Road Map Initiative for Clinical Research in Europe

Report of the

Multidisciplinary Workshop on

A Single CTA in Multinational Clinical Trials - Dream or Option?

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'where science & ethics meet'

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1. Introduction: Not just a dream

Is the idea of a single authorisation process for multinational clinical trials a fantasy, or a real possibility? That was the subject on the agenda of a meeting in Brussels on 7 July 2009 that brought together regulators, researchers, patients and industry.
It's not an abstract question. Some 60 per cent of all clinical trials in Europe involve more than one country – and so have to cope with different regulators, different languages, different ethics committee structures and requirements, and so on.

The complexities can be mind-boggling, especially for trials involving many countries. And not just the complexities: the time delays and financial costs mount up, too, and along with them, delays in patients' access to treatment.

Although the Clinical Trials Directive has broadly been acknowledged as a successful first step towards harmonisation, its implementation in 2004 has intensified the problem by requiring the detailed review of a dossier leading to a Clinical Trial Authorisation (CTA) from each national Competent Authority involved in a multinational clinical trial. Recently, the Heads of Agencies' Clinical Trial Facilitation Group (CTFG) has come up with a pilot process for harmonising authorisations, and organisations like EFPIA, the European Federation of Pharmaceutical Industries and Associations, have elaborated a proposal for solutions – but there is no concerted effort among all stakeholders. Now, though, there is the germ of a plan that might take us into a new era for multinational clinical trials.

It is called the "Road Map Initiative for Clinical Research in Europe", and the Initiative is being pursued by a formidable array of organisations: 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.
Does a clinical trial for a single medicinal product really need up to 27 different evaluations in different countries from national competent authorities and ethics committees? Obviously not, said

Jacques Demotes from Inserm, France, introducing the discussion. But getting to a single clinical trial authorisation is not going to be simple, easy or quick.

The day's discussion did not produce an agreed plan for moving to a single process for authorising multinational clinical trials, nor was that the aim. What it did achieve was to clarify the issues, the difficulties, and more significantly the options for the way forward.
These options are the focus of this report, though it necessarily touches on aspects of the background and of the discussion. The options will be discussed at a meeting in April 2010, which will review not only this workshop but others to be held in the coming months dealing with particular roadblocks in Europe's clinical trials process.

The idea is intensely practical. "Hopefully at the end of the process, we will come up with agreed recommendations on how the process could be improved – and how the European Commission could work to make our lives easier and get drugs to patients quicker," explained Ingrid Klingmann from the EFGCP.

2. Executive summary: Broad conclusions and options

There is never going to be unanimity in a subject as broad and complex as clinical trial authorisation in Europe, hedged around as it is by institutional sensitivities and often by powerful emotions. However, it seemed clear to the author of this report that a number of clear options were laid out, and a number of general principles established. The feeling came over strongly that almost anything might be possible, given the shared will.
In particular, workshop delegates were not prepared to rule out options simply because their achievement might require legislative change and lengthy timescales.
There was also realism about the time it might take to introduce a Community Clinical Trials Authorisation for multinational trials. So alongside the proposals for systemic change, the workshop also came up with a number of ideas for immediate action to fix the existing system, some of which would involve amendments to the Clinical Trials Directive.
This workshop was part of a process of discussion that has not yet ended. Nonetheless, the conclusions listed here – the threats inherent in the current system, the principles that should guide short- and long-term reform – may be fairly said to represent a general (if not necessarily unanimous) consensus among the participants. They are listed here as an aid for the discussions that will take place in further sessions under the aegis of the Road Map Initiative for Clinical Research in Europe.

The threats

- The implementation of the Clinical Trials Directive has been associated with an increase in administrative burden and costs.
- Europe as a whole will suffer if it is unable to ensure the attractiveness of clinical research within its borders, while ensuring the safety of trial subjects.
- The requirements for insurance are stifling some clinical trials.

Guiding principles

- The regulatory oversight of a clinical trial should be proportionate to the risks to the patient.
- No duplication of reviews of the same aspects of clinical trial proposals.
- The best available expertise should be used, regardless of which country it comes from.
- Consistency: as far as possible, a trial should not be acceptable in one country and unacceptable in another.

