



Federation of the European Academies of Medicine

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FEAM Response to Consultation on Functioning of the Clinical Trials Directive

Consultation item 1: Introduction to achievements and concerns

In a Statement published in 2004¹, the Federation of European Academies of Medicine (FEAM) welcomed the potential benefits for multinational collaboration in clinical research that could result from the Clinical Trials Directive (CTD) but raised concerns about the inflexible application to academic, non-commercial trials.

To a significant extent, these initial concerns have been substantiated and a negative impact has been compounded by variable implementation of the CTD by Member States, leading to inconsistencies in practice. The CTD has not solved the problems it was designed to do, **but has dramatically increased administrative burden and costs for academia**, resulting in a deterrent effect on new clinical research. Clinical trials are essential in the development of medicines to address hitherto unmet societal needs and are also a vital part of improving current medical care. But in consequence of the CTD, the EU has become a less attractive location for such research.

We welcome this Consultation initiated by DG Enterprise and our answers are based on recent discussions organised by the Academies (members of the Working Group and Academies responsible for reviewing the response are listed in Appendix 1). With regard to the specific questions posed in Consultation item 1, we are not aware of evidence indicating a systematic improvement in patient protection as a consequence of the CTD nor are we aware of any quantifiable evidence to document the claim that the CTD has resulted in important improvements in the ethical soundness of review across the EU. The European Commission could support future discussions by collecting and validating such evidence. In addition, updating the evidence base to document the negative impact of the CTD will be of great importance. The net impact on the number of clinical trials varies between different Member States, according to the data

¹ “Recommendations to the European Commission on the clinical trials directive”, www.feam.eu.com

collected by ICREL² with a slight overall decrease of investigat or-initiated trials. The markedly negative experience in the UK may not initially have been shared by other countries. But there is reason to believe that a negative impact is now also being seen more widely in the EU for commercial trials (latest data in Eudract database) and the experiences described by individual researchers suggest that the problem for non-commercial trials is also worsening. Thus our response to this Consultation is prepared at a time when there is rising concern in the clinical academic research sector³.

Our main message is that there must be **urgent** reform of the CTD legislation together with early clarification of definitions and guidance. We make some specific suggestions in the responses to the Consultation items but we also take this opportunity to emphasise some guiding principles for the regulation of clinical research. It is essential that changes to the framework for clinical trial regulation conform to these principles:

- Clinical research must be recognised as an essential component of high quality health care systems .
- The effective management of safety is critically important and a right balance must be achieved between protecting research participants, ensuring reliability of data and supporting the development of new or improved health care.
- The regulatory supervision of a clinical study should be proportionate to the risks to the participant.
- The roles, responsibilities and support mechanisms for sponsors, researchers, ethical reviewers and national competent authorities (NCAs) must be clarified to ensure coherence and consistency in practice.
- Reforms should aim to reduce administrative burden and costs for researchers, streamline processes and avoid duplicate review by allocating responsibility for review to the most experienced and capable organisations.

² Report of project “Impact on Clinical Research of European Legislation” December 2008 on www.efgcp.be/downloads/icrel_docs/Final_report_ICREL.pdf.

³ Typical concerns arising from research experience in academia are described in the following literature; many but by no means all come from the UK: AD McMahon et al, The unintended consequences of clinical trials regulation, PLoS Medicine 2009 3 (11) doi: 10.1371/journal.pmed. 1000131; P O’Donnell, Disharmony stifling research in Europe, Applied Clinical Trials online 2009 August 1, <http://appliedclinicaltrialsonline> ; A Burton, Special report: Is paperwork suffocating British clinical research? Lancet Oncology 2009 10 749 -750; A Gulland, Number of clinical trials done in UK fell by two thirds after EU directive, BMJ 2009 doi: 10.1136/bmj. b1052; L Duley et al, Specific barriers to the conduct of randomized trials, Clinical Trials 2008 5 40 -48; A Hemminki & P-L Kellokumpu-Lehtinen, Harmful impact of EU clinical trials directive, BMJ 2006 332 501 -502; CD Hanning & P Rentowl, Harmful impact of EU clinical trials directive. Trial of alerting drug in fibromyalgia has had to be abandoned, BMJ 2006 332 666; M Watson, Harmful impact of EU clinical trials directive ...and so has trial of melatonin in cancer related weight loss, BMJ 2006 332 666; CD Mitchell, Harmful impact of EU clinical trials directive... while paediatric oncology is being scuppered, BMJ 2006 332 666

