EORTC
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EORTC reply to public consultation

Revision of the "Clinical Trials Directive" 2001/20/EC

Concept paper **SANCO/C/8/PB/SF D(2011) 143488**

Introduction

EORTC reply is meant to be applicable only for international trials which are the domain of our expertise.

EORTC understands the current consultation does not intend to address all issues which have been raised by previous consultation and focuses on selected subject only. However, we would like to suggest bringing specific proposals to solve pharmacovigilance issues and its possible adaptation to the risk based approach into public consultation.

Everyone agrees that the current pharmacovigilance requirements are cumbersome and should be revised to be clarified, simplified and adapted to the risk, but there is no clear consensus on what should be modified and how. A better understanding on the different responsibilities between ethics committees (ECs) and Competent Authorities (CAs) is therefore needed. Initiatives have been taken, but a change in the Clinical Trials Directive itself is still needed as, for example, it is not clear if there is consensus on whether individual SUSAR information should no longer be sent directly to the ECs, and that it should be the responsibility of CAs to ensure safety in the studies. ECs could be given (controlled) access *via* predefined queries to the Eudravigilance database.

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Consultation topics

Authorization procedure (items 1-3)

Consultation item N°1

The EORTC fully agrees on single submission (understood as being the submission of full dossiers to Competent Authorities and Ethics Committees through a central portal). This will greatly reduce administrative burden for sponsors and harmonize requirements among member states.

This statement is correct only under the condition that no parallel national database or submission of additional information on a national level would remain at the level of Member States (MSs) for international trials. We therefore suggest that the use of the proposed single "EU portal", following the EudraCT format, entirely supersedes national systems and portals, i.e., Osservatorio, IRAS etc.

We would also suggest using a system similar to the existing EudraCT but with the possibility of submitting country specific information attached to the main part of the clinical trial application dossier. Indeed, even in case of full harmonization, some information relevant for CAs may vary from country to country. For instance, facilities used for drug distribution may be different in different countries. Moreover, CAs need to verify drug labels written in the national language. Without the possibility of supplementing the core dossier with specific national documents through the central portal, the "2nd submission step" (when CAs request the submission of country specific information) will remain and negate the benefit of the single portal.

It is also essential to consider those instances where local feasibility is not assessed by ECs but is delegated to the local management boards / directors / national health system officers. In such cases, these stakeholders currently use national portals / systems which require information already submitted through the single portal. We would propose that member states assume responsibility for the transfer of this information to appropriate bodies by their own means.

The central portal should be interactive with an integrated tracking system whereby all parties (sponsor, its representatives / subcontractors, and evaluator) can see trial submission and approval status. The sponsor should have the possibility to manage country specific access permission for its representatives / subcontractors.

Additionally, this portal should be sufficiently flexible so as to enable future extension to other aspects of the clinical trial (in case additional authorizations are needed for radioprotection, bio-banking, etc). Over the long term, this portal should be able to distribute parts of dossiers to all concerned bodies within a trial (not only those required by the clinical trials directive).

EORTC would suggest sponsors fill in this portal in English.

Consultation item N°2

Yes, maintaining separate assessments would result in a situation where in many of the difficulties would remain unchanged.

Indeed, separate parallel assessments done by CAs lead to duplication of efforts. This method increases the risk of inconsistencies between assessments (contradictory statements) as evaluations issued by different evaluators can be very heterogeneous and may focus on different issues. Efforts are multiplied by the number of participating countries without offering any added scientific value or added benefit for the patients. This results in longer delays in activation of international trials and lapses in the approval of country specific amendments which may jeopardize trial data and consistency. Duplication in CTA assessment results in major and unjustified additional costs for trial sponsors and members states.

This approach makes the EU clinical trials environment highly unattractive.

Consultation item N°3

We do not agree with the fact that the central assessment is not feasible. EORTC pleads for the central assessment system for international trials but not in the form presented in this document (below proposal of CAP corresponds better to our understanding of centralized submission).

The scientific committee illustrated by item 1.2 is a very rigid structure and, in our opinion, not appropriate for evaluation of international clinical trials. Furthermore, it is not advisable to create a new EU administration. The current Voluntary Harmonization Procedure is an example of a centralized review, and future models should build on its experience.

A mechanism for progressive mutual recognition would be more suitable in the long term (see comments on CAP).

Regarding workload, countries with a large number of clinical trials are already dealing with a large number of CTAs. Therefore centralized review should be feasible.

