FEAM submission to the 2011 European Commission concept paper: revision of the 'Clinical Trials Directive' 2001/20/EC

In a Statement published in August 2010, the Federation of European Academies of Medicine (FEAM) provided an Academic Perspective on the opportunities and challenges for reforming the EU Clinical Trials Directive[1].

This submission includes the summary from that Statement, followed by extracts that relate to key issues raised in the 2011 European Commission concept paper (SANCO/C/8/PB/SF D(2011)).

Summary

The introduction of the Clinical Trials Directive (CTD), intended to harmonise authorisation of EU Clinical Trials on medicinal products and to improve the collection of reliable data, has been controversial. While increased support for multi-national collaboration is very important, the CTD has dramatically increased the administrative burden and costs for academia and has deterred academic clinical research.

There must be urgent reform of CTD legislation together with clarification of definitions and guidance. FEAM advises particular attention should be devoted to the following points:

- The majority of clinical trials are currently based within a single Member State. These must not be subjected to additional bureaucratic burden and costs in consequence of future reform to the authorisation of multi-national studies.
- More streamlined assessment of multi-national studies is essential. The options for voluntary cooperation in assessment between national competent authorities (NCAs) must be thoroughly evaluated. If voluntary cooperation is found to be insufficient, our preferred approach is the "common agreement" whereby a designated lead NCA reviews and approves the trial with other NCAs providing

[1] Federation of the European Academies of Medicine (2010). "Opportunities and challenges for reforming the EU Clinical Trials Directive: an Academic Perspective. http://www.feam.eu.com/docs/FEAMctdstatementaugust2010.pdf

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expedited approval for their country. The creation of new, centralised, assessment bodies should be avoided.

- The function of national Ethics Committees must also be streamlined to improve their efficacy and their working towards common approaches. FEAM advises that the creation of a system where there is a single Ethics Committee assessment of multi-national trials is not feasible or desirable in the foreseeable future. But there is a lot to be done now to introduce standardised procedures, training and accreditation in Ethics Committees across the EU.
- FEAM recommends the introduction of a more differentiated assessment system, based on classification of trial risk-benefit. The appropriate classification of studies according to risk and the implications (in particular, in terms of ethical review, monitoring, safety reporting, drug labelling and insurance) requires much more discussion. It is vital that a proportionate, risk-based, approach is agreed and implemented successfully before there is further consideration of extending the scope of the CTD. We advise those who would like to extend the scope that there are many types of clinical research and it is important to retain this flexibility in research design when thinking about the implications of extending the scope of the CTD.
- There are a number of other current problems in the operation of the CTD arising from lack of clear definition, inconsistencies in implementation and, in some cases, weaknesses in the infrastructure for clinical research. Among the main issues that need to be addressed are: (a) Submission of Substantial Amendments – clarification and simplification to focus on what is truly important; (b) Reporting of Suspected Unexpected Serious Adverse Events – creation of a system where key information is acted upon by a responsible body, requiring clarity in assignment of roles but also better methods for safety signal detection; (c) Insurance – development of consistent risk-based insurance systems across the EU; (d) Sponsorship – clarification of options for multiple sponsorship or delegation of responsibilities.
- The further improvement of the clinical trial framework must take account of the needs of special research populations. These include those involved in studies in paediatrics, emergency situations, mental health disorders, and when using radioactivity or controlled drugs.
- Creating a strategy for improving the EU clinical research environment requires much more than reform of the CTD. FEAM recommends that policy-makers also prioritise action to: (a) Increase funding for academic clinical research and its infrastructure; (b) Identify and implement new approaches to multi-disciplinary research and to partnership between academia and industry; (c) Support clinical research training, career pathways and mobility between the sectors; (d) Develop integrated clinical research databases to register all research and, in due course, document research outputs; (e) Ensure that the clinical academic community has early awareness of impending EU policy developments.

FEAM does not ask for a Regulation to govern the changes detailed elsewhere in this Statement. But to expedite CTD reform, we do ask that the European Commission now

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organises 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. While we seek CTD revision as soon as possible, it is vital to introduce well-conceived and relevant changes so we acknowledge that significant further debate is needed.

Key issues in the 2011 Concept Paper

Cooperation in assessing and following up applications for clinical trials

Approximately 70% of clinical trials are currently based within a single Member State. It is vital that any changes to the processes for regulatory or ethical review for multinational trials do not, inadvertently, increase the burden on trials organised within a single Member State.