Consultation item 2: Multiple and divergent assessments: National Competent Authorities and Ethics Committees

We agree that there are current problems arising from the multiple assessments incurred. We provide more detail on these points in subsequent Consultation items. One of the most important issues to resolve is whether it will be possible to devise a system for a single CTA (Consultation item 4) and, in attempting to resolve this issue, we commend the work of the Road Map Initiative⁴. In the time available for FEAM to develop a response to the Consultation, it has not been possible to reach definitive conclusions on how the present situation can best be reformed but we suggest that the European Commission should support further discussion based on the outputs from the “Single CTA workshop⁵” and the other ongoing activities of the Road Map Initiative.

In our view, any new system must be flexible in orientation so that a sponsor can choose what is most appropriate for the trial – either following the existing arrangements or applying through a centralised process (whether based on mutual recognition or full harmonisation) but, in either case, subject to the other improvements proposed in our responses to subsequent Consultation items. It is also very important to ensure that any changes to the processes for multinational trials do not, inadvertently, increase the burden on trials organised within a single Member State.

Consultation item 3: Costs, inconsistencies and inefficiencies

We agree that there have been major adverse impacts since the introduction of the CTD in terms of increasing administrative costs for clinical trials and lengthening delays before recruiting patients, as quantified in the ICREL report. Because these impacts have been felt in most Member States, we conclude that they are a direct consequence of the CTD itself relating, for example, to the requested double approval, IMPD and safety reporting requirements as well as partly attributable to variable Member State implementation approaches.

We are aware that some Member States do not use their resources efficiently insofar as they impose multiple assessments of protocols that may lead to contradictory as well as burdensome implications for researchers. In some Member States, there are multiple assessments of a single study by different Ethical Committees and other (governmental/hospital) organisations, who may ask for different information and provide different advice. These Member States could use resources more efficiently by simplifying and minimising their demands for duplicate review.

⁴ “A Road Map Initiative for Clinical Research in Europe”, October 2008, www.efgcp.be

⁵ A multidisciplinary workshop on “A single CTA in multinational clinical trials – dream or option?” was held in July 2009 and the report has been published on www.efgcp.be

Variability in Member State insurance arrangements is also a particular problem. This variability is associated with increased bureaucracy and costs without a beneficial impact on quality of science or safety. We suggest that the community should aim for consistent insurance conditions throughout a multinational trial. One way forward to resolve this issue, as proposed by the European Science Foundation (ESF)⁶ would be to constitute a multinational task force of experts with a mandate to advise on how to harmonise insurance requirements. Among the possible options for change could be the creation of a not-for-profit insurance organisation for clinical trials and exploration of the feasibility to insure studies through the national public health systems in all Member States; but it is vital not to introduce further unnecessary bureaucracy .

Other variabilities in Member State interpretation and definitions, for example of sponsor and types of trial included within the scope of the CTD, also cause inefficiencies and complexities in operationalising trials. There is need to clarify key definitions (see subsequent Consultation items).

Consultation item 4: Options for streamlining assessment by the National Competent Authority

A system of voluntary cooperation (VHP) as described in the Consultation would be valuable if comprehensive. This may be difficult to institute in practice as we note that some Member States are already opting out, but it is worthwhile continuing to explore feasibility. The system could be improved in two ways: (a) Reducing the number of requested reviewers to avoid duplication of effort in all Member States who are involved. Mutual recognition of the review would have to be ensured; (b) Acceptance of the same submission dossier by all Member States to avoid the need for individualisation of the subsequent national submission dossiers.

Some in the FEAM Working Group tend to favour a graded system where researchers in a single or national multi-centre study centre would apply, as now, to their NCA. A sponsor in an international multi-centre study could proceed as with the current practice or choose a new, centralised procedure (see also response to Consultation item 2). In the first instance, the option to specify the centralised route might be piloted in selected therapeutic areas, perhaps those requiring particularly complex scientific expertise .