Conclusion for the items 1-3

- Single interactive portal for submission of the dossier to CAs and ECs in all MSs, covering documents relative to all aspects of the trial (those to be evaluated by all involved parties)
- No separate assessments, but centralized coordinated system for CAs and ECs (outside local aspects)
- No 2nd step national portals or databases or dossiers to be submitted by the sponsor in addition to EU portal requirements
- English accepted (outside documents directed to patients)

- For clarity on the EORTC position, we attach schematic proposal of the submission and review system in EU at the end of this document (Annex I).

Scope of Cap (items 4-5)

Consultation item N°4

Yes, we agree that the above catalogue is complete, although aspects to be taken into account for risk/benefit assessment may be nuanced further.

Indeed, risk/benefit assessment should also take into account the medical needs and condition of the patient. The acceptance of the risk of injury is obviously not the same for a patient whose survival chances are good as they are for those whose illness is life threatening.

Although this list is intended to describe what should and what should not be evaluated and by whom, the EORTC would like to express its opinion on this as well.

It is our understanding that aspects grouped under "a" (the risk-benefit assessment, quality & relevance of the trial and characteristics of the medicinal product itself) should typically be the remit of CAP assessment which would combine evaluation by CAs and lead/central/single ECs on all aspects of the trial and which should apply EU wide. Aspects grouped under "b" (ethical aspects related to informed consent recruitment and reward) should be evaluated by the ECs at the national level.

As far as aspects grouped under "c" (local aspects related to suitability of sites, investigator and compliance with national law) are concerned, it is our opinion that these should be the sole responsibility of the sponsor (provided requirements for insurance are clearly defined by law(s)/regulation(s)) without any need of verification by CAs or ECs prior to the trial start. The sponsor's legal obligations together with the presence of regular inspections by authorities are sufficient to ensure appropriate selection of sites and investigators and compliance with applicable law (in any field – data protection, insurance, or any other legislation applicable to a give project).

EORTC would also suggest that a system be put in place for sponsor accreditation prior to the start of an international clinical trial (which require a higher level of organization and expertise as compared to single country trial). Such accreditation should be put in place by the country in which the sponsor is based (with a mutual recognition system by other MSs). It should be a global accreditation (not one given on a trial by trial basis) and be valid for five years). CAs would verify that a number of minimal requirements in terms of structure and training be met before granting such an accreditation. We would also like to propose that further inspections of the sponsor's premises would be done by the MS where the sponsor is based and be recognized by other authorities.

Similarly, accreditations could be put in place for sites and/or investigators.

Consultation item N°5

Yes, we agree that only the aspects grouped under "a" should be the remit of CAP.

The EORTC would like to emphasize, that it is essential that the general risk /benefit and a general ethical assessment of the trial takes place in a centralized coordinated way and not on a country by country basis.

It is also essential to clarify respective roles of the CAs and ECs with respect to the patient information or to stimulate the coordinated review of this document; the results of CAP may be severely jeopardized by later divergent local assessments in those countries where authorities review this document in addition to ECs.

Further, single EC review should be imposed on a trial by trial basis for these aspects. Different versions of patient information in different sites in the same country for the same trial should not be allowed. The number of ECs should in general be reduced within the EU and its MSs.

Conclusion for items 4-5

- CAP should review all aspects of the trial which are meant to be applicable in all concerned MSs, and it should include ethics.
- For national aspects, clarification of the roles of the CAs and ECs or their collaboration are needed and should be through single review.
- Local aspects related to suitability of sites / investigators, compliance with national legislation (including insurance) – should be under full responsibility of the sponsor without any prior review (but could be verified during accreditation process or inspection).

Other issues related to CAP (items 6-8)

Consultation item N°6

EORTC is in favor of the 1st option which enables individual MSs to opt-out from the trial. A country should be allowed to decide whether or not to authorize a new study within its territory. Such assessment may take place on the grounds of this country's cultural specificity which could lead to a divergent assessment of the patient safety and public interest. In turn, this country should not be allowed to block other countries from having favorably assessed this trial.

However, appeal systems should be foreseen in case the Sponsor would wish based on the new / additional information, to convince a MS which "opted-out" to re-consider (separately from other MSs).

Similarly, there should be a general appeal process for CAP and a *rapporteur* replacement process in case a r*apporteur* renders a negative evaluation, which is not endorsed by other CAP participants.

Consultation item N°7

EORTC is in favor of the 2nd option with CAP being mandatory for all international trials. Allowing such procedures to be optional will create confusion and unnecessary complexity. Europe should avoid the establishment of double standards.

Of course, a short pilot phase could be foreseen on a voluntary basis for sponsors, and it would be mandatory for all MSs to validate the system (portal and internal coordination of CAP).

Consultation item N°8

Yes, we believe pre-assessment is practical and could be implemented on an optional basis.

