Assessment of the functioning of the "Clinical Trials Directive" 2001/20/EC

Evaluation of

Public Consultation Paper ENTR/F/2SF D(2009) 32674

Submitting party: European Group for Blood and Marrow Transplantation (EBMT)

Stakeholder: Sponsor – academic

Consultation • 1: "Overview, achievements but also shortcomings" – Can you give examples for an improved protection? A re you aware of studies/data showing the benefits of Clinical Trials Directive?

Berendt, L., Hakansson, C., Bach, K.F., Dalhoff, K., Andre aen, A. , Petersen, L.G., Andersen, E. and Poulsen, H.E. (2008). Effect of European Clinical trials Directive on academic drug trials in Denmark: retrospective study of applications to the Danish Medicines Agency 1993 -2006. British Medical Journal, 336:33-35.

The majority of the scientific publications on the directive, however, report that the initial goal to simplify the burocracy is not met in the academic environment and that the number of Academic sponsored trails in Hematology and Oncology decreased considerably in several countries (see Hemminki et al. BMJ 332 501 -2; see also Lancet publications). Th is is also the experience by the EBMT, which noted a reduction of new trials and an increase in trial costs including insurance costs. Even if the original idea was excellent the results are quite disappointing and need immediate actions . The diagnosis for having failed reside in the generalization of clinical trials (industry sponsored, academic, observational ecc.), in the different implementation in mem ber states, in the increased and often redundant requests from national authorities and in vague definitions and descriptions within the directive. By fixing these points we might have a predominance of the positive effects of the directive.

Consultation • 2: "KEY ISSUE • 1: Multiple and Divergent Assessments o f Clinical Trials" – Is this an accurate description of the situation? W hat is your appraisal of the situation?

The issues described paint an accurate picture of the current situation. There appear to be varying levels of in-depths assessments in the different Member States (MS), with some requesting no or little changes, whereas other MS request many detailed changes of the same protocol.

Our organisation has never had a clinical trial application (CTA) rejected in any MS.

Consultation • 3: " General weaknesses" – Is this an accurate description? Can you quantify the impacts? Are there other examples for consequences?

The description is correct and the points raised are regularly encountered in our experience.

The cost of an application to the NCAs varies considerably across the Community and is unclear even within a single MS. In one MS a CTA may cost in the range of hundreds of Euros, whereas in another MS the assessment of the same protocol can cost thousands of Euros. For example for a double blinded, placebo controlled trial (with an academic sponsor) our organisation has been invoiced € 102, € 2'700, and € 3'204 from the Spanish, German and Swedish NCAs respectively.

Certain trials sponsored by our organisation are treatment trials comparing the therapy of the gold standard medicinal product with an experimental treatment, such as haematopoietic stem cell transplantation. Especially for such studies it can be difficult to plan ahead what the overall cost of approvals will amount to across the different Member States. For an academic sponsor it is often challenging to acquire sufficient funding, especially for international trials. At the same time it is of the upmost importance that the budget planning and calculation are sufficient and realistic. This unclear costing structure makes the planning stage especially difficult. Furthermore, having to spend thousands of Euros for the same protocol to be reviewed many times over is a waste of funding and adds up to a significant percentage of the total budget.
As outlined in the consultation paper, the varying assessments of the same protocol by the NCAs leads to different versions of the protocol that need to be combined into one single protocol at the end of the approval process. This not only delays the progress of the trial, it also increases the overall cost of the approval process even further.
Harmonisation of the costs for CTA and substantial amendments would be welcomed.
Free assessments for academic sponsors would also aid the academic community and would help boost investigator initiated trials.

Consultation • 4: "Options addressing the assessments by NCAs" – 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 detail?
The NCAs must be congratulated for their cooperation and implementation of the VHP. Our organisation has not yet had the opportunity to use this procedure but aims to do so in future.

Option b) is preferable out of the two examples put forward. As pointed out, the main advantage of this genuine one-stop shop authorisation applicable throughout the Community is that no new authorisation would need to be requested in case the clinical trial is started up in a new MS, not originally anticipated during the application process.
In order not to overburden the 'single body' assessing the thousands of clinical trials applied for in a given year, it would make sense to continue to submit the CTA to a NCA for trials only to be performed in a single MS. However, the decision to submit to either body should preferably be optional and at the discretion of the sponsor.