- The roles and responsibilities of competent authorities and research ethics committees should be clear and uniform across Europe.
- The fees of an application for a clinical trial should be the same in all countries, and preferably zero.
- Any new system must reduce the administrative burdens on trial sponsors.
- It must become faster, not slower, to get a clinical trial started.
- Academic sponsors should be appropriately funded for the administrative costs of running clinical trials.
- There should be a single CTA application dossier, in English, accepted by all national regulators (though of course patient information and informed consent documents must be in appropriate local languages).
- Co-sponsorship: it must be possible for the sponsorship of a trial to be shared among stakeholders, based on a contractual agreement.
- End the confusion: the basic definitions of what constitutes an Investigational Medicinal Product, a Substantial Amendment or a non-interventional study must be clarified and harmonised across Europe.

Options for progress

The longer term: Possible new procedures

1 Centralised application with centralised review.
A trial sponsor would submit one application centrally to a centralised body (e.g. the EMEA, the European Medicines Agency), which would review it and reach a decision.

2a Centralised application with disseminated review.
The trial sponsor would submit one application centrally to a centralised body (e.g. the EMEA), which would select a rapporteur country to carry out the review, thereby capitalising on the expertise and strengths of the national regulators (especially in paediatrics and orphan conditions). With one body to validate applications, there would be no divergent definitions to deal with, and it would be easier to change or extend a protocol.

2b As above, but as an optional system in parallel with the existing system.

3 Single national application with disseminated review.
The sponsor would apply to his/her own national regulator or any other selected Competent Authority, which would take the application to the EMEA as rapporteur for a "mutual recognition procedure".

4 A single ethical opinion for Europe – incorporating the opinions of the individual national ethics committees.

The shorter term: Fixing the existing system

Harmonisation and changes to the Directive

- There would continue to be multiple applications to national regulators, and multiple reviews – but the application dossier would be identical and either submitted into a centralised database once, accessible to all concerned competent authorities, or submitted to all national competent authorities involved. The Clinical Trials Directive should be adapted to allow co-sponsorship: allowing the responsibilities of sponsorship to be shared between stakeholders.
- Remove some of the burdens associated with the reporting of SUSARs (suspected unexpected severe adverse reactions) by setting up a single database for reporting them and removing the need for submissions to all national Competent Authorities, ethics committees and investigators.

- Harmonise the definition of what constitutes an Investigational Medicinal Product.
- Harmonise the definition of what constitutes a Substantial Amendment to a clinical trial authorisation.
- Harmonise the definition of what constitutes a non-interventional study.
- Establish in all countries the principle that sponsors of multinational trials may submit applications in English only, in collaboration with the national coordinator.

Ethical approval

- Clarify and harmonise across Europe the roles and responsibilities of research ethics committees, clearly differentiating between these and the roles and responsibilities of the regulators, the Competent Authorities.
- Establish in all countries the principle that ethical review should proceed in parallel with regulatory review (rather than in sequence).
- As a first step, seek to establish the principle that there is only one ethical opinion per Member State.
- Have clear European Union guidelines on the content required in Patient Information Sheets and the process of informed consent (while leaving presentation to be determined at a national level).

Funding and training

- Academics should receive the resources to support the infrastructure requirements of clinical trials.
- Governments must act to relieve the burden of insurance on academic trials – which is preventing some trials from even taking place.
- Remove some of the financial burden by not requiring the fee of an application to be met by the sponsors.
- Training remains an urgent issue – both for researchers and for members of research ethics committees. It needs funding.

Political will

- Responsibility for the Clinical Trials Environment in general should be shared with Directorate General Sanco, rather than residing entirely with DG Enterprise as at present (trials not involving investigative medicinal products also entail risk and the need for risk information/assessment to patients).

