

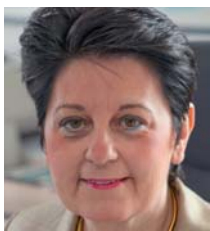
European Union clinical trial legislation and cancer research



Marie-Anne Meeus
MD, FBCPM



Remy von Frenckell
PhD



Professor Françoise Meunier
MD, PhD

The European Directive 2001/20/EC of 4 April 2001 [1] was written not only with the intention of providing better protection to the human subjects participating in clinical trials, but to improve standards by ensuring the application of Good Clinical Practice in all clinical research. The Directive sought to harmonise and regulate the conduct of clinical research throughout Europe by means of a common legal framework. Each Member State has had to change its national laws for clinical drug research to meet the requirements of the Directive, which came into force on 1 May 2004.

However, even by 2003 experts from the cancer field [2], including the European Organisation for Research and Treatment of Cancer (EORTC), had raised concerns that national implementation by the Member States would possibly not take into account pan-European research settings and the independent academic trials not intended for drug approval. This means that all trials, whether for drug registration or not, have the same level of requirements.

The EORTC experience

Two years after the Directive came into force and now with experience of its application, those early predictions by EORTC of the potentially damaging effects on academic

The European Directive on clinical trials has had a significant impact on the timelines and costs to conduct clinical research on medicinal products and the access by cancer patients to innovative medicines through clinical research. Further harmonisation across the EU is necessary.

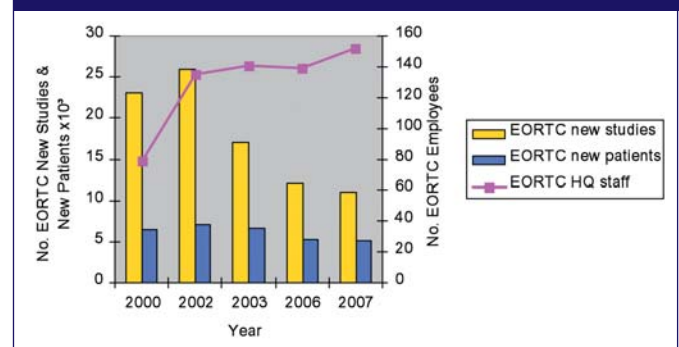
research seem to be true [3]. One of the problems resided in the fact that one sponsor had to take the total legal and financial responsibility for a trial, preventing many charities and academic groups from organising clinical trials due to the financial and administrative burden. Indeed, for the EORTC, costs rose by about 85% because of insurance expenditure, fees to Ethics Committees and Competent Authorities (CAs) as well as the increase in staff necessary to fulfil all the administrative requirements.

Looking at the EORTC experience [4] in activating new trials between 2002 and 2007, clinical trials on medicinal products decreased from approximately 20 per year in 2002–2004 to nine per year from 2005 till 2007. Yet the number of other types of trials (observational, radiotherapy and surgery) remained stable.

In addition, the number of patients treated in clinical trials decreased from 6,500 to 5,000. Meanwhile the number of EORTC staff had increased, despite the drop in the number of newly activated clinical trials and treated patients (see Figure 1).

Due to the new Ethics Committees requirements, there was an almost fivefold increase in the EORTC global costs of insurance coverage compared with 1996; there was a 128% increase for 2005–2006. This was due to the national variabil-

Figure 1: New EORTC studies (2000–2007) compared with the number of patients recruited and EORTC headquarter staff



ity in the type of insurance policy required. Most countries requested a trial-based individual insurance policy according to the number of patients recruited in the country and not an annual based policy covering all the trials carried out in the given country.

Did the Directive expedite the set-up of trials, compensating for the increased costs by time saving?

A report published recently in the *British Medical Journal* [5] evaluated the time taken for the different ethical approval procedures in 40 sites of 10 European countries for a cancer study. Although the Directive states that “in case of multi-centre trials, a single opinion shall be given for each Member State concerned by the clinical trial” [1], the procedures varied substantially among the EU countries (submission to each site, single Ethics Committee approval for the whole country, approval by the lead committee and confirmation by the local committees or separate national and local approvals). This led to substantial differences in time approval, with half of the Ethics Committees taking longer than the authorised 60 days. Interestingly, the most expensive fees requested by Ethics Committees did not ensure the shortest timelines. The fastest procedure was when every site submitted individually to their local Ethics Committee. Although the comments made by the Ethics Committees led to constructive protocol modifications, it delayed the start for study recruitment with increased start-up costs and extended trial duration bringing extra costs. The authors concluded by suggesting improved standardisation of the procedures for multi-centre trials, with regulation of the Ethics Committees’ fees, especially for trials with limited academic funding but with a sound scientific basis.

Examining all the studies performed at the EORTC from

2000 up to July 2009, the mean time elapsed between the protocol release and the first patient entering into the trial showed a regular increase peaking in 2004.

Taking 2004 as the pivotal year of implementation of the Directive, the mean time from protocol release to first patient prior to the Directive was 274 calendar days (calculated from 50 trials) while the mean post Directive was 240 days (calculated from 38 trials). Since 2007 the mean number of days has stabilised at around 150 days (see Figure 2). The period between 2004 and 2007 could correspond to familiarisation of the new Directive both from the CAs and EORTC staff.