However, some members of the FEAM Working Group would like to move directly to option 3.3.2.1(a), “common agreement” proposed in the Consultation document. However, this is not a view supported by all FEAM members. Other members of the Working Group want to see the new option(s) piloted first.

⁶ Report from European Science Foundation, 2009 “Forward Look. Investigator -driven clinical trials”, on www.esf.org

Therefore, we advise that it is a matter for subsequent discussion as to whether and, if so, when, a formalised new model for multinational trials should replace rather than work alongside the present system. There would need to be good justification for allowing multiple options to continue indefinitely. A key issue for the research community will be the timeliness of NCAs to respond and feed into the common agreement process.

What needs to be achieved in any community-wide streamlining process is that the responsible bodies must appoint rapporteurs on the criterion of appropriate expertise rather than seeking to achieve geographical balance in distribution of tasks. Both the ESF report and Road Map Initiative provide further guidance on what is needed if streamlined assessment is to succeed and we recommend that the European Commission, together with experienced organisations such as EORTC and its partners in the Road Map initiative, facilitates further discussion based on these analyses. FEAM and its member Academies are very willing to participate in this further discussion.

Consultation item 5: New options for assessment by Ethics Committee

We agree that the roles and responsibilities of the Ethics Committees should be clarified and that there should be better coordination between them and NCAs (paragraph 3.4.3 in the Consultation). Ethical review should proceed in parallel with regulatory review, but this is not currently the case in some Member States. We believe that the alignment of information reviewed by the Competent Authorities and Ethics Committees will drive other improvements and enable technology-driven review. This will then increase the likelihood, in the longer-term of moving to consider the option of one EU Ethics Committee approval with opt out/opt in at the country level.

We doubt that it will be easy to strengthen networks of national or even establish functioning pan-European Ethics Committees (paragraph 3.4.2) as there is little present basis for doing this and there is still considerable variation in practice among the Member States⁷.

FEAM members hold differing views on whether it will soon be possible or desirable to create a system where there is single Ethics Committee assessment for multi-national trials. We do all agree, however, that benefits would come from greater consistency across Europe and that better organisation and accreditation of Ethics Committees within each Member State is an important first step. A good case can also be made for Member States developing centralised Ethics Committees with more expertise, necessary to provide the robust review of more complex trials using advanced therapies (such as gene therapy, stem cell-based therapies, device-therapeutic combinations, clinicogenomic studies in cancer). In

⁷ For example, current variation is documented in: AA Schnitzbaer et al, Procedures for ethical review for clinical trials within the EU, *BMJ* 2009 338b1893; R Hernandez et al, Harmonisation of ethics committees practice in 10 European countries, *J Med Ethics* 2009 35 696 -700

one scenario these centralised Ethics committees, with demonstrable expertise might then be allowed to take a lead in a pan-European review of multi-national study protocols, but accompanied by national ethics review of the local issues - that is the investigator, site and information for patients - for each participating Member State.

However, there are differences between Member States in ethical views on fundamental research areas, for example, embryonic and stem cell research, and any unifying system will need to take account of these differences. We advise that there is need for further discussion and, as a first step, the European Commission should work with its partners from the scientific community to lay out the options for change – or for retaining individual country ethical inputs into multinational studies.

Consultation item 6: Inconsistent implementation of the Directive: Substantial Amendments, Suspected Unexpected Serious Adverse Reactions (SUSARS) and scope

We share the concern based on evidence compiled by ICREL about the practical problems associated with the increasing number of Substantial Amendments and SUSARS.

Substantial Amendments We agree that there must be much more clarity in definition and interpretation between countries but we advise that this is accompanied by a re-assessment and an extensive reduction of what is submitted as an amendment for approval so as to focus on what is truly a substantial change. The sponsor's responsibility to judge what is truly substantial for the protection of study participants should be strengthened. We welcome current efforts by the European Commission to increase clarity.

