# Road Map Initiative for Clinical Research in Europe

## Report of the

# *Multidisciplinary Workshop on*

# *Innovative Approaches to Clinical Trial Co-Sponsorship in the EU*

Hammersmith Conference Centre

Hammersmith Hospital

Du Cane Road, London

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*organised by*

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## 1 The report and its aim

This report covers the principal discussions and conclusions to emerge from the workshop entitled "**Innovative Approaches to Clinical Trial Co-Sponsorship in the EU**", held in London on 21 September at the Hammersmith Hospital and organised by the six pan-European networks that have started the Road Map Initiative for Clinical Research in Europe:

- CLINT, which facilitates international stem cell transplantation trials;
- EBMT, the European Group for Blood and Marrow Transplantation;
- ECRIN, the European Clinical Research Infrastructures Network;
- EFGCP, the European Forum for Good Clinical Practice;
- ELN, the European Leukaemia Network;
- EORTC, the European Organisation for Research and Treatment of Cancer;
- and ICREL, Impact on Clinical Research of European Legislation.

The Road Map Initiative has an ambitious objective: to work for improved conditions for multinational clinical trials in Europe. Its opening workshop, on the options for a single Clinical Trial Authorisation, was held in Brussels on 7 July 2009. The Brussels workshop laid down the main lines of discussion and served as an introduction to follow-on workshops on specific areas of concern: co-sponsorship and contractual issues, which are the subject of this report; risk-based approaches and ethical review (January 2010); and pharmacovigilance (8 February 2010).

On the basis of those discussions, and the reports produced, a final stakeholder conference will be held on 17 March 2010. The aim: to be able to submit a clear proposal to the European Commission on the way forward for multinational clinical trials in Europe.

The report has been produced by the rapporteur, Peter Wrobel, who takes full responsibility for its content.

## 2 Executive summary: Broad conclusions and options

From the perspective of those involved in multinational clinical trials, it often seems as if Europe is a one continent divided by a single Directive. The Clinical Trials Directive, which came into force in 2004, introduced a new landscape for trials, but it did so in a particular way. Rather than enact a Regulation, which would have introduced the same legal conditions for clinical trials throughout the European Union, it was decided to agree on a Directive, which had to be transposed into each Member State's national law and national language (or languages). The result is that one ordinance from Brussels has been coloured

by national legal traditions and national cultures, such that different ideas have arisen about what it means and how it is to be carried out.

The aim of the Directive, as Jacques Demotes from ECRIN said at the beginning, was to protect the participants in clinical trials through ensuring that the sponsor takes full responsibility. One requirement of the Directive was that every clinical trial should have a single sponsor to take ultimate responsibility for its conduct. So far, so simple. And yet, five years after the introduction of the Directive, it was clear from this workshop there is still no shared understanding about what "single" means, nor what "sponsor" means.

And that is not all. The general assumption coming into the workshop was that the Directive rules out sponsorship by more than one organisation. It quickly emerged, however, that this is not the case in the UK, where the interpretation of the law provides explicitly for the responsibilities of sponsorship to be shared.

Even in France, where French researchers believe that a condition of trial approval by the competent authority, AFFSAPS, is that there be a single sponsor, it turns out that the authority has approved at least one trial with two sponsors.

### *Defining the problem*

So it was no surprise that the recommendations to come from the three break-out sessions – each on different aspects of sponsorship – started with a call for clear definitions.

Against this background, the summing up by Jane Apperley from Imperial College London, UK, made interesting and, as it turned out, uncontroversial listening. "When starting this workshop I thought that co-sponsorship was the answer to our problems," she said. "After the discussion I'm not so sure." The discussion showed, she said, that five years after the Directive came into effect "we have not solved a number of basic definitions, including sponsorship". Her conclusion – or rather, one of them: "Single sponsorship is not the worst thing that happened to us." She also noted that industry has much less of a problem with sponsorship in general than academia does.

That's not to say that there are no problems with the concepts of sponsorship. Far from it. "That the pressure to have this debate comes from the academic side speaks for itself," said Apperley.

### *Clarifying the options*

The day clarified that for academia as well as industry, single sponsorship is generally the preferred option, though it needs to work more efficiently, be better defined and unburdened of what Apperley called "bureaucratic constraints". But it should not be the only option. "We agreed," said Apperley, "that there are situations – given the complexity and the fact of 27 Member States – where it may be helpful for the efficiency of a trial to have a legally defined co-sponsorship."