Whichever option is decided on, it should be applicable to all clinical trials performed in the Community, regardless of the type of trial, characteristics of the IMP, or whether IMPs are prescribed on or off label.

Trials initiated in the academic setting are often not straight forward IMP trials. To only improve the situation for certain trials could greatly disadvantage the academic community.

Consultation • 5: "Options addressing the assessments by Ethics Committees" – 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 detail?
Again, a true one-stop shop authorisation process would be very much welcomed. From an academic sponsor's point of view an application to a single body in the Community incorporating approval that covers all NCAs and ethics committees in the various MS would be the most preferred option.

Either way, the implementation of a true 'single' Ethics Committee opinion per MS should be the minimum outcome of a revision of the Clinical Trials Directive. There should also be greater harmonisation across the Community in terms of requirements for documentation submitted for the approval process and the lengths of cover of the approval, which can vary from the whole duration of the clinical trial to an approval valid for one year only (with the requirement to renew the approval annually), which is the case for at least some Ethics Committees in Austria.
Standardisation of the costs of application and substantial amendments to Ethics Committees should also be considered as an outcome of this public consultation, since this is again unclear, difficult to anticipate in advance and far too costly for many academic sponsors. For example, for the same clinical trial indicated above (double blind, placebo controlled), the costs of ethical approval in Germany alone have amounted to € 8'850 in total. The invoices ranged from € 5'200 for assessment from the lead Ethics Committee, with invoices ranging between € 200 and € 1000 for local ethical approval. Similarly, the cost of notification of a substantial amendment to the local German Ethics Committees cost between € 50 and € 500 for the same notification, depending on location.

Consultation • 6: "KEY ISSUE • 2: Inconsistent implementation of the Clinical Trial Directive" – Is this an accurate description of the situation? Can you give other examples?
This is an accurate description of the current situation.
Further clarification on what constitutes a substantial amendment should be considered in order to reduce 'borderline' notifications. Understandably a list of substantial amendment can never incorporate all potential amendments requiring notification; however, an attempt to create a comprehensive list would greatly benefit sponsors. This would reduce the burden not only for academic sponsors (with often limited staff resources) but also for the NCAs and Ethics Committees.

The way the current system is set up inevitably leads to multiple reporting of SUSARs. As an academic sponsor we also notify SUSARS to the Marketing Authorisation holders of the IMP in question, who are then also required to report the same SUSAR to the NCAs and Ethics Committees.
Furthermore, the EudraVigilance database does not allow SUSARs to be reported to the Ethics Committees, which means there are still many individual notifications required. However, even for some NCAs it is not possible to report the SUSAR via the Community Database, and these also require a

'personal' mailing of the event . This un-harmonised reporting system is complicated and very labour intensive.

Consultation • 7: "Weaknesse s" – Is this an accurate description? Can you quan tify the impacts? Are there other examples for consequences?

Certain NCAs have asked us not to report all SUSARs to them, and instead are only interested in receiving SUSARs reported in patients within the same MS (e.g. MHRA). This means that in an international trial the various Ethics Committees involved in the trial receive different safety reports related to the same trial.

Consultation • 8: " Options to address this issue" – 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 future detail? In particular, are the divergent applications really a consequence of transporting national laws, or rather their concrete application on a case -by-case basis?

The option of adopting the text of the CTD in the form of a Regulation would be preferable since it would truly harmonise the requirements and processes across the Community. An amendment of the Directive would continue to result in differences across Member States.

Consultation • 9: " KEY ISSUE • 3: Regulatory framework not always adapted to the practical requirements" – Can you give examples for an insufficient risk -differentiation? How should this be addressed?

Pure 'sampling' trials, where the study fulfils the fir st part of the definition of a non -interventional trial, but not the second part because non -routine blood samples are taken at determined intervals, also fall under the scope of the Clinical Trials Directive. This results in an unnecessary regulatory burd en for a very low risk study, with the result that such trial s become prohibitively complicated and expensive to manage for an academic sponsor. Furthermore, the requirement to have one single sponsor for such low risk studies means that most academic inst itutions are not in a position to sponsor such trial s in rare diseases, where it is often necessary to manage the study across multiple sites and multiple Member States.