3. The background

Industry: It's time for a change

It's time for a change, said Mats Ericson, from Amgen and EFPIA: "We now have five years' experience of the Clinical Trials Directive. The problems are not teething problems. They don't go away."
Commercial sponsors of clinical trials are not wholly negative about the current situation. "It has a lot of strengths as a first step in the harmonisation of procedures," said Angelika Joos, from Merck Sharp & Dohme. She saw positives in the introduction of protection for vulnerable subjects and minors and the ability to involve them in clinical research, as well as to the incorporation of the principles of Good Clinical Practice and Good Manufacturing Practice and time limits for decisions to be made, producing a more level playing field across the European Union.

Joos was backed up by Rui Santos Ivo from the Portuguese pharma industry association Apifarma: "Coming from a small country I can see it has improved the quality of clinical research in Portugal," he said.

But industry also sees weaknesses: differing interpretations in different countries, for example in safety reporting and in defining what is an Investigational Medicinal Product (and therefore what comes under the Clinical Trials Directive), or in saying what constitutes a Substantial Amendment to a trial. "Undoubtedly", said Joos, "the administrative burden has grown. In addition, a multiplicity of assessments by different stakeholders has led to divergent outcomes in different countries. "
"The different regulatory standards being applied by the Member States in granting clinical trial authorisations have adversely impacted on the ability of our member companies to initiate and continue to carry out multicentre and multinational trials across Europe", said Christiane Abouzeid of the UK BioIndustry Association, adding "small and medium-sized companies do not have sufficient financial and manpower resources to effectively deal with the administrative burden to identify and comply with additional local requirements".

Overall, the regulatory environment is seen by industry as fragmented and complex, with multiple scientific discussion partners, each with their own (different) focus, and the possibility that issues will be rediscussed at different levels.
What does industry want? A new Clinical Trials Regulation, binding on all Member States, introducing optional Community Clinical Trial Authorisations, plus amendments to the Clinical Trials Directive to make it work better and more efficiently. "A good regulator assessment can add both scientific and protection value, but twenty-seven assessments don't add value," said Ericson. "It would be very difficult [for Competent Authorities] to accept a protocol accepted by someone else, but I see no other solution."

Academia: The resources gap

Academic researchers face the same problems as industry, but they do so without the resources that industry has at its disposal. So the administrative load, with its accompanying cost, is a major issue for academics, said Alan Tyndall from the University of Basel, Switzerland. Academic departments are simply not equipped to translate informed consent documents into different languages, for example. What academics need is funding for the infrastructure of clinical trials, such as that provided by the National Institutes of Health in the United States.
Matthew Sydes from the UK Medical Research Council's Clinical Trials Unit gave graphic examples of the problems non-commercial sponsors have when trying to get multinational clinical trials going. These range from the different roles and structures of research ethics committees in different countries, to difficulties with insurance (in one trial, this meant that Poland was unable to take part) and the general issue of funding. On top of this, each national regulator requires an application dossier in a different form.
In common with others, academics have a problem with the one-size-fits-all approach of the Clinical Trials Directive, and they worry that it is holding back research. Take stem cell transplantation. "If it hadn't been done fifty years ago it wouldn't be done now with the legislation we have," said Dietger Niederwieser from the University of Leipzig, Germany, and President of the EBMT. He called for common sense, and for a risk-adapted approach to clinical trial authorisation.
Niederwieser's criticism was echoed by Ruth Ladenstein from the St Anna Children's Hospital in Vienna, Austria. The success story in paediatric cancer over the past two or three decades is due to academic trials, she said, adding, "It is precisely these trials that are in danger because of the bureaucratic load." One trial on neuroblastoma is going ahead only because it has funding from patients. "We need more support from the European Union," she said.
Ladenstein said that the number of new trial applications in paediatric oncology has declined. In addition, she said, "A lot of old trials have been amended and amended to get round the Directive because there's not enough money for a new clinical trial application."

What do academics want? Jane Apperley from Imperial College London summed it up: one approval process to cover all member states, specified timelines applying across the European Union, a single dossier, and no additional requirements coming in from local research ethics committees, local R&D committees or regional authorities.
The benefits would include time. “Submitting twelve different dossiers takes so much preparation that you submit country by country, one country a week,” said Anastassia Negrouk of the EORTC. “We have calculated what time we would win with a centralised process: with twelve countries we’d save four-and-a-half months.”

