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EORTC Contribution to the public consultation on CTD

European Commission Public Consultation:

Assessment of the functioning of the Clinical trial Directive 2001/20/EC

This EORTC Contribution follows the plan and the numbering of the Public Consultation Paper

Consultation item 1: Can you give examples for an improved protection? Are you aware of studies/data showing the benefits of the CTD?

As of today, only ICREL was structured and methodologically robust to measure potential impact of the CTD. ICREL goal was dedicated to the evaluation of the metrics (quantitative evaluation). Up to EORTC knowledge, there is no project addressing qualitative evaluation of the CTD.

From EORTC experience which is one of the largest international academic sponsors, there is no evidence within EORTC activities that the CTD resulted in an increased protection in terms of patient rights or safety. On the contrary, there is a concern that the pharmacovigilance processes currently in place are inadequately leading to an overload of the involved bodies and potentially dilutes the critical safety information.

Key issue I: Multiple and divergent assessment of clinical trials

Consultation Item 2: is this an accurate description? What is your appraisal of the situation?

EORTC confirms that this is an accurate description at various levels as exemplified by the examples provided here under:

- At the level of trial assessment and classification whether being interventional or not, whether falling under the CTD or not resulting in delays for study activation;

- At the level of protocol content assessment exposing the sponsor to conflicting comments when one single protocol should apply through the community.

Example 1

EORTC protocol SURTIME 30073: “Randomized Phase III trial comparing immediate versus deferred nephrectomy in patients with synchronous metastatic renal cell carcinoma”.

In a first time, UK MHRA considered this study as needing a CT Application while other Member States did not. The different points of view held on the status of the study involving a drug treatment presented as background and standard treatment in a protocol which addresses only a question related to the time of surgery. The background treatment was inconsistently considered as IMP or no IMP by various NCAs. After discussion, the UK MHRA accepted to modify its prior position following appropriate argumentation.

Example 2

Contraception warnings follow different approaches according to the countries requirements and culture as Germany (giving the complete strategy and details on contraception methods even for elderly people without clinical relevance- CT N° 26073 elderly brain tumor with multiple metastasis) and Italy (EC would like to recognize abstinence as an effective method and do not constraint a patient to take pills).

Other levels of divergent assessments not directly linked to protocol evaluation but to the forms and methods of implementation as a result of the protocol assessment are also encountered.

Example 3

In Italy, EORTC as an international academic sponsor does not benefit of any national simplified procedure in place for national academic sponsors such as insurance waivers, leading to 2 speed processes for academic trials in Europe whether nationally or internationally lead.

Example 4

In UK, in certain circumstances such as intergroup setting, NHS handles itself reporting into Eudravigilance database only SUSARs occurring at UK trial sites, therefore splitting the duties of the single European academic sponsor and generating divergences in safety reporting with a possible impact of accuracy for patient protection.

Consultation item 3: is this an accurate description? Can you quantify the impacts? Are there other examples for consequences?

This is an accurate description. Average time to activate clinical trials mentioned in the consultation document was issued by the ICREL report which includes EORTC data.

The cost increase is not always justified. The best tool for the moment to measure how the workload increased seems to take into account the increase of the headcount. We do not have the proof that the increase of the headcount improves quality of the studies and safety of patients.

The resulting impact is the need to increase resources for performing less trials without an identified improvement in quality. Therefore, possibly relevant trials essential for European patients may no longer be conducted due to high costs, inadequate resources and administrative burden. It is important to highlight that there is a substantial shift of the type of trials being conducted after the directive. Indeed, due to the increased costs, academia is forced to establish specific partnership with varying sources of sponsorship which to some extend may be a threat to independence at a time when public transparence, integrity and interpretation of clinical trials are rightly being addressed.

Consultation items 4 & 5: New options for assessment by National Competent Authority and Ethics Committee

Can you give indications/quantifications/examples for the impact of each option? Which option is preferable? What practical/ legal aspects would need to be considered in further details?

Considering the heterogeneity, variability, discordance, delay in Europe for CA and EC assessments, the option of a central assessment or also the mutual recognition process in case of decentralized procedure for marketing authorization must be addressed. There are pros and cons to each approaches and it appears that a mutual recognition or a collegial evaluation may better fit the current European NCA landscape. EORTC confirms that harmonization is required not only at the CA level but also the EC level.

- At the level of NCA

The collegial approach of the VHP process for CA advices, could certainly further evolve toward a more solid and robust central process reflecting the views of the contributing NCAs easily transposable with a local mutual recognition, in the respect of an opt-out option as exception.

