



Taking forward reform of the EU Clinical Trials Directive

Introduction

Implementation of the Clinical Trials Directive (CTD), intended to harmonise authorisation of EU clinical trials on medical products, has been controversial. The accumulating evidence shows that the CTD has deterred academic clinical research. Following publication of the Federation of the European Academies of Medicine (FEAM) Statement “*Opportunities and Challenges for Reforming the EU Clinical Trials Directive: an Academic Perspective*” in 2010, FEAM organised a discussion event in the European Parliament on 25 January 2011 to engage stakeholders from academia, industry, other research bodies and patient interest groups with representatives from the European Commission and Parliament. The objectives were to share perspectives on the key issues and explore options for change.

Professor János Frühling (FEAM) provided background information on the goals and practices of FEAM, which brings together the national Academies to advise the political and administrative authorities of the EU on matters concerning medicine and public health. FEAM has a very active and wide-ranging programme of work: in addition to the CTD initiative, FEAM is currently engaged in activities on mental health policy, genetic testing and personalised medicine, human and animal infectious disease, and medical education, in part in cooperation with the European Academies Science Advisory Council (EASAC).

Making the case for CTD reform

Cristian Silviu Buşoi MEP, hosting the meeting, emphasised that multinational clinical trials are essential for better healthcare and that research should be strongly supported in the EU. Reinforcing the messages from the FEAM Statement, Dr Cristian S. Buşoi observed that the CTD has become burdensome for various reasons that include lack of standardisation and clarity of function in regulatory authorities and ethics committees. A major objective for improving the CTD is to introduce a risk-based, more flexible

approach to regulation. There is political will to reform the CTD but the key messages need to be disseminated more generally to MEPs, beyond the relative few with a medical background.

Professor Françoise Meunier (European Organisation for Research and Treatment of Cancer, Belgium) described how academic clinical research is vital to inform all of medical practice and allow best use of the inevitably limited healthcare budgets, optimising new therapeutic approaches and underpinning medical training. However, presently less than 5% of patients and doctors in the EU participate in clinical trials; if higher participation is to be encouraged then it is essential to reverse the deterrent effect of the CTD on clinical research.

In identifying themes that would recur throughout the meeting, Professor Françoise Meunier highlighted “*streamline, simplify, harmonise*” as the key desired elements for CTD reform. However, this reform must also be accompanied by other actions to improve the clinical research environment in the EU, in particular new funding to support investigator-driven trials and new models for collaborative research.

Dr Stéphane Berghmans (European Science Foundation, France) reinforced the critical importance of coordinating action in support of increasing funding, streamlining CTD authorisation and adopting a risk-based approach to proportionate regulation. Evidence was presented to document the negative impact of CTD implementation on length of time taken for trial approval and start-up, resulting in the withdrawal of prospective EU sites from global collaborative trials.

The OECD Global Science Forum is currently examining the issues for clinical research regulation, infrastructure and education in order to define ways to promote cooperation in international non-commercial trials. Elucidation of this global perspective will be vitally important, both to feed into EU thinking on CTD reform and to facilitate EU involvement in future global trials.

Professor Hubert E. Blum (FEAM and University of Freiburg, Germany) also furnished evidence to illustrate the history of European success in medical research, and the pivotal role of trials in those accomplishments, noting that in 2004 FEAM has warned of potential problems for academia if the CTD was applied inflexibly. These concerns had been substantiated, as described in the FEAM 2010 Statement, without any good evidence that the CTD had brought improved patient protection or ethical soundness of review. Substantial, urgent and coherent action is now needed to reform the CTD. The key issues for attention include: (i) Clarifying the roles of Ethics Committees and National Competent Authorities (NCAs); (ii) Tackling uncertainties and inconsistencies in the operation of the CTD, for example with regard to reporting of safety assessments, amendment of protocols during the trial, arrangements for sponsorship and insurance; and (iii) Identifying how a risk-based approach could best be introduced while also encouraging trials in special populations such as in paediatrics.

The European Commission's plans for revision of the CTD and support for clinical research

Mr Stefan Führung (DG Sanco) presented recent statistics in support of points made in the FEAM Statement. The number of clinical trial applications declined from 5,000 in 2007 to 4,100 in 2010 and the number of patients anticipated to be recruited into those trials dropped from 530,000 to 350,000. It is accepted that the CTD has increased the bureaucratic load and costs without successfully harmonising practice but, in agreeing with points made by the previous speakers, Mr Stefan Führung observed that the current clinical research problems are attributable not just to the CTD but also to weaknesses in research funding and infrastructure.

What is the solution? In the short-term, the European Commission is responding to improve operational functioning of the CTD, for example by revising the rules for safety reporting. In the longer term, the solutions proposed by FEAM and others provide a basis for legislative action in the EU, as part of the aim to create an improved global environment. The Commission's legislative proposal is expected in 2012 and will then involve the European Parliament and Council of Ministers. However, Dr Cristian S. Buşoi advised that it is highly desirable to inform Parliamentarians of the key issues well in advance of the formal proposal and many in academia and elsewhere feel that there is a strong case for accelerating the timetable for reform.

Dr Ruxandra Draghia-Akli (DG Research) observed that the EU is behind its major competitors in terms of the proportion of funding allocated to medical research. Looking forward to Framework Programme 8, Dr Ruxandra Draghia-Akli agreed that there must be increasing commitment in support of investigator-driven clinical trials, "*biomedical research should be given the place it needs*". DG Research identifies particular opportunities for its support in clarifying risk-based approaches, particularly in complex studies with multiple therapies and in rapidly advancing areas such as personalised medicine.