Regulators: Yes, there is a problem

A representative from the Directorate-General Enterprise and Industry (European Commission) acknowledged that there are difficulties for stakeholders applying the Directive. Three avenues for improvement were highlighted.
The first is to improve the guidance that the Commission gives about how to implement the Directive. New draft guidelines for the application dossier have been issued for public consultation, closing on 8 September 2009. The draft clarifies that the rules are exhaustive, so that Member States will be unable to go beyond them, and it remove caveats allowing Member States to ask for extra information in certain situations. Participants were urged to comment in this public consultation.
The second avenue is stronger cooperation among Member States.

The third avenue would be a more structural: a revision of the Directive, or a new legislative instrument to work in parallel with it. But with work still at a “very early stage” nothing more could be said at this stage. It was highlighted, however, that a new legal instrument will take many years, and when it comes it will not necessarily address all aspects in full detail. Therefore, it was highlighted that work on implementation remains in any case crucial.

Martyn Ward from the UK Medicines and Healthcare products Regulatory Agency was another regulator pointing out that radical change would come with “a fairly major time tag attached to it”. A lot could be done, he said, through harmonising and streamlining existing processes.

There is already a form of single application process in the European Union – the Voluntary Harmonisation Procedure produced by the Clinical Trials Facilitation Group (CFTG). “At present, it is mainly restricted to trials of a new substance without marketing authorisation in the European Union,” explained Hartmut Krafft from the Paul-Ehrlich-Institut in Germany, Chair of the CTFG and VHP-Coordinator. The procedure allows for a single application to the CTFG, which then decides whether to take it to take an initial request to the next phase, in which it identifies participating national regulators.

Each regulator will review the application within a 20-day timeline, but the process is coordinated through the Voluntary Harmonisation Procedure (VHP), with the coordinator passing queries back to the applicant. If no Grounds for Non-Acceptance (GNA) exist the process will be finished after 30 days, and in the case of GNA after 50 or 60 days at the latest. In the final phase, the proposed trial goes for formal assessment by the national regulators, with the understanding that this formal assessment will take no more than 10 days. (The procedure can be accelerated for urgent trials, such as for pandemic flu vaccines.)

So far, there have been 17 applications through the VHP, 12 of which are still ongoing. One clear advantage, said Krafft, is that the coordinator can streamline the list of possible grounds for non-acceptance or requests for further information, making it simpler for the applicant to respond. Anastassia Negrouk agreed, calling it a “win–win situation”.

But Krafft warned that a completely centralised procedure might be too inflexible. “At the moment we are quite flexible in favour of the applicants, and so might end up with something country-specific…that would disappear with a centralised procedure,” he said. “Harmonise what’s harmonisable and leave the other things – when good – as they are.”

Chantal Bélorgey from the French regulator AFSSAPS and CTFG's co-chair gave strong support to moves to simplify the administrative side of multinational clinical trials. "It's quite simple," she said. "We need a single Clinical Trial Application dossier, with a single repository. And a common language, English, accepted in all Member States." Those changes, she said, did not need revisions to European legislation.

Bélorgey agreed on the need to adapt trial requirements to risk, and there is in fact an Expert Working Group of the Commission looking at this. But she added that care needs to be taken about who is responsible for assessing the risk. And when it came to the idea that the EMEA centrally should be handling assessments, she wondered whether it had the capacity to deal with the volume of work – around 5,000 multinational clinical trials a year, with between 10,000 and 15,000 substantial amendments and hundreds of thousands of SUSARs.

Patients: End the delays

"When we streamline applications, does it serve interests of researchers and industry, or does it serve interests of patients?" asked Jan Geissler from the European Cancer Patient Coalition. "Everything must serve the interests of patients," he said, noting that only France and the Netherlands explicitly mention patient advocates as members of research ethics committees.
Geissler questioned whether local differences within Europe are really a key question. "Of course, there are differences between countries," he said, "…But are these differences really so crucial. Is the culture that different?" He wants to see more trials, not fewer. "My main fear is that all the trials will go to the US and Far East, and we will be required to adopt what has been tested in the US already, but without being able to take part in trials," he said.