The Voluntary Harmonisation Procedure

To organise the coordination of the implementation of the new Directive across the Member States, the European Union Heads of Medicines Agency established the Clinical Trials Facilitation Group (CTFG) in 2004. This group initiated the Voluntary Harmonisation Procedure (VHP) which makes it possible to obtain a coordinated assessment of multinational clinical trial applications. The VHP procedure, although not yet perfect in the pilot phase (changes to the clinical trials application were requested by several countries during the final phase instead of during the assessment phase), is one proposal to try to solve issues faced

by the different stakeholders of clinical trials [6]. It is a three-step procedure. First the sponsor makes a request for a VHP. Then the draft clinical trial authorisation (CTA) is reviewed by the national CAs of the participating Member States. After collection of the remarks from the Member States, the formal CTA is submitted for approval to each of the participating national CAs.

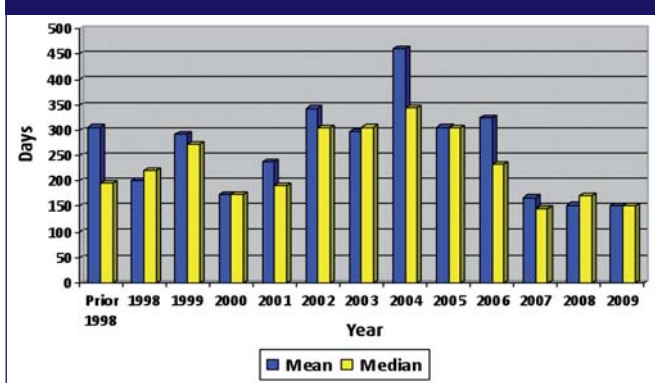
This procedure is normally limited to trials without marketing authorisation which precludes participation of non-commercial sponsors. However, the EORTC has been able to argue that a drug was being used off-label. In this case, for the pilot phase for one study, EORTC was able to obtain all the CA approvals in 135 days compared to the 248 days in multinational trials activated after 2006.

Solutions for academic sponsors

A workshop held in Brussels, Belgium in May 2008 discussed the challenges and solutions for academic sponsors in biomedical research [7]. In order to overcome the problems for European research organisations in the conduct of large academic multinational clinical trials several proposals were made:

- single comprehensive legislation applicable to all types of trials but based on the risk for the participating patients as assessed by one CA and the national Ethics Committees according to a clear guidance on their roles
- joint sponsorship should be possible
- a public health system insurance coverage
- waivers for the CA and Ethics Committee fees
- central support for the declaration of suspected unexpected serious adverse reactions
- information about all trials should be centrally available and results should always be published
- there also should be a clear legislation on biobanking.

Figure 2: The mean number of days from protocol release to first-in patient for EORTC clinical studies



Conclusion

There is still a long way to go to provide new treatments for cancer patients but we may remain optimistic as more than 600 pharmaceutical molecules are currently in development. Subsequently, there is the prospect of numerous clinical trials in the near future. The European Directive on clinical trials presents many challenges, of which hospital pharmacists also have a major role. Investigational products clearly fall within the ICH-GCP guideline [8] referred to in the European Directive 2001/20/EC. For instance, this means it is the duty of the participating institution and where allowed or required of a pharmacist to maintain clear records of drug accountability at the site level and to store the investigational products as specified by the manufacturer, in accordance with applicable regulatory requirements.

Author for correspondence

Marie-Anne Meeus, MD, FBCPM

Head of Operations Department
EORTC

83/11 Avenue E Mounierlaan
B-1200 Brussels, Belgium
marie-anne.meeus@eortc.be

Co-authors

Remy von Frenckell, PhD
Director Methodology and Operations
EORTC
remy.vonfrenckell@eortc.be

Professor Françoise Meunier, MD, PhD
Director General, EORTC
francoise.meunier@eortc.be

References

1. 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. *J Eur Commun.* 2001;L121:34-44.
2. Rowett L. Experts question impact of EU Directive on research. *J Natl Cancer Inst.* 2003;95(6):427-8.
3. Rice M. New data on clinical trials directive in Europe show few favourable outcomes. *J Natl Cancer Inst.* 2006;98(3):159-60.
4. van Vyve D, Meunier F. Facing the challenges of the European Clinical Trials Directive - the European Organisation for Research and Treatment of Cancer Perspective. *European Oncology.* 2008;4(1):14-8.
5. Schnitzbauer A, et al. Europe gets nul points for harmony in trials. *BMJ.* 2009;338:1302-4.
6. European Commission – European Medicines Agency Conference on the Operation of the Clinical Trials Directive (Directive 2001/20/EC) and perspectives for the future. Conference held on 3 October 2007 at the EMEA, London. Report of the Conference. [cited 2009 October 15]. Available from: www.eortc.be/services/doc/EUTCD/EC_EMEA_report_CT_20071003.pdf
7. Lukan C, van Vyve D, Lejeune S, Meunier F, Klingmann I, Demotes-Mainard J, Hohenberger P. Report on the EORTC – CONTICANET – ICREL – ECRIN workshop “Biomedical research in Europe: which challenges and solutions for academic sponsors?” 21 May 2008, Brussels, Belgium. [cited 2009 October 15]. Available from: www.eortc.be/services/doc/EUTCD/EORTC_biomedicalworkshop.pdf
8. Note for guidance on good clinical practice (CPMP/ICH/135/95) of July 2002. [cited 2009 October 15]. Available from: www.emea.europa.eu/pdfs/human/ich/013595en.pdf