EORTC supports the VHP initiative from the CTFG. EORTC suggests a continuation and a close evaluation of this process before any new change in order to identify the bottlenecks and address them as they emerge. This process is in its infancy and should mature. EORTC has already activated 2 studies through the VHP. There is a need to understand why some Member States are opting out. This process could be a model to redefine a harmonized and shorter way and represents an alternative to any new centralized system or at least a step forward.

Annex 1 is an EORTC report on the first EORTC experience with the VHP dated from 09/09/2009.

Another route is adoption of a similar process as the principles of Mutual Recognition with a Reference Opinion of a Member State. The other Member States will confirm or not their acceptance to participate.

- At the level of Ethics Committees

Regarding the discrepancies into a same country, we observe that the single opinion stipulated by the European Directive is rarely a reality. For example, in Italy, a Single Opinion appears to be implemented. However, in reality local discrepancies on protocol assessments, insurance requirements between local EC result in varying evaluation of risks for citizens within a single Member State.

The sponsors are facing multiple national and institutional procedures of variable duration that delay the initiation of studies. Currently, the roles and responsibilities of ECs are not clearly defined (evaluation of ethical and/or scientific aspects of the protocols).

Note on practicalities for CTAs:

EORTC strongly suggests the constitution of a single submission dossier in English according to a unique template and format through EudraCT process.

For international studies there is a major need to discourage any setting of National Databases such as “Osservatorio Nazionale sulle Sperimentazioni Cliniche- OsSC” in Italy and also to discourage any National based solution such as the particular management of SUSARs in UK or the Insurance considerations in Italy as already referred to.

The national laws and legal requirements with respect to insurance are heterogeneous. The amount of indemnity, and therefore premiums, and the duration of coverage vary from country to country or even within the same country between ethics committees. This situation leads to considerable extra costs and administrative burdens. Europeans standards should be established in order to harmonize the amount and duration of coverage in Europe according to a medically sound evaluation of risks. Insurance companies and national health care agencies should be involved in this harmonization process.

Key Issue II: Inconsistent implementation of the CTD

Consultation item 6: is this an accurate description of the situation? Can you give other examples?

EORTC confirms that this is an accurate description and would like to illustrate this with the examples here under harmonization attempt is recognized with the version 8 of EudraCT. This version has been published (presented as final) in Eudralex volume 10 on June 2nd 2009.

However contradictions do persist such as a change of address which should be considered now as a Non Substantial Amendment while the corresponding change for the .xml leads to a Substantial Amendment.

The reporting of SUSARs to EC is not efficient and leads to redundant reports without direct application for the patient’s healthcare and safety. The submission of annual safety report would be more useful.

Example:

In UK, MHRA introduces SUSARs to EudraCT only for UK trials sites as indicated earlier

In the Netherlands the CCMO is planning to introduce a system to report from 1/1/2010 onwards all SAEs in an online system.

This is not in line with what has been proposed by the Directive:

- The information at the moment is only in Dutch
- It requests the reporting of SAEs instead of SUSARs
- Training needs to be followed to understand how it works
- The system doesn’t allow uploading of E2B files which would mean additional administration to encode the information again and allows mistakes
- This will first be imposed on investigator driven trials and later in 2010 also for commercial clinical trials

More info can be found on: http://www.ccmo-online.nl/main.asp?pid=25&sid=49&ssid=178

A better solution would have been to allow ECs to look at the data in the EU database (EVCTM-EudraVigilance CT Modules) via their CA.

The management of SUSARs appears very time consuming, ineffective, dangerous in terms of dilution of responsibilities (sponsor-investigators-ECs) and giving a false sense of security.

The reporting processes are getting even more complex when partnerships are set up between academia acting as legal sponsor and industry /drug manufacturer where not only study related safety events may be duplicated but also global safety reporting such as “dear dr letters”. Despite clear contract dictating split of responsibilities, it is not always possible to set up clear cut processes due to the confusing legal requirements. The same may apply to some extend when academic groups do cooperate on an international basis.

Consultation item 7: is this an accurate description? Can you quantify the impacts? Are there other examples for consequences?

Direct costs linked to CA submissions, ECs and audit have a substantial impact on academic sponsor. EORTC who has just been subject to an audit by MHRA will be charged at a substantial level. The insurance budget has also been substantially increased since CTD implementation without any meaningful justification.

Indirect costs related to the increased resources required to comply with the CTD documentation/information evaluated as up to +150%.

