The Clinical Trials Directive: can we get it right second time around?

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Though well-intended, the European Clinical Trials Directive severely impeded clinical research. The Commission is now trying to revise the Directive, and is inviting researchers, patient groups and others to submit concrete suggestions. But will Europe's clinical trials community be able to exert sufficient pressure at a national level to see the draft safely through the EU legislative process?

By the time the Clinical Trials Directive came into force in 2004, it was already widely suspected that what had been designed as a benign and protective intervention would result in unexpected serious adverse effects. And so it turned out.

The past five years have seen the costs, bureaucracy and time required to carry out clinical trials increase sharply and the number of trials fall, with an even sharper fall in the number of patients enrolled. Worst hit have been the type of 'academic' or investigator-driven trials that are needed to find out how, and in whom, to use existing treatments to their best effect. Bad news for patients, bad news for the European Union's stated goal of becoming a research- and knowledge-led economy, and bad news for Europe's escalating healthcare bills, paying for expensive drugs that doctors don't know how best to prescribe.

Stefan Führing is the man at the European Commission who has been charged with sorting out what the Commission recently described as "arguably the most criticised piece of legislation" in the whole body of EU legal provisions for medicines. He has spent a lot of time trying to understand how legislation that was designed to protect the public from receiving treatments based on flawed and unreliable clinical trials, and to protect the safety and the rights and dignity of patients in trials, could have led to this expensive bureaucratic snarl-up. Most of the problems, he believes, were introduced after the proposed legislation was submitted by the Commission to the European Parliament and the Council of Ministers for consideration.

Speaking at a recent conference on the Future of Academic Clinical Research hosted by the Belgian Royal Academies of Medicine, Führing explained that the differing aims of Parliament and Ministers resulted in a kind of pincer movement on the draft legislation.

"The European Parliament was very interested in raising the status of the ethics committees to the same level as the national competent authorities [national bodies with responsibility for approving trials, medical products and the use of drugs]. And the Council of Ministers was very keen on avoiding anything that would involve a kind of political centralisation – any kind of cooperation in the assess-

ment of clinical trials."

The result is that clinical trial sponsors became accountable not just to the national competent authorities in each Member State where patients are enrolled, but also to ethics committees – organised at a national level in some countries, but at local or hospital level in others – hugely increasing the amount of paperwork involved and the number of hurdles to jump through. This in turn, says Führing, means that under the current directive, "there is virtually no mechanism for cooperation between Member States in assessing the clinical trial, even if this was agreed by the all 27 Member States."

Having spent more than a year conducting a full assessment of how the directive has impacted on clinical research in Europe, the commission is now redrafting the legislation with a view to formulating a proposal by October 2011. If the redraft is to serve clinical research, patients and the public any better than its predecessor, lessons of the past must be learned. "We are open to all kinds of ideas," Führing told the conference.

Risk-adaptive regulation

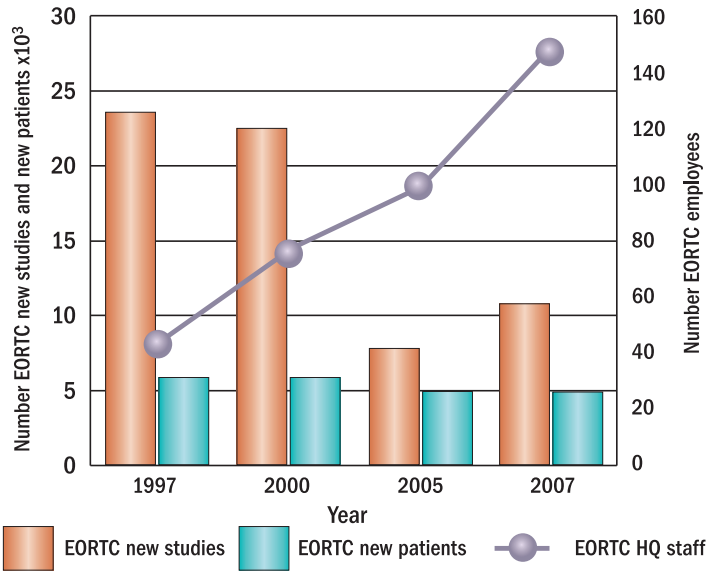
Over the past few years, many clinical researchers have been getting together in groups and forums to attempt to answer Führing's call for concrete proposals. It has not proved easy. One important principle around which a consensus has been building is that when trials involve little or no risk – for instance, an approved medicine used in an approved indication – they should not have to fulfil the same stringent regulatory requirements as more high-risk trials such as experimental gene therapy.

