



Clinical trials today in Europe

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We need to find ways to improve the current systems and guarantee the same requirements for clinical trial authorisation and performance across the EU.

Patients' needs for new treatments of their diseases and symptoms require the development of new drugs and the further improvement of existing medications. Before a new drug or a new galenic formulation can be authorised for access to the market the drug's efficacy and safety have to be demonstrated. This can only be generated in patients during the clinical drug development phase. The gold standard in clinical research is the randomised, double-blind clinical trial. This has huge ethical implications and therefore clinical trials are highly regulated. A clinical trial has to undergo a complex approval process in all countries where the clinical trial takes place. Worldwide high quality standards and strict supervision requirements have been agreed: GCP (Good Clinical Practice), GMP (Good Manufacturing Practice) and GLP (Good Laboratory Practice) have to be applied in the different aspects of clinical trials.

The preparation and management of a clinical trial is a very complex task, especially when the trial is organised with several investigator sites in different countries. Full responsibility for all aspects of the trial has to be taken over by one organisation, called 'the sponsor'. This can be a pharmaceutical company or an academic institution – the conditions are the same. The fact that the generation of the clinical trial results is performed by physicians in their hospitals or private practices, potentially working in different countries under different legislation and healthcare conditions, increases the complexity of clinical trials. In most hospital-based trials the hospital pharmacist is involved in the clinical trials set-up as he or she is responsible for receipt, adequate storage, and distribution of the study medication to the investigator team. A GMP certificate is also required if the pharmacy has to perform any production activ-

ities, which include re-packaging or re-labelling.

Before 2004 all EU Member States had national legislation covering more or less explicitly the protection of subjects in clinical trials as requested by the Declaration of Helsinki [1]. To harmonise the prerequisites, the approval process, and the supervision of clinical trials as well as the safety of study participants Directive 2001/20/EC, the Clinical Trials Directive [2], was released by the European Commission in 2001, to be transposed into national legislation of the Member States by 2004. However, such transposition leaves Member States much room for interpretation. In the case of the Clinical Trials Directive this led to a wide variety of requirements: while Germany decided that the Clinical Trials Directive has to be applied strictly only to clinical trials with medicinal products, France expanded the application of these principles to all kinds of clinical trials, e.g. studies on radiotherapy, surgery techniques, or medical devices. Other countries defined the scope of the new regulatory requirements somewhere in between these extreme interpretations. In the following years more directives and guidance, covering different aspects of clinical trials, were released [3-5].

Consequences of the new legal requirements

The intended better protection of patients in clinical trials was supposed to be achieved by

- compilation of detailed documentation on the study medication to be provided in an 'Investigational Medicinal Product Dossier' (IMPD) together with a long list of other nationally requested documents to the competent authorities,
- approval of the trial by the competent authorities in all countries involved, supposedly within a maximum 60 days,

- ethical review of the trial within maximum 60 days by a national 'lead ethics committee', coordinating the review of all other ethics committees involved,
- registration of the trial in a European database (EudraCT) to ensure an overview over all ongoing clinical trial activity in Europe,
- collection of suspected unexpected serious adverse reactions (SUSARs) in a central European database (EudraVigilance) with expedited reporting requirements to all competent authorities, ethics committees and investigators involved in the trial, and
- regular inspections of clinical trial documentation and performance at sponsor and investigator sites, laboratories and ethics committees.

The result was a massive increase of workload with related staff and cost increases, as could be demonstrated in the ICREL (Impact on Clinical Research of European Legislation) project [6]. ICREL could demonstrate that the preparation phase of multinational clinical trials is prolonged by up to 90%. This means that the overall clinical drug development timeframe is not shortened and so patients do not get faster access to new treatments.

The massive investment into the EudraVigilance database and of the pharmaceutical industry into the required IT infrastructure for expedited reporting of SUSARs in the sponsor organisations has not convincingly increased the safety of patients in clinical trials. Currently the new pharmacovigilance system requires reporting to all competent authorities, ethics committees and investigators – not only involved in this trial but also in all other trials going on with this product world wide. This is complicated by the fact that every Member State has its own set of requirements for whom to inform by when.

