggestion, that an individual member state could be allowed an 'opt out' of CAP only if justified on the basis of a 'serious risk to public health or safety of the participant', is too restricted. There are protocols, which are not associated with risks, but which have no scientific value. Some are performed for commercial reasons only (f.ex 'seeding' trial, comparing an expensive new drug with old cheap drugs, recruiting tens or hundreds primary care centres, aiming at replacing old drugs with a new one without any relevant medical advantage), some have inappropriate comparators, some are not able to answer relevant questions (f.ex. because of insufficient sample size), in some trials the results are self-evident, some may violate national antimicrobial drug policies to prevent microbial drug resistance, some have inappropriate result variables etc. The undersigned has the experience, that some national agencies are more likely to accept these studies than some others. CAP could result in increase of trials lacking scientific value.

The undersigned thinks, that voting and majority decision are not acceptable in Finland. Neither is the referral to the Commission or the Agency for a decision at EU level. There are historical, political and ethical reasons not to violate the independency of member states in this matter. Individual member states should be allowed to 'opt out' for any reason they consider as relevant.

Consultation item no. 6: None of the approaches is acceptable**.**

1.3.3. Mandatory/optional use

None of the approaches is acceptable. The list should include fourth option: CAP is optional for member states. Member state, not the sponsor, should decide its participation in the CAP.

Consultation item no. 7: None of the approaches is acceptable.

1.3.4. Tacit approval and timelines

The concept paper claims, that in practice a tacit approval is the exception. This is not true in Finland. The median assessment time during 2002 – 2009 varied from 41 to 51 days (median in one year), the range was 1 to 60 days. No assessment took more than 60 days. Trials involving medicinal products for gene therapy, somatic cell therapy including xenogenic cell therapy and all medicinal products containing genetically modified organisms are not included in this statistics (http://www.fimea.fi/).

The suggested pre-assesment procedure would complicate application and administration procedures. A new concept, type-A trial, should be defined and introduced. New guidelines would be needed, regulations should be updated, interpretations may vary. Instead of further increasing the complexity of the regulations, the present procedures should be simplified. This requires radical revision ot the application form and abandoning the CAP.

Already at present, a clinical trial can be promptly assessed, if it poses only minimal risks to the safety of the trial subject compared to normal clinical practice. No new concepts are needed. In Finland, many clinical trial applications are assessed by competent authority in one day. This would be impossible in CAP.

Consultation item no. 8: Proposed pre-assessment is unnecessary and not workable in practice.

2. BETTER ADAPTATION TO PRACTICAL REQUIREMENTS AND A MORE HARMONISED, RISK-ADAPTED APPROACH TO THE PROCEDURAL ASPECTS OF CLINICAL TRIALS

2.1.1. Enlarging the definition of 'non-interventional' trials

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 harmonised and proportionate requirements which would apply to *all* clinical trials falling within the scope of the present Clinical Trials Directive

Consultation item 9. The undersigned agrees with the appraisal.

2.1.2. Excluding clinical trials by 'academic/non-commercial sponsors' from the scope of the Clinical Trials Directive

The undersigned agrees with the appraisal, as exclusion of trials by academic sponsors from the directive could result in double standard in science and ethics. Rather than limiting the scope of the directive, it would be better to come up with harmonised and proportionate requirements for all clinical trials. The consultation paper includes some examples of such proportionate requirements. In addition, it

seems essential to find other methods to facilitate non-commercial research. The national authorities should cooperate with academic institutions and assist them in overcoming regulatory obstacles.

National agencies usually are familiar with academic investigators and their institutions. Investigators and national agencies can cooperate and discuss administrative problems in informal and flexible manner. The Finnish National Agency for Medicines (now Fimea) has accepted simplified applications from non-commercial investigators. The national agency then completed the application form, if necessary, before submitting it to EudraCT database.

Consultation item 10. The undersigned agrees with the appraisal

2.2. More precise and risk-adapted rules for the content of the application dossier and for safety reporting

If this approach simplifies, clarifies, and streamlines the rules for conducting clinical trials, it can be supported.

Consultation item no. 11: The undersigned agrees with with this appraisal, <u>if it results in simplification.</u>

2.3. Clarifying the definition of 'investigational medicinal product' and establishing rules for 'auxiliary medicinal products'

Clarification is a laudable goal, if it also means simplification.

Establishing rules and definition for auxiliary medicinal products is superfluous. <u>Any medicinal product used in the clinical trial, having marketing authorisation or not, used as comparator or as 'auxiliary product' or for any other purpose, must be accepted by the competet authority in the context of the trial in question.</u> The use of these products must be justified in the trial protocol. The amount of appropriate information on each product depends on the type of trial. Attempts to use regulatory rules instead of scientific judgment and common sense contradict simplification.

Adding a new class of products would cause confusion without any advantage. Moreover, it would result in considerable increase in size of the application form and other documentation.

Consultation item no. 13: The undersigned disagrees with the appraisal. The concept of 'auxiliary medicinal product' should be abandoned. The undersigned agrees with the simplification of definition of investigational medicinal product.

2.4. Insurance/indemnisation

Trial subjects must always be protected as far as possible and damages must be compensated. In Finland, the Finnish Patient Insurance Centre and the Finnish

Pharmaceutical Insurance Pool also cover adverse events in clinical trials. Similar schemes or other national systems can be established in other member states.

Consultation item no. 14: The undersigned supports the second option, optional indemnisation by Member State.

2.5. Single sponsor

Multinational non-commercial trials are often performed by academic institutions or cooperative scientific networks. These trials have proven value f.ex. in cancer research. These trials have in fact multiple sponsors, usually one for each member state where the trial is conducted.

Consultation item no. 15: The undersigned supports the option 2.

2.6. Emergency clinical trials

Emergency treatment should be based on evidence. This cannot be achieved without clinical trials. Often it is possible to ask someone who knows the patient, if the patients has expressed opinion not to participate in trials. However, in these situations harmonisation may be unfeasible, as opinions of national advisory boards on health care ethics must be respected.

Consultation item no. 16: The undersigned agrees with the appraisal, given that permitted by national advisory boards on ethics.

3. ENSURING COMPLIANCE WITH GOOD CLINICAL PRACTICES IN CLINICAL TRIALS PERFORMED IN THIRD COUNTRIES

Consultation item no. 17: The undersigned agrees with the appraisal.

4. FIGURES AND DATA

Consultation item no. 18: No comments

LITERATURE

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