Such a system could substantially affect investigator-driven clinical trials, it is argued, because while four out of five clinical trials are commercial, non-commercial trials account for quite a high number of phase II trials, most of them looking at new uses (indication/population/condition) for medicines that are already authorised. Most phase IV trials (looking at how best to use approved medicines in the already licensed indication) are also sponsored by academic investigators.

An early exercise to map how such risk-adaptive regulations might work was conducted in January this year. The workshop drew participants from ECRIN (the European Clinical Research Infrastructures Network, set up in 2004), ICREL (set up to assess the Impact on Clinical Research of European Legislation), and various European clinical research networks, including the EORTC. It sketched out the basis for categorising clinical trials into three levels of risk (see p 48), and looked at how the regulatory demands might be adapted accordingly in each of the following areas:

- Ethical review
- Assessment by national competent authorities
- Safety reporting
- Monitoring
- Requirement for a sponsor (a single body with legal responsibility for every aspect of the trial)

FEWER TRIALS MORE RED TAPE



The number of new trials conducted by the European Organisation for Research and Treatment of Cancer (EORTC) plummeted from 24 in 2000 to 8 in 2005, a year after the Clinical Trials Directive came into force. This rose to only 11 new trials in 2007, despite a 50% increase in staffing levels

Source: D van Vyve and F Meunier. Facing the challenge of the European Clinical Trials Directive. www.touchoncology.com. Republished with permission

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Proposed risk categories

The Road Map Initiative for Clinical Research in Europe, held in Barcelona last January, proposed classifying clinical trials into three risk categories, which would determine how heavily they should be regulated.

Category 1: clinical trial on IMP [investigational medicinal product] without marketing authorisation in the EU. (Additional requirements could be proposed for trials with novelty-associated risks, as advanced therapies or first-in-human studies. This would correspond to a fourth, higher risk, category.)

Category 2: clinical trial on IMP with a marketing authorisation in the EU, but for another indication/population/condition. This raises the question of how to categorise low-novelty treatments, like drugs already available under a slightly different formulation (different salt, different routes of administration, slow release etc).

Category 3: clinical trial on IMP with a marketing authorisation in the EU, used in the licensed indication/population/condition. These trials are conducted to find the best way to use the drug.

A full report of the meeting can be found at www.ecrin.org – search for Road Map Initiative

- Insurance requirements
- Labelling (printed information that accompanies a drug specifying e.g. the batch number, and under which conditions the drug must be used)
- Documentation
- Inspections

The final report from that meeting can be found on the ECRIN website (search for 'Road Map Initiative'). As always, the devil will be in the detail, and a great deal of work will need to be done to delineate the boundaries between risk levels – concrete proposals to define exactly what is meant by terms such as 'minimal risk' and 'expedited review' can be sent on a postcard to Stefan Führing. The general principle of a risk-adaptive approach to regulation is, however, very likely to form a key part of the redraft of the clinical research directive scheduled for publication in October 2011.

A question of interpretation

The biggest test for the redrafted legislation, however, may come in the way that it is implemented. European directives are designed to achieve certain results while leaving it up to Member States to decide precisely how to achieve them. This approach has worked reasonably well when, for instance, harmonising legislation covering the rights of people with disabilities or gender equality. It has proved a bureaucratic and administrative nightmare as a means of regulating international clinical trials, requiring trial sponsors to comply with procedures and demands that can differ widely from country to country, depending on how the directive was interpreted.

Framing some of the redrafted legislation in terms of 'regulations' which have legal force across Europe is an option, but cannot be achieved without greater support than the Council of Ministers has so far shown. Harmonisation, argues Führing, can only be achieved through building trust and forging agreement between countries on the 'nuts and bolts' of procedures and guidelines, rather than on basic principles. This is something his office has been trying to promote in a variety of ways, including:

- An ad-hoc group chaired by the Commission on implementing the Clinical Trials Directive guidelines
- A clinical trial facilitation group, chaired by Member States, which is implementing a Voluntary Harmonised Procedure, and
- An inspectors' working party, to help harmonise the interpretation and monitoring of 'good clinical practice' guidelines.

