REVISION OF THE CLINICAL TRIAL DIRECTIVE 2001/20/EC

CONCEPT APPER SANCO/C/8/PB/SF D(2011) 143448

MAY 13TH, 2011

Here are the comments by the European academic consortium for Innovative Therapies for Children with Cancer (ITCC) http://itcc-consortium.org .

This network runs a comprehensive early drug development program for children and adolescents with cancer. Phase 1 and Phase 2 trials, along with Pharmacological studies are run as both Industry –sponsored and Investigator-Driven Clinical Trials.

ITCC is labelled by the European Medicine Agency and member of the recently created European Network for pediatric research at EMA (EnprEMA).

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1. ASSESSING AND FOLLOWING UP APPLICATIONS

Item 1 – YES a single submission of a clinical trial application in EU will greatly reduce the administrative work and the time needed for approval in all member states for an academia-sponsored multinational trial

Item 2 – YES, keeping a separate assessment of the application would maintain all the current difficulties. In addition, it would wreck the expected positive effect of a single submission

Item 3 – YES, a centralised assessment at EMA of all clinical trial applications is neither appropriate nor feasible.

Item 4 – YES a single submission with a subsequent coordinated assessment procedure that involves ONLY the member states concerned by the clinical trial is the way to reduce administrative work, to speed up timelines and to facilitate sharing opinions from the agencies of the EU member states towards an harmonization at the EU level that will alleviate the consequences of the transposition of the Directive into each Member state.

The Voluntary Harmonized Procedure (VHP) of the Clinical Trial Facilitation Group (CTFG) at EMA has made the proof of concept of a single submission with coordinated assessment procedure (CAP) among the concerned member states which is proposed in the document.

IGR, acting as European sponsor for ITCC trials, has been through the VHP with a very positive opinion.

The catalogue provided in 3.1 describing the areas which are considered in a clinical trial application is complete.

Item 5 - The scope of the CAP should definitely include area a) risk-benefit assessment and quality of the medicines.

Area [b) ethical aspects] is definitely the competence of the Ethic Committees and not of the national competent authorities. There is a need to have a separate ethical evaluation considering that this is an issue that can be impacted by cultural and societal differences from a member state to another one. However, there should be ONLY ONE ETHIC COMMITTEE APPROVAL IN EACH MEMBER STATE as already in place in some member states.

Area [c) local aspects] are related to national expertise and should not be in the scope of the CAP. However, there should be ONLY ONE EVALUATION/APPROVAL for each Member state.

Item 6 – An individual member state could be allowed to opt out, if there are differences in the assessment and no agreement can be reached. This may happen due to national specificities or sensitivity with regard to the trial. However, this should not block the other member states to go on.

Authorisation of a clinical trial should not be the result of a vote. This should come from a consensus allowing those strongly against to opt out.

There should not be a role for the Commission or the Agency. Indeed, since both will not be involved in clinical trials authorisation, they will not have the knowledge and the experience required to make a final decision that would be needed.

Item 7 – the CAP should be MANDATORY for all multinational trials.

Indeed, there is no need of a coordinated assessment for a single member state trial.

In order to impact significantly and positively the clinical research activity in EU, this should be mandatory with no concern since all sponsors will benefit from it, providing that the resources are available to allow the CAP to comply with the mandatory deadlines for response.

Item 8 – The 60 days rule should remain.

From a clinical trial sponsoring academic institution point of view, shorter timelimes for trials with a low risk will be very much appealing. This would definitely need a pre-assessment of the trial with regard to whether or not the trial is a “type-A trial”.

Whether or not such a pre-assessment is workable is an issue to be addressed by the National Competent Authorties and NOT the sponsors.

2. HARMONISED, RISK-ADAPTED APPROACH

ITCC, as an academic network running clinical trials, strongly supports a risk adapted approach.

Item 9 – This is a key one.