SUSARS We do not believe that the current situation – increasing numbers of SUSARS and variability between Member States – helps to improve patient safety. There is a false sense of security in maintaining the current system. We recommend that a common definition is used in all countries but, even more importantly, that a system is created where the SUSAR is entered by the sponsor directly into EudraVigilance with a copy to one responsible body (together with the study coordinator/Principal Investigator) to act on SUSAR alerts, cascading the information to others, as appropriate. This means that in a multinational trial, one NCA (e.g. the sponsor's country) should be given the responsibility to act for all Member States, irrespective of the location of the SUSAR, instead of the present system where the NCA generally sees its role as only applicable to its own Member State. To be successful, this increased responsibility must be accompanied by better capacity for safety signal detection. Moreover, in the present system, SUSARS are reported to Ethics Committees, who do not act on this information. It would be better for the Ethics Committees to receive only the

annual safety report and be aware that the NCA is discharging its responsibility to act on SUSARS. While some FEAM Working Group participants advise that the other investigators in the trial also should only receive annual safety reports, other participants emphasised that each investigator is an important conduit to the patient, highly relevant for example if side effects influence the willingness of the patient to continue in the trial.

There is a particular issue for EU-US collaborative studies because the USA does not usually adopt the SUSARS format. We suggest that there should be further discussion as to whether it might be better for the EU to return to the previous approach based on Serious Adverse Events.

Scope of the Directive

In the short term, it is very important to clarify the scope of the CTD, for example to agree the definition of “non-interventional study”, together with more consistent application of guidance relating to what is covered. We recommend that there is also further discussion of the longer-term options for changing the scope of the CTD. Already, national law in some Member States has implemented the CTD with a scope broader than trials with medicinal products only, but there is still often lack of clarity in these cases. Furthermore, in some Member States in consequence of the CTD excluding Competent Authorities from reviewing some categories of research, Ethics Committees take on a lot of responsibility for reviewing non-drug trials, for which they are not qualified.

Some FEAM members propose that the CTD scope should be widened to cover **all** other clinical research, such as surgical research, to deliver adequate and equivalent protection to all participants, based on common ethical principles, in any clinical research conducted in the EU. However, such a change would increase the burden on the clinical academic community unless reform to introduce the risk-based approach (Consultation item 9) was first introduced.

We note that the transfer of responsibility for pharmaceutical policy from DG Enterprise to DG Sanco is likely to stimulate further discussion of the governance requirements of all clinical research. It is very important that the clinical academic community is involved in these discussions and FEAM stands ready to support DG Sanco in its new responsibilities. We advise that the pre-requisite for any discussions on the options for extending the scope of the CTD is the adoption of a coherent risk-based approach to provide a rational and proportionate system to define and manage risks for all clinical research.

Consultation item 7: Other weaknesses arising from inconsistent implementation of the Directive

As noted in the previous Consultation item, we agree that the unnecessary burdens on researchers dictated by excessive Substantial Amendments and SUSAR reporting do not improve patient safety. In fact safety outcome may be undermined because the committees that assess the reports are overloaded with reportable data. Safety is further undermined because one consequence of the increasing costs of applications for academics and smaller companies (evidence presented in ICREL report) is a limitation on affordable trial size and, hence, the study power and ability to detect side effects.

Consultation item 8: Legislative options for reform of the Directive

There is no substitute for a full review of the CTD . Lesser options run the risk of returning to a scenario where there is no harmonisation, core process or common documentation. In our view, there must be both short-term action, in modifying guidelines to improve the current environment as far as is possible, together with changes to the CTD to ensure long-term sustainability of an improved system. For revision of guidelines to be effective in the short term, we consider that there is a major concomitant responsibility for those Member States who are most experienced in clinical research to provide leadership to ensure the supportive environment for trials. This has implications for availability of resources and for legislation in some Member States .

In the time available for responding to this Consultation, the FEAM Working group did not come to consensus on whether there should be a Regulation to govern changes. As we have detailed elsewhere in this response, there are a lot of changes that need to be agreed – in particular, on a risk-based approach, SUSAR reporting, ethics review and single CTA procedures – before we could be confident that a Regulation might be one option to consider. Where we are agreed is that the procedures for reforming the CTD, whether or not this involves a Regulation, need to be expedited. We ask that the European Commission now facilitates regular meetings on the key issues to be addressed and involves the European Parliament at the earliest opportunity. FEAM reiterates its willingness to be involved and we anticipate that the newly acquired responsibility of DG Sanco for pharmaceutical policy will facilitate these discussions.