Where co-sponsorship is the option, it was seen as preferable to split responsibility by function rather than by geography.

*What next?*

The partners and stakeholders in the Road Map Initiative are now committed to working out how to define, across countries, the responsibilities of sponsorship and co-sponsorship, each of which may also involve the delegation of some duties to others. This report is but one step in that process. The next step will be a working group, as part of the Road Map Initiative, to produce a proposal for consideration by a broad audience at the final workshop in March 2010.

On that basis, said Apperley, "We can tell the Commission what needs better definition, what needs a new guideline or a revision of the Directive, and what needs national modification. Then we will have a chance that something can change. If we do not move it, it will not move."

## 3 Managing multinational clinical trials within the current legislation

It is undeniable that academia has trouble with multinational trials under the current legislation. Selim Corbacioglu from the University of Ulm, Germany, related the twists and turns of organising an investigator-instituted trial with children. The story had a happy ending – a positive result that a small company was able to implement – but it could have been so different, said Corbacioglu. The cost, the complexity and above all the length of time involved were huge problems, and the company nearly ran out of money before the trial concluded.

And yet if you want to do clinical trials to improve the treatment of children, Corbacioglu said, there are few cases in any individual centre – so large multicentre trials are essential. Given that the potential market is often too small for industry, things have to be made simpler for academia to initiate a trial.

Anne Larcheveque, from the University of Nantes, France, spelled out the legal issues for sponsors and the complexities involved in dealing with multiple national legislations and multiple ethics committees. She also referred to the running theme throughout the meeting – the uncertainties introduced by the Directive. Because it fails adequately to specify the different categories of clinical trial, she said, trial sponsors find that some study projects fall under one category in one country and another in others, a mess that sponsors have to untangle.

Larcheveque concluded that having a Regulation rather than a Directive would introduce certainty about roles and responsibilities – though she felt that it would be better to keep to what she called the Directive's "principle" of a sole sponsor, to avoid any misunderstanding.

Perhaps interpretation is inconsistent within national competent authorities as well as between them. Larcheveque said that in France AFSSAPS has recently affirmed that there can only be one sponsor in the European Union for a given multinational clinical trial. Later, however, Anastassia Negrouk from the EORTC said that her organisation had recently had a trial involving co-sponsorship approved by AFSSAPS.

Enter Christopher Roy-Toole, a barrister and member of a UK NHS research ethics committee. “It is clear to me that the Directive does not preclude multiple sponsors. In the UK we specifically allow this,” he said. Roy-Toole referred to the European Commission’s “Q&A” of July 2009, which says, and he quoted, that “a number of parties may agree in writing to form an organisation…and to distribute the sponsor’s tasks and duties between various sponsors and organisations.”

Whatever the legal situation, Larcheveque’s preference for single sponsorship was echoed by Susan Kerrison from University College London, which sponsors some 100 trials in the UK: “Quite honestly we would be very averse to going down any risk of co-sponsorship… The complexity is huge. Where you have one sponsor you know where responsibility lies. When you start to spread responsibility, you have big problems,” she said.

The EORTC is one organisation with a great deal of experience running large multicentre, multinational trials, and Anastassia Negrouk gave a detailed exposition of the issues involved. Before the Directive, she said, the EORTC was taking part in trials with multiple sponsors. Now the preferred model is single sponsorship.

Negrouk summed up the pros and cons. Single sponsorship makes coordination and negotiations easier, she said: “You don’t have to spend time discussing different legislations.” It is also more attractive for industrial partners, who have a single point of contact. In addition, the decision-making process is easier, as is harmonised trial management.

Against this, single sponsorship carries heavy responsibilities. It may also jeopardise access to funding, since some charities (and national bodies) will only want to fund sponsors in their own country.

Multiple sponsorship, on the other hand, may facilitate some collaborations, said Negrouk, especially in paediatrics. “It is more attractive for national support and limits the burden on each organisation. But it requires a high level of coordination, is prone to misunderstandings about tasks; decision making may be lengthy and divergent, with overlapping responsibilities; and you have the issue of co-liability.” She continued: “It’s like marriage without a contract…You can’t really split responsibilities like that.”