EORTC welcomes the notion of the type "A" trial.

The primary responsibility for the assessment of the risk should belong to the sponsor. During the evaluation, CAP would endorse or object to this evaluation. The possibility of a pre-assessment could be of an added value at early stages of borderline cases, ones in which the sponsor would like to know, given potential implications for the budget, if such a trial may indeed be classified as type "A". The procedure should have a maximum duration of one calendar week. We suggest that pre-assessment should preferably be done by the *rapporteur* country in charge of leading the CAP.

Conclusions items 6-8

- Principle of "opting-out" with an appeal processes
- Mandatory for international trials
- Optional pre-assessment

Scope of the directive (items 9-10)

Consultation item N°9

Yes, we agree with this appraisal. Harmonized and proportioned legal requirements should apply to all clinical trials. The risk based approach will be the corner stone of such an approach. Double standards should definitively be avoided.

This, of course provided that registries, pure data collections (prospective or retrospective) and data linked to bio-banks of residual biological material are not considered in the scope of the directive. Indeed, they are already covered by different legislations)

Consultation item N°10

Yes, we agree with this appraisal. The risk based approach is much more appropriate. Patient exposure to specific risk related to the clinical trial, and the methodological/

logistical complexity of the trial which could impair quality of the data, should drive the level of requirements to be applied to this trial.

However, there should be no amalgam made between quality requirement for the trial and the financial help to non-commercial sponsors. At the end of the document we address this issue separately.

Conclusion items 9-10:

- Same standards for all

Risk adapted regulation (items 11-13)

Consultation items N°11 and 12

Yes, we agree with this appraisal. Guidance documents will be needed on top of the basic legal act (the directive).

Should be adapted to the risk for the patient:

- Content of the dossier
- Drug labeling (and the need to provide it for free)
- Safety reporting
- Monitoring (on-site visit frequency, central monitoring, DSMB, IDMC, periodicity of reviews, etc.).

In terms of adaptation of the monitoring to the risk, two types of risk should be considered separately: risk to the subject and risk to the data.

In terms of the risk to the subject, three categories (A, B, and C as mentioned previously) could be applicable.

In terms of the risk to the data, criteria should be different.

We would propose to consider the following aspects:

- complexity of endpoints
  (i.e., overall survival *versus* progression free survival)
- complexity of the trial design
  (number of steps, central reviews, sub-studies etc.)
- degree of deviation of the protocol treatment and examinations from the standard clinical practice

Consultation item N°13

Yes, we agree that the IMP definition should be revised. However, we would suggest a slightly different approach.

Indeed, we believe that the definition of the IMP should be limited. Non-modified comparators available on the market and used in accordance with the standard clinical practice (for international trials used in accordance with the standard clinical practice in at least one of MSs) should not be considered as IMP. Of course, placebo and modified or non-standard comparators should remain within the definition.

Also, there will still be a need to provide information on the comparator, which makes complete sense in a randomized trial, but some requirements, such as drug accountability up to investigational standard may be disregarded and replaced by standard practice accountability without any harm to the patient.

Similarly, background medication and concomitant medication should not be considered as IMP provided it is not modified for the purpose of the trial (which we understand is meant by "auxiliary medicinal products").

In case any of the treatments (IMP or not) would not be covered by the social security systems, sponsor would need to put in place measures to avoid additional financial burden to the patient, unless it is not significantly different from the expenses that the patient would have otherwise incurred outside the trial. These measures should not be fixed by legislation but be left to the sponsor (as there may be multiple solutions, including in exceptional cases the patient's agreement to support the burden).

Concerning the reporting of safety information, we see that investigators are not fully aware of their responsibilities in case a serious adverse drug reaction (SADR) has occurred due to the nIMP. Also, when there is or might be an interaction beween the IMP and the nIMP in the study, the responsibilities are not always well defined.

We specifically suggest clarifying and simplifying pharmacovigilance reporting for non-IMPs.

Conclusion items 11-13:

- Requirement should be adapted to the risk
- IMP definition should be limited to what is under investigation

Practicalities (items 14-16)

Consultation item N°14

EORTC would be in favor of putting the MSs under the obligation of providing an indemnification for damages incurred during clinical trials performed in their territory regardless of the country where the trial sponsor is established andthis at least for academic sponsors. International trials should be covered in all concerned MSs by a public pool funded by each MS (e.g. such an indemnification

within the UK would be possible for a trial where the EORTC, based in Belgium, is the sponsor).

Indeed, according to the current data on the total amount of indemnification, the financial impact on the MSs's budget should be limited.