Consultation item 9: Differentiating risk within the regulatory framework

We agree that in the current system the requirements are not commensurate with the expected risks. **This weakness is central to the current problems.** We strongly recommend a more differentiated system in terms of risk. The strategic outline of risk categories produced by ESF (see footnote 6) is one starting point but we advise that further discussion is needed to clarify the options for developing a risk-based approach and the criteria to be used in establishing a system that is flexible enough to accommodate different types of research.

We advise that there must be a focus on benefit-risk rather than safety alone. Elucidation of risk categories requires much more analysis and sharing of perspectives and we recommend that the European Commission stimulate further discussion on the nature of the risk involved in different types of study and on the implications for risk-based governance of research. In particular, to determine what would be the consequences for a research study in terms of ethical review, intensity of monitoring, safety reporting, insurance requirements, quality assurance and other issues for study medication provision, commensurate with its assessed risk.

We suggest that studies viewed as minimum risk would require only Ethics Committee oversight (assuming that Ethics Committees are standardised and accredited as described previously).

We reiterate that it is essential that a risk-based approach is agreed and adopted before any options for extending the scope of the CTD can be contemplated, but there is a clear need, for example, to consider how the management of cancer involving surgery and radiation therapy can be included within a coherent risk-based system together with chemotherapy.

Consultation item 10: Practical issues for sponsorship

While there had been initial concern expressed from the academic sector about the challenges inherent in acting as a single sponsor for a multinational study, it now seems that the problems may not be so formidable⁸.

Nonetheless, we urge that there should be a flexible system which permits multiple (co-) sponsors: the UK has already interpreted the CTD to achieve this situation. We recommend that a multi-sponsor system should be based not on nationality but on functionality, that is involving different sponsors, where appropriate, for functions such as protocol construction and data collection. It is also important to clarify sponsorship under conditions where the funder of the trial is different from the operational management: it should be made very clear that the sponsor should have operational management responsibility which includes ensuring adequate funding for the trial from whatever source. Instituting a multi-sponsor system requires clear definition and agreement of responsibilities, defined in a contract and recognising that there will always be joint liability. It would be helpful to have available a standard EU contract template for co-sponsored trials.

At the same time, it is necessary to build academic capacity to act as a sponsor – this has implications for researcher education, training and funding (see Consultation item 18). The ESF report offers detailed suggestions for what kind of support should be provided to academic institutions who act as sponsors.

⁸ Roadmap Initiative multidisciplinary workshop on “Innovative approaches to clinical trial co-sponsorship in the EU” was held in September 2009 and the report has now been published on www.efgcp.be

Consultation items 11 and 12: Options for reviewing guidelines and amending the Directive

As discussed in previous Consultation items we agree that it is important both to review the implementing guidelines, to provide advice on how the current directive can be applied, and **reform the CTD** itself. Clear guidelines with definitions and examples would enable NCAs, first, to determine whether a trial is covered by the CTD and, secondly, to ensure that requirements are proportionate to the risk involved. Guideline review must take into account the need to make them sufficiently compelling so as to enable similar practice within a short period of time in all Member States, even if this requires changes to national legislation and ordinances. All reform must be consistent with the basic principles stated in our answer to Consultation item 1 and incorporate the necessary changes outlined in previous sections. To summarise – this requires harmonisation of key definitions, exploration of single CTA, progress towards unifying ethics review, expedited SUSAR reporting, simplification of Substantial Amendments and risk-based requirements for study review.

Consultation item 13: Option for excluding academic sponsors from the scope of the Directive

We do not agree that academic sponsors should be excluded from the scope of the CTD. There must be one conceptual framework, one standard of uniform quality for patient protection. In practice, we expect that many academic studies will be treated as low risk in the risk-based continuum (Consultation item 9).

Consultation items 14 and 15: Adaptation to special requirements of trial participants and design

Paediatrics research FEAM strongly supports the encouragement of good quality paediatric research and such encouragement is more likely if it is not automatically assumed that the research will fall into the higher risk category (consultation item 9). In addition, however, support for paediatric research requires public funding and the EU could learn from the initiatives of the NIH in the USA and the Programme Priority Medicine for Children in the Netherlands to encourage this area.