Given the complexity of what the EORTC is doing with “very different levels of trial”, said Negrouk, there is probably room for both models. But she made a plea for a focus on the quality of the trial rather than on the responsibilities in the abstract.

Industry’s experience is rather different from that of academia. Raymond Bratty from Orion Pharma[1] said categorically that the Directive has had little effect on the company. When it comes to sponsorship agreements, he said, “It’s either us or the investigator,

[1] The views expressed are those of the individual and may not be representative of Orion Pharma

nothing in between." He noted that some countries define sponsors in "slightly different" ways than others, but said that had not been a problem for his company.

But after running through the advantages of sponsorship by a company or an investigator, he also speculated (in a personal capacity) on the "third way" – sponsorship between industry and academia. "There may be an advantage in co-sponsoring what would otherwise be an investigator-initiated study," he said, adding that co-sponsorship could reduce costs and provide a business model for less-prevalent diseases.

In fact, he said, industry would consider any innovative solution as long as the quality of the trials is maintained. Kai Chan[2] from Genzyme was also wary about the idea of co-sponsorship (as opposed to collaboration or support): "We should all collaborate, but the definition of co-sponsorship needs to be careful because we have to remember the implied principles," he said, namely to protect patients and have optimal trial quality.

Negrouk also picked up on the aspect of quality. "The fact that cooperation is complex is there anyway," she said. "It's not down to the number of sponsors." The complexity comes from the "very tough legal environment", she said. She assumed that the aim of concentrating responsibility in one sponsor was to have someone take it seriously. "I disagree with that: a group of collaborators taking it seriously may achieve the same result as a single sponsor. Instead of thinking about quality we're thinking about laws," she noted, with disapproval.

## 4 Proposals for more research-friendly sponsorship conditions

The situation in the UK appears to be clearer than in some other countries – or at least it seems to be different. Julia Brown, from the Clinical Trials Unit in Leeds, explained how the UK regulations provide for a single sponsor, joint sponsorship (where two or more sponsors act jointly to take on responsibilities) and co-sponsorship (where the discrete responsibilities are held by different sponsors). Many functions can be delegated, she said, but the sponsor (or sponsors) remains ultimately responsible.

The multisponsor models are complex, she said. In joint sponsorship, organisations would have "to trust each other and have excellent communications. For me, it is difficult to envisage many organisations in the UK willing to take on a joint sponsorship." In fact, she knew of none that has done.

With co-sponsorship, said Brown, the responsibilities need to be clearly spelt out in contracts. But she drew attention to UK Department of Health guidelines. The Department's interpretation of the Directive has two important sentences, she said: first, that it is not the intention to subdivide responsibilities between many co-sponsors; nor to divide responsibilities geographically or in other ways that would allow protocol to be amended in isolation.

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[2] The views expressed are those of the individual and may not be representative of Genzyme Corporation

A survey by her National Institute for Health Research Clinical Research Network Coordinating Centre (NIHR CRN CC) found that some organisations were using co-sponsorship, sometimes even in the way the Department of Health intended. Some said they used co-sponsorship on a per-country basis (including one with France): the duties were detailed in contracts, and where there was ambiguity it was recognised that all parties remain jointly liable.

Overall, though, academic organisations see the co-sponsorship model as risky, with potential for inappropriate or unclear allocation of responsibilities. Brown added that the model does allow more options for sponsors, but added: "Some academic institutions felt it important to explore whether the model can be used on a per-country basis."

But Brown concluded that co-sponsorship alone is not *the* solution for international trials. Other issues need to be addressed: new models of insurance and indemnity; one point of call for accessing information on EU-wide regulations; standardisation of ethics processes; information on clinical trials across the EU; and so on. Individual institutions are not going to be dealing with a large number of international trials, she said, so it is hard to maintain the required resource infrastructure. They need help, she said, and working models.

From Germany, Jürgen Grebe from the Centre for Clinical Trials (KKS) in Münster spoke about the way that university hospitals cooperate to run clinical trials. The KKS Network in Germany, he explained, has a great deal of experience in the structures needed for effective multicentre collaboration, and he listed many of the lessons learned. However, sponsorship remains in the hands of one organisation, even if tasks are often delegated widely.

Grebe wanted to see a revision of the Directive to allow sponsorship to be split on geographical lines. This is the opposite of the view taken by the Department of Health in the UK. Delegation is fine, she said, but she said it is "almost unworkable" to allocate co-sponsorship responsibilities to different countries.