Another example are l ate phase clinical trials comparing 2 standard therapies with med icinal products used for many years in the specific patient population or disease in question . Such studies carry a substantially lower risk compared to early phase trials with new products. Such treatment trials are mainly initiated in the academic settin g and become prohibitively expensive to manage under CTD requirements. Again, the fact that a single sponsor must be found if they are multi-site or multi-national means that many such investigator initiated trials can no longer be performed.

Shared sponsorship between academic organisations and institutions should therefore be allowed to facilitate research in the academic sector.

Consultation • 10: "Requirements not always adapted to the practical circumstances" – Do you agree with this description? Can you give other examples?

The issue highlighted is an important one and does indeed impede investigator -initiated trials across the Community due to the reasons described.

Although there is the provision for a sponsor to delegate any or all trial related functions, there is still the need for a single sponsor. In multi-centre and especially multi-national trials it is often not possible for a single academic institution to take on the responsibilities of other institution s. This therefore hinders true collaborations within the academic sector. As a consequence patients could be deprived of improved treatment options in orphan diseases or othe r areas where there is limited interest of the pharmaceutical industry to invest in.

Consultation • 11: "Review of existing implementing guidelines" – Can a revision of guidelines address this problem in a satisfactory way ? Which guidelines would need r evision, and in what sense, in order to address this problem?

The existing guidelines are very useful in advising on specific aspects of managing clinical trials . Revision of the guidelines could be an interim step on the path of improving the shortcomings of the Clinical Trial Directive.

Consultation • 12: "Review of the existing Directive and adaption of the requirements to practical necessities" – In what areas would amendment of the Clinical Trials Directive be required in order to address the issue It this was addressed, can the impact s be described and quantified?

Section (11): 'implicit' authorisation reduces the communication burden of the regulatory authorities but is unsatisfactory from the sponsor's point of view in the sense of a document trail in the Trial Master File. NCAs should always provide a written reply in response to applications and notifications . This could be achieved with via email or fax and does not necessarily have to be a formal letter .

Section (14): standard patient therapy, and therefore also clinic al trials conducted within the field of haematology or oncology regularly administer medicinal products that are prescribed off -label but have been used efficacious and safely in this patient population for up to decades. Simplified labelling requirements should be allowed for or such well established medicinal products.

Article 2 (c): the definition of 'non -interventional trial' should be broadened, especially with regards to the last sentence, referring to " No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data ", to avoid conflicting interpretation of what constitutes a 'non -investigational trial' across the Community.

Article 2 (k): there should be a clear d ifferentiation made between a lead and local Ethics Committee in this definition . An amendment to the Directive should also lay out the different responsibilities of the two committees.

Article 6.2.: the notion of a single ethics opinion in a given MS sho uld be reinforced and truly implemented.

Article 4: to establish a higher level of harmonisation across the Community there should be a clear definition as to the matters/documentation reviewed by either the Ethics Committee or the NCA.

Article 7: the notion of a single ethics opinion in a given MS should be reinforced and truly implemented.

Article 10 (a): there is a need for more detailed description of what constitutes a substantial amendment to avoid notification of borderline cases. At the same tim e it should be better defined which kind of substantial amendments require approval or notification from the Ethics Committees and/or the NCAs.
Like the Ethics Committees, the NCAs should also notify the sponsor in writing of their acceptance of amendments submitted to them and issue a notification of receipt for those not requiring approval.

Article 10 (c): a differentiation as to various reasons why a clinical trial is terminated early would be greatly welcomed by academic sponsors. If a trial is closed due to, for example, unexpectedly high toxicity, then the short notification period of 15 days is justified. However, if a trial is closed due to, for example, recruitment failure a prolonged notification period of 30 days would greatly facilitate trials managed with little staff resources.

Article 14: In haematology/oncology patients it is not uncommon for medicinal products to be prescribed off-label, with treating physicians nevertheless having many years of experience in using these products in their patients. One such example is Thymoglobuline, which has Marketing Authorisation in solid organ transplantation, but is also commonly used for conditioning in patients receiving haematopoietic stem cell transplantation . If a clinical trial uses such a product from commercial stock, i.e. from the usual pharmacy resources, and it is prescribed in the same manner as in the normal clinical setting , then there should also be a provision for less stringent requirements for labelling for these products.

