The health of European medical research

Attempts are under way to update EU regulations, with the aim of harmonizing clinical research across the continent

Philip Hunter

Medical research, similarly to finance and business, works best with light regulation; however, protecting patients during clinical trials, and afterwards when treatments have been approved, requires regulation. Attempts to square this circle and the challenge of testing sophisticated drugs and therapies have resulted in increasingly strict regulation of clinical research, particularly in Europe's leading medical research powers Germany, France, the Netherlands and the UK. There is growing concern among these countries with established pharmaceutical industries that clinical trials are increasingly hard to conduct; in fact, the number of applications has declined significantly during the past decade (Cressy, 2010).

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Meanwhile, the number of applications for clinical trials has increased in the USA, Canada and some southern European countries, notably Italy and Spain, where the regulatory touch has been lighter and combined, in some cases, with financial incentives, according to Paul Stewart, Dean of Medicine at the University of Birmingham in the UK. There is a danger therefore that Europe's leading research nations could lose their competitive edge in medical research at a time when radical new treatments are on the horizon. "Europe's weight in clinical research is diminishing," commented Markus Hartmann, senior consultant at European Consulting & Contracting in Oncology (Saarbrücken, Germany), which provides advice about medical regulatory affairs. The risk of falling behind extends beyond drug-based therapies to

surgery and medical devices, Hartmann added. He explained that the European Commission now considers medical devices and drugs as 'products' that can be sold in the internal market, and therefore require a common and harmonized regulatory framework.

Hartmann, along with other researchers, traces the recent decline in European clinical trial activity back to the European Union (EU)'s Clinical Trials Directive (CTD) 2001/20, which was supposed to provide a common framework for unifying regulation within the EU by 2020. "The Clinical Trials Directive is contributing to this effect, but is not the only factor," said Hartmann.

The root cause of the problem might be growing aversity to risk—which puts more emphasis on patient protection even when this is not necessary—but the EU directive has certainly fuelled this mood. "That initial EU Directive was actually quite a sensible document, but what was crazy was the legal creep that followed," said Stewart. "What the lawyers did was legislate for the worst possible scenario, instead of seeing the directive as a facilitating document enabling people to go and do research."

The directive actually had the opposite effect from the original intent: it led to even more regulatory fragmentation within the EU. This was first identified in a 2006 report, co-authored by Hartmann, which cited significant divergence in the national implementations of the EU directive (Hartmann & Hartmann-Vareilles, 2006). France was found to have the strictest regime, in which all trials including those involving cosmetics were rigorously supervised.

This divergence still exists. "Basically, the lack of harmonisation has not been resolved, as the Clinical Trials Directive has been transposed into national legislation in the form of laws, ordinances and

rules of implementation that still differ in so many procedural and technical aspects," said Hartmann.

Moreover, although the 2001 directive underlined maintaining current levels of patient protection, Hartmann argued that it has done little if anything to improve safety. "Do not forget the TeGenero disaster with compound TGN1412, tested in spring 2006 in a Northern London hospital," he said. "This was Europe's largest clinical research catastrophe so far and happened in the UK, after the UK switched from a very liberal trial notification system, where phase I trials with healthy volunteers were even exempted from notification or authorisation, to the provisions laid down by the Clinical Trials Directive."

These problems have now been acknowledged by both national governments and the EU itself, according to Liselotte Højgaard, chair of the Standing Committee of the European Medical Research Councils, and a medical imaging specialist at the University of Copenhagen in Denmark. "We have had very many meetings in Brussels about the issue [...] and in the last year the EU has become convinced it is a problem," she said. As a result the directive is going to be redrafted well before it runs its full 20-year course. "We have been invited to help them draft a new directive," said Højgaard. "That is a major achievement."

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The aim is to learn from previous mistakes and frame the new document to encourage harmonization and a reduction in bureaucracy and paperwork. "We must make it easier to implement in each member state," commented Højgaard, who added that the approval process also needs to be streamlined so that clinical trial teams do not have to repeat the same steps at different stages of the approvals process. "One of the things we are thinking about here in Denmark is whether we can make a one-stop-shop approvals process so you don't have to go in and send an application to the medicinal agency, and also to the ethical committee, and also to clinicaltrials.gov,"

said Højgaard. She hopes this new structure will be in place by the time Denmark holds the EU presidency in early 2012, and will encourage the rest of Europe to adopt a similar approach.

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Hartmann also acknowledges progress on the harmonization front. He cited the Voluntary Harmonisation Procedure (VHP), which was introduced in early 2009 by a network of national authorities, the Clinical Trials Facilitation Group (CTFG). It was set up precisely to coordinate implementation of the 2001/20 directive across EU member states, with little success at first. Now, the VHP allows applicants to submit protocols for trials to be conducted in many EU countries to the respective authorities, which agree on an assessment. "Then in a subsequent step, the applicant can submit

the protocol to the national authorities for authorisation," said Hartmann. "The VHP pilot aims to prevent divergent outcomes in the trial authorisation process, for example when a protocol approved in one country is blocked in another country."