Panel discussion on opportunities and challenges

The chairmen of the Panel discussion, Professor Dermot Kelleher (Trinity College Dublin, Eire) and Professor Dragos Vinereanu (Romanian Academy of Medical Sciences) invited further stakeholder perspectives on the key themes relating to the critical importance of investigator-driven clinical trials, the negative implications of the CTD in current activity and the potential value of taking a new, risk-based, approach.

- Patient perspective. Mr Jan Geissler (Patvocates) agreed that healthcare improvements come from both academic as well as industry research and welcomed the FEAM commitment to catalyse a broad discussion. The bottlenecks attributed to the CTD -for example, in slowing and reducing trial recruitment,

- leading to the delay of producing meaningful results in trials - are not in the interest of patients. Patients with life threatening diseases need good progress in research in Europe. It is important that patients are being involved in progressing the reforms, not least by contributing their perceptions of risk to the consideration of the options for risk-based approaches.
- Industry perspective. Dr Christiane Abouzeid (EuropaBio, the European Association for Bioindustries, and BIA) also welcomed the intention of the meeting to bring together all stakeholder perspectives on how to make Europe more attractive for clinical research. Industry shares many of the points made by the Academies regarding the need for clearer definition of roles and responsibilities of NCAs and Ethics Committees, harmonisation of data requirements, proportionate to the protection of the safety and well-being of trial participants and the imperative to pilot reforms to demonstrate what can work, before widespread implementation.
 - Newer Member State perspectives. Professor Vytautas Basys (Vilnius University and Lithuanian Academy of Sciences) and Professor Sándor Kerpel-Fronius (Semmelweis University, Budapest, Hungary) reported on their academic experience. When introduced in 2004, the CTD was initially seen as helpful for those countries with less established traditions in clinical trial research but now the newer Member States share the general perspective that CTD reform is essential if their national research endeavours are to develop. It is acknowledged that individual countries have their own needs to modernise their clinical trial assessment procedures, for example to create a centralised ethical opinion, and there are often major issues for upgrading research infrastructure. Nonetheless, there are also areas where there is significant opportunity for the European Commission to display leadership, for example making best use of the research infrastructure network, ECRIN, to share best practice and build research capacity.

Other issues for improving the clinical research environment

Professor Andrzej Górski (Polish Academy of Sciences) focused on raising ethical standards, in particular with regard to openness in reporting clinical protocols and outcomes. As discussed in the FEAM 2010 Statement, there are new opportunities for enabling access to information on clinical studies in registries and these would help to maximise the value of research investments already made. Although construction of databases and trial registries was often conceived to be a responsibility for action at the national level, Dr Ingrid Klingmann (The European Forum for Good Clinical Practice (EFGCP)) proposed capitalising on those stakeholder contacts already made as part of the efforts for CTD revision in order to seek pan-European coherence for improving other elements in the clinical research environment.

Professor Juan Tamargo (Universidad Complutense Madrid and Real Academia Nacional de Medicina, Spain) returned to the importance of education and training, recommending

that the Academies should become increasingly active in analysis and advice regarding European objectives. This suggestion is very timely in view of the forthcoming FEAM annual meeting session on medical education.

In conclusion, all participants at the meeting agreed that it is urgent to resolve the issues identified in order to improve the functioning of the CTD and clinical research more generally. The concerns expressed by academia are shared by patients and industry and the current problems also endanger the training of future researchers and future innovation.

The FEAM initiative has been welcomed within the European Commission and European Parliament. However, there is much more to be done:

- To communicate the messages to all opinion-leaders and decision-makers in the European Parliament, Commission and Council of Ministers.
- To enlist the help of successive Presidencies of EU Council to accelerate the pace of reform.

In earlier discussions about the CTD organised by others, it was notable that debate was dominated by a relatively small number of Member States - not surprisingly, those who were most active in leading multinational studies. But the issues encompassed by CTD reform and the associated needs for building EU clinical research are relevant to all EU countries. FEAM has demonstrated that it is well-placed both to draw on the experience of Academies in many Member States and also to engage with all interested parties outside of academia. FEAM accepts its continuing responsibility to use this experience in generating independent, evidence-based advice as the voice of medical science and to communicate the strong messages in a coherent way at national and EU levels. As Professor János Fröhling (FEAM) stated at the close of the meeting, we need a European solution not merely an aggregation of individual national views.

Dr Robin Fears, FEAM, 17 February 2011

The Federation of the European Academies of Medicine (FEAM) was founded in 1993 in Brussels with the objective of promoting cooperation between the national Academies of Medicine and of extending to the political and administrative authorities of the European Union the advisory role that the Academies exercise in their own countries on matters concerning medical sciences and public health. Since 31 March 1995, FEAM has enjoyed the civil status of an international association with a scientific objective. As an umbrella organisation, it brings together national Academies of thirteen European member states (Austria, Belgium, Czech Republic, France, Germany, Greece, Hungary, Italy, Portugal, the Netherlands, Romania, Spain and the United Kingdom) and aims to reflect the European diversity by seeking the involvement of additional Academies and experts in its scientific activities and by collaborating with other pan-European networks on scientific matters of common interest.