No surprise, then, that his organisation thinks there could be "a lot of benefit" if there were central discussion of a clinical trial application and a centralised ethics review. "The differences are not enough to justify the delay [in the present system]," he said.
"The idea is not just to protect patients from bad trials," said Cor Oosterwijk from EGAN, the European Genetic Alliances Network, "it is to protect them from disease and death."

Ethics: The biggest obstacle?

Many of the problems that the sponsors of clinical trials face are related to the diversity of the European ethical review landscape. Some countries have centralised committees, some regionally based committees, while other countries have a multiplicity of committees. Worse, these committees often have radically different perceptions of what their role is.
Can anything be done to harmonise ethics committees in Europe – or, as Jiri Simek from the University of South Bohemia, Czech Republic, suggested to the workshop, do fundamental ethical values "differ substantially across countries, families, groups and geographically in and across Europe"?
As Simek cogently pointed out, "If the task [ethical review] includes to respect local values and norms, then the idea of creating one common ethical opinion in Europe is a delusion." Simek's view was that a single opinion is not possible. Instead, efforts must be made to cultivate a research ethics community in Europe.
But many others disagreed. Matthew Sydes did not accept that the cultural differences were so great that a common ethical opinion would be unachievable. "The world is changing. Closer communication enhances shared values" he said. Ruth Ladenstein could not understand why it would be unethical to develop effective therapies for children in one country, but ethical in another. "I think we are missing the common aim," she said. "I can see the point of diversity, but we have a desperate need for new treatments. It can take years. That's not ethical."
If you start saying different regions had fundamentally different ethical cultures, there is no limit to how far down you could go, said Xavier Carné from the Hospital Clinic 1 Provincial de Barcelona, Spain: "If you take it further, each village has its traditions," he said. "We should have European values. The US has a common ethic – why can't we have one?"

Anastassia Negrouk strongly disagreed with the idea that a single ethical opinion for large-scale trials in the European Union is impossible. “If it were so difficult we would never have Europe-wide or global trials,” she said. The long-term solution has to be a two-level decision, whereby the general judgement and ethical opinion are reached at a centralised level, with the national regulators either accepting that or not taking part in the trial; additionally, she said, there would need to be national-level implementation of the Patient Information Sheet and the process of informed consent.
But she had some short-term proposals as well: parallel assessment by regulators and ethics committees, with the roles and responsibilities of each clarified and harmonised; central ethics committees per country or per project (although she thought per country “definitely preferable”); accept applications in English; and clear guidelines on the content of information for patients.
No one thinks any of this will be easy. “It is not hard for national Competent Authorities to come to an agreement on how to work, because that’s their ancestry; it will be much more difficult for the ethics committees, even though there are not that many technical differences between them,” said Yannick Plétan from Pfizer, France. “But there are cultural differences. We need to educate them, first in seeing how similar they are.”

4. What next? Writing the Road Map

There was widespread conviction at the workshop that a single authorisation procedure is now on the agenda. “Some years ago, in a conference about the future implementation of the Clinical Trials Directive, I asked whether one day a central approval or single opinion would be possible,” said Negrouk. “The answer was laughter: it was impossible, and I was very naïve. But now it does seem very possible, and even on ethical level people don’t laugh at you. The only problem is that six years have passed. We all believe that one day it will become possible, we just know we have a way to go, so maybe we have to work out how to get there.”

Over the coming months, the group of organisations that launched the Road Map Initiative for Clinical Research in Europe will be holding further workshops on specific areas of concern: co-sponsorship and contractual issues (September 2009); risk-based approaches and ethics committees (January 2010); and pharmacovigilance (February 2010). On the basis of those discussions, a final stakeholder conference will be held in April 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.

For more information on this Initiative, how to join this Initiative or how to register for a workshop, please contact:

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