We believe that all clinical trials, even those at low risk, should be insured. In turn, the coverage, the duration, and therefore the cost of the premium should be adapted to the trial associated risks for patient safety.

Since we are not an insurance company, it is difficult for the EORTC to propose specific solutions for insurance, e.g. public pool in each MSs or single policy covering one trial in the entire EU (one single territory). We acknowledge it will not be possible to harmonize national legal requirements in Europe like the liability regime. We acknowledge also that the main factors driving costs for insurers may not only be the risk associated with a trial but also the costs of maintaining local capacities in order to comply with national requirements. Therefore, we believe the new version of the directive should at least try to harmonize the national insurance requirements such as the risk, the duration of the risk, etc. The risk based approach should be used irrespective of the liability regime and types of insurance required locally.

The same level of indemnity should apply to all participants in the same clinical trial.

Consultation item N°15

The EORTC is in favor of the option 1: single sponsor within EU.

The EORTC believes the burden of being a single sponsor will be substantially decreased by the improvement of the regulatory environment. In addition, sponsors now have the option of delegating trial related tasks to other parties while maintaining the final responsibility for the trial. Therefore, single sponsorship should be the preferred option.

However, in duly justified cases co-sponsorship should be permitted provided there is a contractual agreement and a clear specification of a lead sponsor. Indeed, this could give for academia additional possibilities for fund raising without any harm to the trial quality and thereby facilitate the conduct of IDCTs (Investigator Driven Clinical Trials).

Of course, there might be, in addition, third country sponsors implicated in the trial (i.e., in case of transatlantic collaborations, a different sponsor on the third country's territory would be allowed to have responsibility for activities performed on the other continent).

Consultation item N°16

Yes, EORTC agrees. We suggest that a healthcare proxy should be considered when there is no parent or legal representative.

Consultation item N°17

Wrong term used: “third countries” should be in this context “non-ICH countries”.

Consultation item N°18

7.2 Though the price of insurance may be related to recruitment numbers, EORTC observes huge differences even between countries with comparable figures (e. i. Poland, Ireland, and Greece).

Data from 7 recent projects cumulated in euro per patient

Poland (trial specific policies) 133-250€/pp

Belgium (trial specific policies or global policy) 36-58 €/pp

France (global policy) 32 €/pp

Germany (trial specific policies or global policy) 90-226€/pp

Ireland (trial specific policies) 35 €/pp

Italy (global policy) 27.00 €/pp

Portugal (trial specific policies) 79 €/pp

Spain (trial specific policies) 59 €/pp

CH (trial specific policies) 70.00 €/pp

NL (global policy) 27.00 €/pp

Greece (trial specific policies) 131 €/pp

UK (trial specific policies or global policy) 36-78 €/pp

7.3. The listed data are in line with the general perception that damage claims incidence and paid compensations are very limited compared to the number of patients at risk. According to EORTC data: ten damage claims from two countries (only one of which was an EU country) and a total of 60,000 euros indemnity are recorded for the last five years from a population of approx. 30,000 patients recruited in 43 clinical trials involving around 11 countries.

Other aspects: Academic sponsors and their support.

It should be emphasized that given the financial burden of clinical trials within the current legal framework, IDCTs being conducted without any industrial support or within the framework of a partnership with a limited support have been heavily jeopardized and have decreased in number (at least within our network). The fact that their costs have dramatically increased is generally admitted.

Moreover, such financial pressure on academia causes more difficulties for academic trials to remain independent from the industry, and this is a major concern.

Specific means should be put in place to stimulate academic research:

- academic funds on the national and EU level set-up by all MSs which would allocate budgets for IDCTs
- no or reduced submission fee arrangements for academic sponsors should be maintained
- solutions should be found for insurance coverage
- we would suggest emphasizing the importance of the allocation of core funding. For example, small contributions can be requested from industrial sponsors, and the monies collected could be allocated to accredited academic sponsors (see reply to consultation item 4) – similarly to the support given by NCI US to academic research groups, and this approach should be pursued at the EU level.

We would also propose emphasizing the importance of independency of trials recognized as academic at the EU level. This recognition should take into account the fact that partnership with industry may and should exist, but under certain conditions:

- academic sponsor for a trial
- academic ownership of data until the final analysis of the primary endpoints
- data and biological material are controlled by academia or a subcontracted organization
- It should also be recognized that in exceptional cases, and without having been pre-planned in any drug development plan, a trial may reveal interesting features leading to potential drug registration. In this case there should be clear, realistic, and transparent rules to change a non-commercial trial into a commercial (*via* switch of sponsor and other modalities with appropriate “a posteriori” funding of expenses made by academia).

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