Differences in interpretation of the Directive's principles during implementation into national legislation have also led to differences in definition of what is, for example, an 'investigational medicinal product', a 'non-interventional study' or a 'substantial amendment' with the related handling differences. And as a lot of national requirements are only available in local languages on the Internet the organisation of a multinational trial is a real challenge requiring considerably more staff and hence financial resources than before.

Nearly every respondent in the ICREL survey agreed that the Clinical Trials Directive is aiming in the right direction. But we need to find ways to improve the systems and guarantee the same requirements for trial authorisation and performance in all Member States. Only then will we ensure the original goals of better patient protection, higher attractiveness of

clinical research in Europe and faster drug development will be achieved. This may need improvement of existing and the development of new legislation. A decision on the next legislative steps can be expected in 2010.

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References

1. World Medical Association, Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects. [cited 2009 September 16]. Available from: www.wma.net/e/policy/b3.htm
2. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and

administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. Official J Eur Commun. 2001;L121:34-44.

3. Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products. Official J Eur Commun. 2005;L91:9-19.
4. Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use. Official J Eur Commun. 2003;L262:22-6.
5. VOLUME 4, Good manufacturing practices, ANNEX 13, Manufacture of investigational medicinal products. Brussels July 2003. [cited 2009 September 16]. Available from: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-4/pdfs-en/an13final_24-02-05.pdf
6. Impact on Clinical Research of European Legislation (ICREL), Project Final Report, February 2009. [cited 2009 September 16]. Available from: www.efgcp.be/ICREL

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HEALTH DATA

'Nul points' for EU harmonisation of clinical trial ethical approval procedures

Getting approval for a multinational clinical trial is still time consuming and expensive, despite EU legislation in 2001 to promote good practice [1]. An article in the *British Medical Journal* by Andreas Schnitzbauer and colleagues [2] relates their experiences of an investigator-initiated trial in 10 European countries and three non-EU countries with a total of 40 sites in the EU and four sites outside the EU. The trial approval process started in July 2006.

The main difficulties involved time and money (see Table 1). The time taken for approval ranged from 30 days (Sweden) to 266 (UK). The UK required the most substantial changes, adding up to 100 days in response times from the study team (not stated in the table). However, queries from Belgium and the UK were regarded as most helpful in improving the study. Fifteen committees made no charge for their work, while in Italy five committees charged over Euros 2,000.

Forty-six per cent of ethics committees had queries about the insurance, even though certificates were obtained from an international broker in accordance with the national requirements. Countries that required submissions to local committees did not comply with the European law. Although the approval process led to constructive protocol modifications, the time taken affected study recruitment, which is critical in a trial with

Table 1: Time taken to get ethics committee approval and fees charged (2006–2007)

Country	No. of committees	Median no. of days (range)	Median charge (Euros)	Minimum (Euros)	Maximum (Euros)
Austria	2	35 (26 to 44)	0	0	0
Belgium	3	119 (119 to 181)	1,250	300	1,250
Finland	1	47	400		
France	1	123	0		
Germany	14	43 (29 to 93)	400	0	600
Italy	7	61 (35 to 107)	2,400	0	6,000
Netherlands	2	91 (61 to 120)	0	0	0
Spain	2	75 (72 to 77)	632	632	632
Sweden	2 *	30	1,460	1,000	1,920
UK	4 ♦	246 (192 to 266)	0	0	0

* simultaneous approval; ♦ national + local

limited financial and human resources. Striking the optimal balance between turnaround times and identifying important critical ethical issues is essential to ensure clinical trials in the EU are safe and cost-effective.

Andreas Schnitzbauer and colleagues suggest that factors such as the use of a single language (English) for protocols and communications, standardising ethics fees, and centralising the review process, perhaps to an EU committee, may help achieve harmonisation.

References

1. Directive 2001/20/EC. Article 7. Available from http://eur-lex.europa.eu/smartapi/cgi/sga_doc?smartapi!celexapi!prod!CELEXn.umdoc&numdoc=32001L0020&model=guichett&lg=en
2. Schnitzbauer AA, et al. *BMJ*. 2009;338:b1893. doi:10.1136/bmj.b1893.