Industry, of course, has a great deal of experience in collaborating across national boundaries. Chris Wilks[3] from AstraZeneca, UK, said that the main thing is to have crystal-clear allocation of responsibilities. For him, a properly defined collaboration agreement is the basis for the distribution of roles and responsibilities. Within that context, he could see potential advantages of co-sponsorship, though he warned academia that more support and money from industry might come with more strings attached. But co-sponsorship might, for example, facilitate indemnification and liability, as well as pharmacovigilance. On the other hand, it might make matters more complex on issues of trial management and the ownership and use of data.

[3] The views expressed are those of the individual and may not be representative of AstraZeneca

Wilks concluded that co-sponsorship would be a "valuable option", but would not be appropriate in all – or even most – cases. "Don't make it the preferred option – that's single sponsorship," he said, adding that single sponsorship by the investigator's institution "gives less opportunity for industry to interfere with academia". Harking back to Brown's definitions of sponsorship, he said he would "definitely prefer co-sponsorship to joint sponsorship", which he saw as a potential legal nightmare.

Kai Chan from Genzyme was less hopeful about co-sponsorship. "Going down the line of co-sponsorship with the pharma industry is probably going to be met with great difficulties," he said. Academic centres looking for help in multinational trials would be better looking for support from industry, rather than co-sponsorship. "If you talk about the word 'support', that is generally available," he said. "But sponsorship carries with it a lot of legal liabilities, especially regarding patient safety and the quality and conduct of a study," he continued, adding that large companies supporting hundreds of investigator trials had no way of monitoring down to that level. Best, he said, if "the investigator knows that the buck stops with him".

## 5 Detailed conclusions and recommendations

Three break-out groups considered how to optimise conditions for co-sponsorship in, respectively, the private sector, the public sector, and in public–private collaborations. Covering the same landscape, but from different perspectives, their conclusions were similar.

### *Eliminate the confusion*

Confusion still reigns about terminology – in the case of the group looking at public-sector collaborations, "extreme confusion" was reported. The group looking at the private sector noted that it was not clear whether all agreed on a definition of co-sponsorship.

The current definition of sponsor is insufficient, over-complex and unrealistic –and in practice unhelpful. As the group looking at public–private collaborations concluded, tellingly, the definition does not ensure that medicines reach patients faster, does not help (in practice) to minimise risk for patients in clinical trials, and does not help to make clinical trial organisation faster and cheaper. Nor does it stimulate treatment optimisation and other investigator-initiated trials, or promote public–private development in drug development and in clinical trials.

The solution is straightforward:

1. The European Commission and national governments must clarify and harmonise their definitions of what a sponsor is.
2. In particular, and while single sponsorship will remain the preferred option, the conditions under which co-sponsorship are appropriate must be clearly defined.
3. There must be a clearly understood line between sponsorship and delegation, eliminating the lack of clarity in, for example, Paragraph 25 of the July 2009 update of "Q&A" guidance the Clinical Trials Directive [the first time the Commission has

said in writing that a clinical trial may have multiple sponsors which allocate functions between them].

4. It would be helpful for the European Medicines Agency to produce a template to be used when defining the roles and responsibilities of co-sponsors.

### *Ease the way to collaboration*

If co-sponsorship is not practicable, collaboration is still often required, and needs help. Some suggestions:

1. Academic sponsors need a ready source of information providing local knowledge about what is required when, for example, a country joins a clinical trial.
2. A guideline on how to do collaborative research.
3. Improve the working relationship between academia and industry by promoting transparency, especially in setting expectations, with a fair partnership between the two and discussion about appropriate and reasonable costs.
4. Promote the use of tools such as RACI [responsibility, accountability, consultation, information] charts to clarify roles. This would also help in redirecting resources away from bureaucracy and towards patient safety.
5. Remove some of the national barriers to co-sponsorship by increasing the funding available for clinical trials at a European level.
6. Everybody mentioned insurance and indemnity as key problems, and called for new models to facilitate research.
7. And finally, as Ingrid Klingmann from EFGCP said, a single Clinical Trial Approval and a single opinion from a Research Ethics Committee would be a huge step forward in simplifying the tasks of sponsorship…and in allowing the focus to be on the patient and on the trial.