Article 15.5: there should be a provision for a more simplified Trial Master File in certain types of studies, and in particular those of low risk. For example, the requirement to collect normal laboratory values from each study site for blood tests that are routi nely performed in standard clinical practice should be removed.
Similarly, there should only be the requirement to collect the curriculum vitae from the principal investigator (PI) at a site, and not also from sub -investigators. It should be the responsib ility of the PI to ensure his sub-investigators have the necessary background and training to assist him in the trial duties. Arguably it is the responsibility of the institution where the investigator is employed to ensure they have a suitable background to be able to participate in a clinical trial. This could be confirmed in a clinical trial agreement between the sponsor and the host institution of the principal investigator.

Article 17.1(a): there should be provision to report SUSARs to a single database, accessible by both NCAs (and all NCAs at that) as well as Ethics Committees. In the best case scenario such a database should also be accessible to investigators, so that the sponsor could refer all relevant stakeholders to the particular posting on the database.

Article 19: the text should be amended from "medicinal products…shall be made available free of charge by the sponsor" to "medicinal products…shall be made available free of charge to the patient". This change would especially benefit academic sponsor by allowing the use of commercial stock (paid for by the participating institution or the patient's insurer) without the prohibitive cost of having to provide the medicinal product. This is especially pertinent in clinical trials where compatible patients not on the trial receive the exact same medicinal product in the standard care setting.

Consultation • 13: "Review of the existing Directive and excluding clinical trials of "academic" sponsors from the scope of the Directive" - Would you agree to this option and if so what would be the impact?

For multi-national trials the exclusion of academic sponsors from the rules of the Clinical Trials Directive would be counter-productive. It is widely acknowledged that the implementation of the Clinical Trials Directive has lead to some degree of harmonisation, and it is anticipated amongst the different stakeholders that the review of the Directive will lead to even greater compatibility across the Community. To be excluded from the advantages that this harmonisation has brought (and will bring) would be a step backwards for the academic sector.

Rather than creating different rules and regulations according to type of sponsor (pharmaceutical versus academia, or national versus international) clinical trials should be regulated according to a risk adapted approach.

Another reason why the scope of rules should remain the same for all types of sponsors is to avoid the risk dual standards of clinical trial management between different types of sponsor.

Although rare, the academic sector should not be prevented from sponsoring clinical trials where the results could be used in an application for marketing authorisation.

Consultation • 14: "KEY ISSUE • 4: Adaption to peculiarities in trial participants and trial design" – In terms of clinical trial regulation, what option could be considered in order to promote clinical research for paediatric medicines, while safeguarding the safety of the clinical trial participants?

Implementation of Regulations EC 141/2000 and EC 1901/2006 provide positive steps towards encouraging clinical research in the paediatric population. Nevertheless, the pharmaceutical industry is commonly unwilling to develop medicinal products where the costs for research and development will not be covered by expected sales revenue. Furthermore, investigator-initiated trials are designed to be of high scientific relevance but often with little potential economic benefit. The cost of clinical research is therefore a stumbling block for initiating trials in this population. One way to promote research in

paediatrics would be to create new funding opportunities, for example through possibilities for specific grants through the European Union or its Member States.

Consultation • 15: "Emergency clinical trials" – 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 favourable in view of past experiences?
(No experience in clinical trials in an emergency setting)

Consultation • 16: "KEY ISSUE • 5: Ensuring compliance with GCP in clinical trials performed in third countries" – Please comment? Do you have additional information, including quantitative information and data?

Consultation • 17: "Options to address the weaknesses" – What other options could be considered, taking into account the legal and practical limitations?
Generally the strengthening of international cooperation to align GCP requirements is a positive step forwards. Similarly, strengthened capacity-building should always be encouraged.
Although 'self-regulation' is welcomed by those concerned and also less complicated to oversee, it does have the potential for sub-standard clinical research, and would therefore not fully address the concerns highlighted with regards to patient protection.

All clinical trials sponsored by a sponsor based in the Community should be registered in the EudraCT database to ensure greater transparency.

The publication of cases of non-compliance with GCP requirements following inspection would be welcomed. However, cases should only ever be published anonymously. Nevertheless, if the findings are so severe that an individual physician is struck off or an institution is banned from performing future clinical research, there should be a list where these persons/institutions are named for potential future sponsors to protect themselves.

Consultation • 18: What other aspect 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?