Consultation item 8: Can you give indications/quantifications/examples for the impacts of each option? Which option is preferable? What practical/legal aspects would need to be considered in further details? In particular, are the divergent applications really a consequence of transposing national laws or rather their concrete application on a case-by-case basis?

We recommend guidelines setting up and harmonization of the EC assessments and requirements rather than a CTD rewriting. This process seems to be more effective in short term.

EORTC is an organization conducting only international therapeutic clinical trials and we are not against the position that all clinical trials would fall under the scope of the Clinical Trial Directive provided that harmonization is guaranteed such as within the Belgian law does.

Key issue III: regulatory framework not always adapted to the practical requirements (item 9-13)

Consultation item 9Q: Can you give examples for an insufficient risk-differentiation? How should this be addressed?

Currently, all clinical trials are subject to the same requirements in terms of regulatory, pharmacovigilance, insurance and monitoring regardless the level of risk related to the study. None of the assessments done by Ethics Committees and Insurers for example are made on a risk-based approach to distinguish clinical trials leading to specific requirements.

We support the ECRIN initiative to contribute to a comprehensive risk based approach.

EORTC is working on a setting of a risk-approach model which is currently under evaluation. You'll find attached it in annex 2.

Consultation item 10: Do you agree with this description? Can you give other examples?

EORTC leading international trials has gained the capacity, despite the limitations and tremendous increase of costs to act as a single sponsor through multiple Member States.

Unique sponsorship for international studies whatever their status (academic or commercial) remains the most transparent and valid approach.

Consultation item 11: Can a revision of guidelines address this problem in a satisfactory way? Which guidelines would need revision, and in what sense, in order to address this problem?

This review could certainly be useful but may not be sufficient (see position on EC requirements harmonization).

A monitoring of the implementation of the Directive into national laws in order to assess also all the deviations and discrepancies should be set up.

EORTC suggests however a pragmatic approach building on the experienced gained over the years rather than reviewing the full process under a regulation.

Consultation item 12: in what areas would an amendment of the CTD be required in order to address the issue? If this was addressed, can the impacts be described and quantified?

Important areas to be addressed:

- Central processing and access to SUSARs by all involved bodies
- A true single opinion/single Ec process within each country
- A medically meaningful, risk-based, harmonious transnational clinical trial insurance implementation.

Consultation item 13: Would you agree to this option and, if so, what would be the impact?

EORTC does not plea for a split between commercial and non commercial sponsor as an option. This would marginalize academic research. A pragmatic implementation on a risk-based approach is preferred.

Key Issue IV: Adaptation to peculiarities in trial participants and trial design (item 14-15)

Consultation item 14: In terms of clinical trials regulation, what options could be considered in order to promote clinical research for paediatric medicines, while safeguarding the safety of the clinical trial participants?

No experience.

Consultation item 15: Should this issue be addressed? What ways have been found in order to reconcile patient's rights and the peculiarities of emergency clinical trials? Which approach is favorable in view of past experiences?

No experience.

Key Issue V: Ensuring compliance with GCP in clinical trials performed in third countries (item 16-17)

Consultation item 16: please comments. Do you have additional information, including quantitative information and data?

According to our experience, compliance with ICH E6 requirements is requested for any collaborative country.

Additional information: in the collaboration with US non-commercial groups it is clear that not the same language is spoken. SUSAR is not used and it therefore very difficult as "European sponsor" to receive US data in the ICH E2B format, hence a limit for academic global studies required to address rarer clinical entities, and therefore resulting in higher burden to ensure compliance of these trials.

Consultation item 17: What other options could be considered, taking into account the legal and practical limitations?

We cannot answer to this topic because of lack of marketing authorization goal.

Consultation item 18: What other aspects would you like to highlight in view of ensuring the better regulation principles? Do you have additional comments? Are SME aspects already fully taken into account?

Setting up a regulation oriented to pharmaceutical drug appears to be too restrictive.

Pure academic end-points/public health issues studies, translational research, radiotherapy, surgery studies do represent 50% of the overall European study portfolio and therefore the full scientific environment should be taken into account.

The importance of investigators driven trials must be remember taken into account:

- Independent objective evaluation
- Large scale trials to change practice and establish state-of-the-art treatment
- Multidisciplinary strategies
- To test new concepts and develop new approaches
- Rare tumors (niche trials)
- Translational research component.

ANNEXES

Annex 1:

- **EORTC Report: Report on the Voluntary Harmonization Procedure-Pilot Phase-09/09/2009**

Annex 2:

- **EORTC Study Risk Assessment- Scoring Sheet under Evaluation- v3.0- 2009**