FEAM fully supports streamlining of the assessment process for multi-national trials. The current system of voluntary cooperation (VHP) would be valuable if it could be 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.
FEAM recommends that the creation of a new centralised assessment body should be avoided. Our preferred option is the formalised "common agreement" whereby a designated lead NCA reviews and approves the project (usually the NCA in the country of origin of the trial) while other NCAs provide expedited approval. If, in the longer term, there are pressures for a wholly centralised route for a multi-national study, then this option should be rigorously piloted in selected therapeutic areas, perhaps those requiring particularly complex scientific expertise, and taking into account current best practice from individual Member States.
FEAM also supports the streamlining of the function of national Ethics Committees to improve their efficiency and to work towards common approaches. The roles and responsibilities of the Ethics Committees should be clarified and there should be better coordination between them and NCAs. 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.

Better adaption to practical requirements and a more harmonised risk-adapted approach to the procedural aspects of clinical trials.

Limiting the scope of the Clinical Trials Directive

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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. It is crucial to retain academic sponsors within the scope of the CTD. There must be one conceptual framework, one standard of uniform quality for patient protection.

We acknowledge that some are also calling for 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. However, any increase in formal scope of the Directive can only be contemplated after reform of the CTD is agreed and successfully implemented to introduce a proportionate, risk-based approach. We advise those who are thinking about extending the scope that there are many different types of clinical research and there is need for much further discussion about the implications for that research. It is important to retain flexibility in research if any proposals were to be made to expand the scope of the CTD.

More precise and risk-adapted rules for the content of the application dossier and for safety reporting

In the current system the requirements set by the CTD 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, although we recognise the difficulty in agreeing a robust classification of risk. The strategic outline of risk categories in interventional studies has been produced by ESF and by the Road Map Initiative. For example, the Road Map Initiative proposes a framework of categories based on marketing authorisation status although the boundaries are debatable and marketing authorisation can be regarded as a surrogate marker for the amount of quality data available on the intervention. In addition to the further work needed to define the level of intervention associated with each risk category, it is important to be clear on who proposes the risk level for a new study (assumed to be the sponsor) and who validates this assignment (assumed to be NCA or Ethics Committee). 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 also 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.

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The regulatory burden on low-risk trials must be decreased. 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), for example, where the risk involved is similar to that of "usual care".

Other variations in Member State interpretation and definitions also cause inefficiencies and complexities in operationalising trials. Two significant operational difficulties relate to the processes for making Substantial Amendments and for reporting SUSARS (Suspected Unexpected Serious Adverse Reaction):

- **Substantial Amendments:** There must be much more clarity in definition and interpretation between countries but this must also be accompanied by a re-assessment and an extensive reduction to 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 clarity2.

- **SUSARs:** We do not believe that the current complex situation – characterised by variability between Member States in definition and reporting – helps to improve patient safety. We recommend that a common definition of SUSARS is used in all countries but, even more importantly, that a system is created where the SUSAR is entered by the sponsor into EudraVigilance with a copy sent to one responsible body (together with the study coordinator/Principal Investigator) who act on SUSAR alerts, cascading the information to others, as appropriate. 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.

Insurance/indemnisation

Variability in Member State insurance arrangements is 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 risk-based insurance conditions throughout a multinational trial.

Among the possible options for change proposed by other groups are the creation of a not-for-profit insurance organisation for clinical trials and exploration of the feasibility of insuring studies through the national public health systems in all Member States. However it is vital that care is taken not to introduce further unnecessary bureaucracy.

[2] Some clarification is already available in the Communication from the Commission 2010/C 82/01 (March 2010).

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Because of the complexity of the current situation and the need to create a better system that is flexible enough to cover insurance needs for both national and international trials, we endorse the proposal by the European Science Foundation (ESF)[3] to constitute a multinational task force of experts with a mandate to advise on how to harmonise insurance requirements.

Single sponsor

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 formidable[4].

Nonetheless, we urge consideration of a flexible system which permits multiple (co-) sponsors[5]: the UK has already interpreted the CTD to achieve this situation. We recommend that a multi-sponsor system should be based primarily 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 and a summary of the current practice in sponsorship in every Member State.

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. The ESF report offers detailed suggestions for what kind of support should be provided to academic institutions who act as sponsors.

Brussels, 12 May 2011

[3] Report from the European Science Foundation, 2009 "Forward Look. Investigator-driven clinical trials" on www.esf.org. Further analysis of the issues and identification of options for improving the insurance framework is also being taken forward in an EORTC-organised workshop (June 2010).

[4] 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

[5] There is another alternative – a single sponsor with delegating powers to share responsibilities. This option was discussed in detail in the final workshop of the Road Map Initiative (March 2010, www.efgcp.be).

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FEAM is grateful to its member Academies for contributing to the elaboration of this response and for endorsing it. The FEAM membership includes the following Academies:

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