Progress in this arena could lay the basis for moving towards the sort of mutual agreement procedure that already operates for approving some drugs in Europe, whereby approval to start a new clinical trial from a competent authority in one country would open the way to approval by all.

Reporting suspected unexpected serious adverse reactions, (SUSARs), is another area with great scope for harmonisation. Currently, national competent authorities, ethics committees and the EU's own EudraVigilance all require different processes for reporting SUSARs, which involves significant additional work for the sponsors, the competent authorities and ethics committees, with no evident benefit for patients.

There may also be scope for streamlining the way insurance is dealt with. One suggestion at the Royal Academies conference was to make legislative changes to enable single deals to be nego-

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tiated that would cover all EU patients in a given trial regardless of where they were enrolled. An alternative suggestion is to agree guidelines with the insurance industry on risk levels, terms of cover and premiums. This could speed up and simplify proceedings and cut costs, which many delegates argued are unjustifiably high given the very strong safety record of clinical research and the strict ethical and good clinical practice controls in place. The problem is, commented one delegate, there is no one who can speak on behalf of Europe's clinical researchers in the way that the National Institutes of Health do for researchers in the US.

Ethics committees

The hardest nut to crack will be how to streamline and harmonise the approval and monitoring of clinical trials at the level of ethics committees. Current procedures, say researchers, cause delays for no apparent benefit. Not only does approval have to be obtained in each Member State where the trial is running, but (in many countries) separate applications have to be made to each hospital where patients are enrolled. Convincing committees of the need to take biospecimens, and discussing how the privacy, dignity and rights of patients will be protected, can be particularly difficult; a lot of time is spent responding to requests from committees for detailed information. After all this, researchers may end up with a patient consent form that is 13 or 14 pages long, which can be complex and off-putting for patients to read and increases the time doctors need to spend with each patient invited to join the trial.

Proposals have been floated to change the system so that trials are referred to national ethics committees (a system already in operation in some Member States), or to go even further and have national ethics committees with mutual recognition, whereby getting approval in one Member State opens the way to approval in all. This is highly unlikely to happen. As delegates to the conference heard, Belgium alone has 200 ethics committees and they will quite understandably fight any move to undermine their independence.

After all, ethics committees are the only lay civic watchdog bodies amongst the multiple interlocking legal and administrative networks overseeing clinical research. It is surely right that the medical profession should have to explain itself to them and that they operate close to the patients where the trial is being conducted.

That said, there are clearly issues that need to be looked at. Training, first and foremost, so that ethics committee members understand the science behind today's personalised therapies. Guidelines could also be agreed to avoid repeatedly going over the same ground – a key example would be on harvesting and storing biospecimens and on procedures for anonymisation and access. These issues can take huge amounts of time to agree, even though they vary little from trial to trial. There is also scope for committees at different hospitals to work together in evaluating trials, even if this does not tie them into a single decision.

Patient groups

The trump card in the effort to remove unnecessary shackles from clinical trials has to be the involvement of patient groups. When it comes to finding ways to improve treatments, no one has a greater sense of urgency than patients. As Kathy Oliver, Co-Director of the International Brain Tumour Alliance told delegates to the conference, "Patients don't want to be just subjects of research, they want to be allies of research."

Involve them in the design stage of protocols, and you decrease the likelihood of later problems with ethical committees and increase the chances of quick enrolment. Include them on ethics review bodies, and they will defend the rights of patients, but will also recognise the price patients pay for unnecessary delays. Involve them in drawing up consent forms, and they will help to ensure that forms are user friendly, that the language is clear and that they contain an appropriate level of detail. (You can also expect them to demand that more detailed patient-friendly information is also available elsewhere.)

In redrafting the Clinical Trials Directive, Europe has a second chance to devise a system that serves the needs of research, public and patients. Getting it right requires formulating workable proposals and then convincing the Parliament and the Council of Ministers to back them. Europe's clinical research community will need to speak with a coherent voice if it is to avoid a repeat performance of the four-year stand-off that saw the last directive batted to and fro between Parliament, Commission, and Council, becoming less and less workable with each journey. A strong alliance with Europe's patients is likely to prove very valuable.