Emergency research Similarly, FEAM supports good quality research in emergency situations and we recommend the development of guidelines to incorporate the current best practice that allows research in defined circumstances with request for patient consent subsequently as soon as practically possible. There is one particular point that needs to be clarified – whether or not study-related data must be withdrawn if the subject does not

consent subsequently (this may have implications for the Data Protection Directive).

Other particular research designs FEAM members noted two other clinical areas where research is difficult in some Member States. First, research using radioactivity (for example, imaging studies) – where there are accepted international norms which need to be taken into account by all Member States. Secondly, research using controlled drugs, where we recommend that conditions (including insurance requirements) across the EU should be harmonised according to current best practice .

Consultation items 16 and 17: Compliance with GCP in clinical trials performed in third countries

We do not have much advice at this stage. We agree that, in principle, such research should follow the same quality criteria although consent may need to be sought according to local cultural conditions. All research must conform to the principles of GCP and other international standards which ensure rights, safety and the wellbeing of subjects and the integrity of data.

Consultation item 18: Other aspects

In our view, the challenges facing Small and Medium Enterprises (SMEs) are similar in many respects to those faced by the academic sector and the adoption of a risk-based approach would be helpful for all. The academic sector perceives companies, large and small, as partners in clinical trials and we ask that reform of the CTD does not inadvertently constrain new models of collaboration.

As we observed previously, in building the supportive environment for clinical research in the EU, it is necessary for public policy -makers to do more than reform the existing legislation, highly important though that is. It is also vital at both EU and national levels to increase funding for clinical research and its infrastructure, to explore opportunities for joint programming and to combine research funding with proper education and training. For example, we suggest that the scope of the European Research Council might be extended to include translational and clinical research. Creating a strategy for an improved environment requires further discussion across several Directorates -General.

It is also important, building on the proposal in the FEAM 2004 Statement , to develop integrated clinical trial databases that register all research, not just commercial studies involving IMPs. However, there are now several databases that require clinical trial registration and we ask the European Commission to take a lead in instituting global discussion to rationalise the reporting. Furthermore, databases should also, in due course, provide the results from trials for access and use by all researchers , but it should be appreciated that the

results from long, complex studies may take a number of years to complete. It should also be taken into account that academic research data may have economic value subsequently for companies (including SMEs that spin out from the academic research group); it is important for access and data protection issues to be considered further when designing databases to contain research results.

Brussels, 7 January 2010

Appendix 1: FEAM Working Group members and Academy discussants and reviewers

Prof. Hubert E. Blum (Germany), President of FEAM and member of the Presidium of the Deutsche Akademie der Naturforscher Leopoldina

Prof. Gilles Bouvenot (France), Fellow of the Académie Nationale de Médecine

Dr. Marisa De Rosa (Italy), CINECA, for the Accademia Nazionale di Medicina (Genova)

Prof. E.G. E. de Vries (The Netherlands), Fellow of the Royal Netherlands Academy of Arts and Sciences

Prof. János Frühling (Belgium), General Secretary of FEAM and Secrétaire perpétuel of the Académie Royale de Médecine de Belgique

Prof. Cyril Höschl (Czech Republic), Past President of FEAM and President of the Czech Medical Academy

Prof. Dermot Kelleher (United Kingdom), Fellow of the UK Academy of Medical Sciences – in collaboration with Dr. Mary Melody (Irish Clinical Research Infrastructure Network) and Dr. Michael Barry (Trinity College Dublin)

Prof. João Lobo Antunes (Portugal), President of the Academia portuguesa da Medicina

Prof. Françoise Meunier (Belgium), Fellow of the Académie Royale de Médecine de Belgique and General Director of the European Organisation for Research and Treatment of Cancer

Prof. Jaromír Švestka (Czech Republic), Fellow of the Czech Academy of Medicine

Prof. Volker ter Meulen (Germany), President of the Deutsche Akademie der Naturforscher Leopoldina

Prof. J. W. M. van der Meer (The Netherlands), Fellow of the Royal Netherlands Academy of Arts and Sciences

Prof. Dragos Vinereanu (Romania), Fellow of the Academia de Stiinte Medicale din Romania

Other projects

Dr. Ingrid Klingmann, EFGCP Representative "Roadmap Initiative for Clinical Research in Europe"

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Dr. Robin Fears