CENTRALE
COMMISSIE
MENSGEBONDEN
ONDERZOEK

**CENTRAL
COMMITTEE
ON RESEARCH
INVOLVING
HUMAN
SUBJECTS**

European Commission
Unit SANCO/C/8
BREY 10/114
BE- 1049 Brussels
Belgium

12-5-2011
your reference: NA, our reference:CCMO11.0747/GK

CCMO (NL) response consultation paper revision Clinical Trials Directive 2001/20/EC

Dear Mr/Ms,

Herewith I send you the CCMO (Competent Authority in the Netherlands) response to the draft paper for public consultation on the revision of the Clinical Trials Directive 2001/20/EC.

I hope to have informed you adequately.

Yours sincerely,

Prof dr GH Koëter
Chairman

postal address:
P.O. Box 16302
2500 BH The Hague
the Netherlands

office address:
Parnassusplein 5
2511 VX The Hague
The Netherlands

phone +31 70 340 6700
fax +31 70 340 6737
ccmo@ccmo.nl
www.ccmo.nl

Response CCMO (Competent Authority NL) to the draft paper for public consultation on the revision of the Clinical Trials Directive 2001/20/EC

General remarks

The CCMO welcomes the idea of revision of the Clinical Trials Directive 2001/20/EC and appreciates the initiative that the European Committee has taken to streamline the assessment system for clinical trials with medicinal products.

Unfortunately, the consultation paper does not address the most fundamental issue *i.e.*, the current two tier assessment system that was introduced in the EU member states by the Clinical Trials Directive 2001/20/EC. The introduction of this two tier assessment system was not carefully considered and resulted in a complex situation and unnecessary bureaucracy in which both the competent authority and the ethics committee have an ill-defined role in the review of clinical trial applications. This consultation paper builds further on this ill-defined two tier assessment system without considering a fundamental change and more rational approach to the assessment of clinical trial applications.

The current proposal suggests that the European Committee has little confidence in the review of the ethics committees and basically relies on the assessment of these competent authorities without providing data that supports a leading role for the competent authorities in the assessment of clinical trial applications. If the current proposal is accepted, the role of the ethics committees is in theory, but not in practice, (see later) limited to the patient information sheets, recruitment of trial participants and compensation. However, the European Committee has no mandate to regulate the role of ethics committees in the member states. In addition, different member states have established different review systems. Some member states developed a decentralised review system in which a limited number of qualified accredited ethics committees are responsible for the assessment of the complete clinical trial applications. In other member states a more central approach was taken and the scientific-medical assessment was laid in the hands of the competent authority. Thus in different member states ethics committees have different roles and responsibilities.

In our view the current attempt of the European Committee to limit the role and responsibility of the ethics committees will not result in reducing the bureaucracy and delays and does not lead to a better review system in the EU. Instead it could easily lead to numerous discussions on the role, responsibility and competence of the ethics committee versus the competent authority, the mandate of the European Committee and discussions of the principle of subsidiarity as was established in the 1992 Treaty of Maastricht.

We therefore propose a different approach to streamline the review system. The main issues of our proposal are:

1. change the <u>two</u> tier assessment system so that only <u>one</u> body is responsible for the assessment and approval of clinical trial applications in each member state. That single body is fully responsible <u>and</u> accountable for the assessment;
2. respect the principle of subsidiarity for the assessment system in the different member states and streamline the submission process and

provide adequate support for the applicant and reviewing body using efficient IT-systems;

3. consider a role for the EMA to provide excellent expert advice on the information of (a specified category) unlicensed medicinal products in the IMPDs. The advice should be incorporated in the clinical trial application that will be submitted through a single portal for the reviewing body in the members states.

Detailed response to the issues from the consultation paper

#1 Single submission through a single EU portal with separate assessment.

It is an excellent idea to built one electronic portal for the submission of the clinical trial application to the reviewing body in each member state. Depending on the review system in the member states (see the principle of subsidiarity above) the body that is responsible for the review can be an accredited ethics committee or the national competent authority.

#2 Separate assessment by each member state generates difficulties.

It is important to note that different member states have different historical and cultural backgrounds and thus developed different views on the ethics of research with human subjects and have as a result different review systems. A one-size-fits-all regulation does not take this into account. It would seem more appropriate to concentrate instead on the process and provide support by building efficient IT-systems for submission and assessment.
A supportive role for the EMA could be considered for providing an expert advice on the information of (a specified category) unlicensed medicinal products in the IMPD. We realize that the EMA does not have the capacity nor the expertise to fulfil this task alone, but will need the expertise that is available in the European Union at the competent authorities and academies and university centres. The EMA can play a coordinating role in making this expertise available for the expert advice. If this advice is of high quality, the reviewing body in the member state will regard this as an added value to their assessment and will be happy to use it. This approach is also a positive incentive to the EMA to generate excellent advice. The expert advice will also have an educational value for the reviewing body in the member states and will generate more sympathy for a role for the EMA than by forcing a top down role for the EMA through EU regulations.

#3 Single submission followed by a central assessment by a scientific committee with representatives from all member states is not possible.