These developments could eventually lead to a Europe-wide agency dedicated to clinical research regulation, along the same lines as the European Research Council for fundamental research, which Højgaard described as a great success. Such an agency would organize trials across the whole continent through a single streamlined approvals process, thereby covering a population of 500 million people.

Attempts to amend the EU 2001 directive have also been welcomed by big funding bodies such as the Wellcome Trust in the UK, a charitable foundation that funds medical and clinical research globally. "We recently issued a response to a public consultation paper from the European Commission, *Assessment Of The Functioning Of The "Clinical Trials Directive" 2001/20/EC*, in which we highlighted areas

where the Directive could be streamlined to reduce bureaucracy, while maintaining an appropriate regulatory framework," said David Lynn, Head of Strategic Planning and Policy at the Wellcome Trust. "We would like to see a more risk-based approach to regulation of clinical trials, a rationalisation of the multiple layers of bureaucracy and the approvals process."

Bureaucracy notwithstanding, a fundamental problem is finding the right balance between risks associated with different drugs or therapies. The 2001 directive has instead led to a one-size-fits-all approach, according to Stewart. "Part of the work we've been doing at the level of the UK Clinical Research Consortium is to look at risk-benefit analysis, so that you have a lower level of regulation on some things and higher on others that are unproven." If, for example, an existing drug turns out to be effective against a disease for which it was not originally developed, it would not be necessary to conduct thorough safety trials. This was the case with aspirin, initially developed as a pain killer over a century ago, which also protects against both vascular disease and bowel cancer

(ATT Collaboration, 2009; Din *et al*, 2010). During these trials, safety was still an issue as the drug was being used in a different context, but, even so, it was clear that acute side effects were highly unlikely.

While medical regulations in Europe err on the side of safety, they do little to regulate and harmonise the reporting of results after trials have occurred. The results from many clinical trials are never published as they fall victim to reporting bias for various reasons, notably because the pharmaceutical companies providing funding have an interest in promoting results favourable to their products and suppressing negative findings. A recent study by the Institute for Quality and Efficiency in Health Care (IQWiG) in Cologne, Germany, confirmed widespread publication bias in the past, which harmed patients through under-reporting of side effects (McGauran *et al*, 2010).

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"The most prominent example of harm caused by publication bias is probably the case of Class I anti-arrhythmic drugs," said Beate Wieseler, deputy head of IQWiG's Drug Assessment Department. In this 1980 trial, 9 of 49 patients with suspected acute myocardial infarction who were treated with a class I anti-arrhythmic drug (lorcainide) died, compared with only one patient in the placebo group, and yet the investigators ludicrously dismissed this as chance (Cowley *et al*, 1993). The results of the trial were not published until 1993 and, although the development of lorcainide was discontinued for commercial reasons, the investigators concluded that as a result of this delay in publication, the continuing use of class I drugs had led to several unnecessary deaths.

By the same token, ineffective drugs have sometimes gained market approval after over-reporting of their benefits, in some cases ignoring other, more negative, studies. Wieseler and colleagues found that studies reporting positive results for a particular drug were published in higher impact journals and were more likely to be picked up by other publications and the mass media.

Many cases of reporting bias, especially involving suppression of negative results, occurred 10 or more years ago. According to Stewart the situation has improved, although he concedes that, almost inevitably, journals will be drawn towards positive results given the increasing competition for readers and advertisers. "Whether publication bias goes on to the same extent now is debatable," said Stewart, pointing out that clinical trials now have to be registered in Europe and the USA so that the data is public, even if it is not published in a journal.

There will inevitably be some risk of bias in research funded by pharmaceutical companies, which, after all, are in the business to make money. It is therefore important to support 'investigator-driven' trials that are independent of any company, and it is here that the Wellcome Trust has an important role. "The Wellcome Trust supports the proposal for Investigator Driven Clinical Trials as joint collaborations across Europe," said Lynn. "We fund academic clinical trials, which are usually independent of drug company interests."

Independent money for academic clinical trials has indeed been more crucial during the past few years, since the EU 2001/20 directive tends to favour research funded by drug companies with the money and resources to overcome the increasingly high bureaucratic hurdles. Lynn commented that universities had not been well served by recent legislation. "Academic institutions are less-well resourced and equipped than commercial sponsors to deal with the bureaucratic burden imposed by the Directive," he said.

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promising research because they cannot stomach the paperwork involved, according to Højgaard. "For the first time in my life as a boss, I had the experience when I came in to a morning conference and asked one of the young consultants 'shouldn't we do a clinical study on this' and he said 'no I simply haven't got the energy for all this paper workload'." This experience spurred her to lobby for change. Critics such as Højgaard and others therefore hope that the redrafting of the amendment and the ensuing changes in national legislation will liberate European medical research from the regulatory shackles that have held it back.

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EMBO reports (2011) **12**, 110–112.
doi:10.1038/embor.2010.212