Indeed, rather than excluding non interventional trials for the scope of the Directive, it would be definitely better to have harmonised and proportionate requirements which would apply to all clinical trials. BUT this may be a dream. The Directive will be transposed in each member states and thus differences will still occur between member states, jeopardizing the willingness to reach harmonised and proportionate requirements. The best example is that within the current Directive, a member state can consider a trial as non-interventional while another member state will consider the same trial as interventional. We do have examples.

Item 10 – This is a key one as well, since the proposal is either to exclude academic trials from the Directive or to keep each trial within the scope of the Directive, whatever the sponsor is.

However, it has to be highlighted that the current Directive has significantly and negatively impacted academic research.

Having a separate Directive for academic trials will be extremely difficult to handle by the fact that the text is mixing two items – academic *versus* industry / commercial *versus* non commercial – and that there will be differences from a member state to another one to qualify a trial as “commercial or non commercial”. We do have examples.

BUT the transposition of the Directive in each member state should not end up with differences that will render clinical authorisations still more difficult for academic sponsors.

Item 11 – YES precise risk adapted rule should be applied for the application dossier and the safety report.

Item 12 – The key point is that there is a mass of information on safety sent by sponsors according to the current regulations and guidance. There is a question, from an academic sponsor point of view, regarding the optimal analysis of this mass of information by the NCA.

Item 13 – IMP and auxiliary medicinal products

The definitions provided seem relevant providing that, in a phase III trial comparing the addition of a new agent to a standard chemo regimen *versus* the standard chemo regimen, all drugs (other than the new one) are not considered as an IMP, ie for a sponsoring academic institution should not be labelled to the trial and specifically delivered to the centers with the usual monitoring. On the other hand, this should not apply to a industry sponsored trial.

In addition, for an academic trial using a already marketed compound as an IMP in such a randomized trial as the "new product to be investigated", provision should be made that the "new product" is not labelled to the trial and not paid by the academic sponsor.

This should be a difference between academic and industry sponsored regarding who pays which drugs.

Item 14 – This one concerns insurance and indemnisation

WE strongly support the risk-adapted approach for safety reporting and insurance coverage.

We are **EXTREMELY VIGILANT** on the item – subject population involved – among the criteria to define the risk level of a trial.

WE CANNOT accept that ALL trials in CHILDREN are at risk. The needs in pediatric oncology to run clinical research are well indentified. There is a strong track record of academic clinical research run by cooperative networks with a strong integration of research and care. This has been the only way to progress from less than 30% to more than 75% overall survival. Those patients suffer from life-threatening disease and participation to prospective clinical trials is an opportunity to have access to innovative therapies for patients with a poor-prognosis disease and to less-toxic therapies for children with a good-prognosis disease. Care and research are integrated on a daily basis. Children and adolescents are treated only in specialised academic centers (no private practice) that are used to clinical research. In pediatric oncology, all criteria for risk assessment should apply but **BEING A CHILD SHOULD NOT BE PER SE AN ADDED RISK**.

Insurance and insurance costs should be harmonised all across Europe. Currently, major discrepancies in coverage and costs from a member state to another one jeopardizes the implementation of multinational Investigator-Driven Clinical Trial

Item 15 – NO, multiple sponsorship through co-sponsorship agreement should be allowed for academia – sponsored trials. +++++

The current text says ‘ since there is a clear difference between responsibility of the sponsor *versus* liability vis-à-vis the trial subject, there is no problem for a single sponsor that will allow a truly harmonized process in EU’.

It is not that simple and this would still be an extreme limitation for academic sponsored trials.

Thus WE, as academia, ask, that the revised Directive contains a chapter that differentiates industry and academia sponsorship, ie:

- a single sponsor for industry - mandatory
- the possibility to use a co-sponsorship agreement (including a EU coordinating sponsor and a co-sponsor in each member states) for academic sponsored trials.

Even though responsibility and liability are different from a legal point of view, it is clear that hospitals will still be extremely reluctant to be the unique sponsor all across Europe. In addition, this might jeopardize co-funding from national public bodies. Indeed, one government may be reluctant to fund a trial that is sponsored in another member state.

Item 16 – YES

3. GCP COMPLIANCE IN THIRD COUNTRIES

Item 17 – No opinion