We agree that central assessment by a scientific committee is not possible. As discussed above, an advisory role for the EMA for the information of (a specified category) unlicensed medicinal products in the IMPD might be considered.

#4 Single submission with a subsequent coordinated assessment procedure.

The CAP approach builds on the current ill-defined two tier assessment system and the irrational separation of the scientific-medical assessment versus an ethics review (see above). It creates a one-size-fits-all regulation, could easily lead to capacity problems and lack of expertise in the CAP assessment and does not follow the principle of subsidiarity of the EU.

However, a coordinated advisorye procedure that will result in high quality expert advice on the information of (a specified category) unlicensed medicinal products in the IMPD might be useful. Clearly this requires the setup and maintenance of such a group of high level experts that have sufficient stature to be accepted throughout the EU, in view of the diversity and complexity of clinical trials.

#5 The only aspects that should be included in the CAP are (i) risk-benefit assessment, (i) the quality of the medicines and (iii) their labelling.
See also the response to #4 above. The items suggests that these three issues can be reviewed by the representatives from the competent authorities and should not be reviewed by the ethics committees. As described, the European Committee does not have the authority to limit the scope of the ethical review in the member states. We therefore propose a different approach in which the EMA provides excellent expert advice on the information of (a specified category) unlicensed medicinal products in the IMPD. For this the EMA could build a network of experts for this type of products. These experts could be employees of the competent authorities in the different members state and/or professionals in the European universities/medical centres.

#6 Resolving disagreements amongst member states.
See above. This proposal introduces a new worrisome item: a role for the European Committee in the decision-making process for approval of a clinical trial. This will give a non-expert political body a decisive role in the assessment of an individual clinical trial. This is unacceptable to the CCMO. The assessment of clinical trial applications should be based on an expert review. A clear separation between science and politics is warranted for the evaluation of individual research projects.
The proposal for the revision of the Clinical Trials Directive focuses to a top-down approach. It will without doubt lead to a negative response and more discussions and delays. Authority cannot be gained by centrally forced regulations. Instead the EMA may gain authority by providing excellent expert advice as described above that adds value to the assessment by the reviewing body in the different member states.

#7 Three options as described for the use of the CAP (mandatory or optional).
See above.

#8 Concerns an attempt to define low risk clinical trials. For these trials the timelines could be shortened.
The proposal should be rejected. Products that may seem safe can be very risky depending on the dose, patient group, route of administration, formulation, combination with other medicinal products etc. Furthermore, the proposal provides a great incentive to classify the products as a low risk product. Finally, the proposal shows an over-fixation on timelines and the attempt to 'solve' this through enforcing more regulations.
The alternative is not to enforce more regulations but to streamline the submission process through the use of efficient IT-systems so that the

assessment can be carried out more timely. That is a more rational and positive approach than the current proposal.

#9 Limiting the scope of the Clinical trials Directive.
No comment.

#10 Excluding clinical trials by academic/non-commercial sponsors from the scope of the Clinical Trials Directive.
Do not exclude these trials from the scope of the Clinical trials Directive.

#11 More precise and risk-adapted rules for the content of the application dossier and for safety reporting.
See for the risk-adapted rules above. The current safety reporting is not adequate. Ethics committees receive unstructured and divergent SUSAR reports that are not study-based but product-based and lack an informative follow-up system. A substantial number of the reported SUSARs are in fact SAEs. In most member states these committees do not have an IT-system that provides an informative overview of the reports per study that would allow review of the safety information. The current view that SUSARs should not be reported to the ethics committees is the result of inadequate reporting systems.
The SUSARs from commercial trials are reported to the EudraVigilance database, but it is unclear who at the EMA and competent authorities are monitoring that information and how effective this is.
It is clear that for a vigilance system several layers of monitoring should be in place. The ethics committee could play a useful role on a study basis if they are provided with an adequate IT-system for standardised submission and review of safety reports.

#12 Are there other key aspects on which more detailed rules are needed?
See above. Instead of focussing on more detailed rules that make matters more complicated, the European Committee should consider providing efficient IT-tools that allow for an adequate safety monitoring on a study basis.

#13 Clarifying the definition of investigational medicinal product and establishing rules for auxiliary medicinal products.
Agree

#14 Two proposals for insurance/indemnisation are given: (i) no insurance for low-risk trials and (ii) optional indemnisation by member states.
The CCMO rejects option (i) since even in low risk studies (which are difficult to define), trial participants can be harmed or experience injuries. Option (ii) is interesting. We suggest that the European Committee considers with some urgency a fund that covers damage which its citizens may experience in trials using a no-fault approach. Such a fund would greatly support innovative trials in the EU and requires little cash flow, but only a strong capital base, which the governments of Europe can supply. This would end the undesirable situation of widely divergent protection of subjects and patients throughout the EU whilst participating in trials.

#15 Single sponsor.
A single sponsor is preferable since this make it clear who is responsible. If a national or EU compensation fund is established, this will probably not pose a problem for academic trials.

#16 Emergency clinical trials.
Emergency trial without informed consent should be possible, but should be restricted to therapeutic trials.

#17 Ensuring compliance with GCP in clinical trials performed in third countries.
Agree

#18 Comments ...
See text under General remarks at the top of this document.