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Does the European Clinical Trials Directive really improve clinical trial approval time?

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Keywords
ethics committee, European Clinical Trials Directive, multicentre clinical trial

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- The European Union adopted the European Union Clinical Trials Directive in 2001 to facilitate clinical drug research within Europe.
- The European Clinical Trials Directive has raised concerns over increased costs and complex administrative procedures, but the impact on duration between submission of a clinical trial application and approval by regulatory authorities is unknown.

WHAT THIS STUDY ADDS

- The introduction of the European Union Clinical Trials Directive appears not to shorten the duration of regulatory procedures within Europe.
- Duration of regulatory approval procedures is shorter in the USA compared with Europe.

AIMS

To facilitate and improve clinical research within Europe, the European Union (EU) adopted in 2001 the Clinical Trials Directive (EUCTD). The aim of this study was to compare duration between submission of a clinical drug trial application and approval by regulatory authorities in EU countries regulated by EUCTD *vs.* EU countries regulated by local legislation and, second, to compare the duration of regulatory approval in Europe *vs.* the USA and Australia.

METHODS

Application for clinical drug trial initiation was submitted to the regulatory authorities of 14 European countries, to the USA and to Australia. In Europe, 10 countries were regulated by EUCTD and four by local legislation.

RESULTS

In Europe, the median duration of regulatory procedures was longer in EUCTD countries compared with countries following local legislation (75 *vs.* 59 days; $P < 0.001$). Five EUCTD countries had a time to approval of >60 days (maximum within EUCTD rules). The long duration of regulatory procedures was the consequence of (i) sequential instead of simultaneous submission of trial application to regulatory authorities, and (ii) involvement of local ethics committees in procedures that should be followed only by central ethics committees. The duration of regulatory procedures was similar in Australia (67 *vs.* 68 days, $P = 0.388$), but significantly shorter in the USA (67 *vs.* 15 days, $P < 0.001$).

CONCLUSIONS

In this early stage of implementation, EUCTD appears not to shorten the duration of regulatory procedures for clinical trial initiation. Furthermore, Europe lags behind the USA in speed of regulatory procedures.

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Introduction

Randomized clinical trials (RCTs) are essential to assess safety and efficacy of new drug treatments. Clinicians and policy makers increasingly rely on RCTs to distinguish between worthwhile, useless or harmful drug therapies. However, the design and execution of clinical trials is a very costly, administratively demanding and time-consuming process. To facilitate and improve clinical research within Europe, the European Union (EU) adopted in 2001 the Clinical Trials Directive (EUCTD) [1], whose purpose was to harmonize clinical research practice within the EU and align Europe with international standards while further improving patient safety, so that drug development within EU will be facilitated and Europe will remain at the forefront of clinical research.

A country's competitive position in clinical research is determined among others by the duration of the regulatory procedures to initiate a clinical trial. To limit the duration of regulatory procedures for trial initiation, the EUCTD stipulated a couple of important changes [2, 3]. First, a clear role of central and local ethics committees was defined [4]. Furthermore, the central ethics committee should provide a single opinion for that country. This is a major change, since under previous legislation both local and central ethics committees had to perform the same procedures and give separate opinions on trial approval. Second, in parallel with submission to central ethics committee, the trial application should be submitted to (so-called) country's competent authority (responsible for drug safety and drug manufacturing procedures at national level). This is also a major step forward, since in most countries these applications had to be submitted sequentially before EUCTD came into play. Third, both ethics committees and competent authorities (regulatory authorities at country level) should give an opinion within 60 days from the receipt of trial application. These changes aimed to create an environment in which the regulatory approval process is rapid and consistent.

Although EUCTD was adopted in 2001, in 2005 some countries had still not implemented the directive, and were following local instead of EUCTD legislation. This provided the opportunity to compare clinical drug trial performance in EU countries with and without EUCTD implementation.

We therefore assessed country clinical drug trial performance in a single worldwide drug trial by measuring the duration (days) between submission of trial application and trial approval. We first compared EUCTD-regulated countries *vs.* EU countries regulated by local legislation. Second, we compared the duration of regulatory approval procedures in Europe *vs.* the USA and Australia.

This multicentre trial was approved by medical ethics committees and was performed in accordance with the guidelines of the Declaration of Helsinki. The trial with sulodexide in diabetic nephropathy is registered at ClinicalTrials.gov under NCT00130208.

Table 1

European countries following either European Union Clinical Trials Directive (EUCTD) regulation or local legislation

Europe	
EUCTD countries	Austria, Belgium, Denmark, Hungary, Italy, Poland, Portugal, Spain, Sweden, United Kingdom
EU countries local legislation	France, Israel, the Netherlands, Switzerland

Methods

The analysis of the approval process was based on the experience in a multi-continental clinical trial that evaluates the effects of the glycosaminoglycan sulodexide in patients with diabetic nephropathy. The trial is coordinated from three academic coordinating centres, i.e. Chicago (USA), Groningen (the Netherlands) and Melbourne (Australia) for, respectively, the American, European and Australia regions. After receiving US Food and Drug Administration (FDA) approval, the trial application was submitted to medical ethics committees of all participating sites between July and December 2005. Of the 14 European countries (116 sites), 10 countries (78 sites) were regulated by EUCTD and four countries (38 sites) were still regulated by local legislation (Table 1). Of the 83 US sites involved, 50 sites followed central ethics committee procedures, whereas 33 followed local ethics committee procedures. The 22 sites located in Australia followed local ethics procedures. We used Mann–Whitney *U*-test to compare the median duration of regulatory procedures across different countries. $P < 0.05$ (two-sided) was considered statistically significant. Data were analysed with SPSS version 14.0 software (SPSS Inc., Chicago, IL, USA).

Results

The median (interquartile range) approval duration was significantly longer in EUCTD sites (overall) when compared with EU sites following local legislation (Figure 1; 75 *vs.* 59 days; $P < 0.001$). However, when the data at country level were further analysed, it turned out that five EUCTD countries (42 sites) did not follow the legislation appropriately. The long duration of regulatory approval procedures in these countries was the consequence of (i) sequential instead of parallel submission of trial application to regulatory authorities (e.g. central ethics committee and competent authority), and (ii) involvement of local ethics committees in procedures that should be followed only by central ethics committees. When these countries were excluded, the duration of regulatory approval was similar in EUCTD and EU local legislation countries (Figure 2; 59 *vs.* 61 days, $P = 0.117$). The variation in duration of regulatory

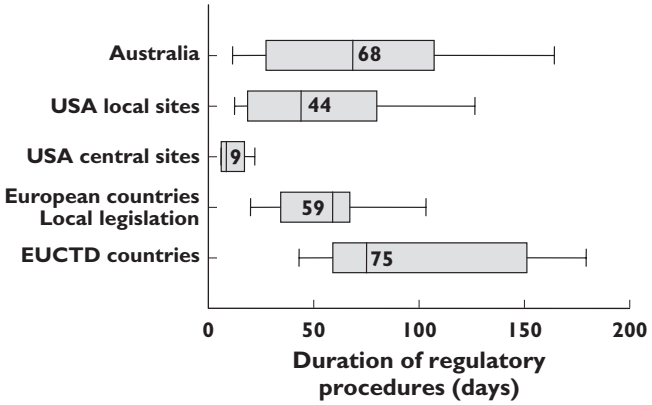

Figure 1

Duration of regulatory procedures (days) in Europe, the USA and Australia. European Union Clinical Trials Directive (EUCTD) countries *vs.* EU countries following local legislation, $P < 0.001$. EUCTD countries *vs.* US Central sites, $P < 0.001$

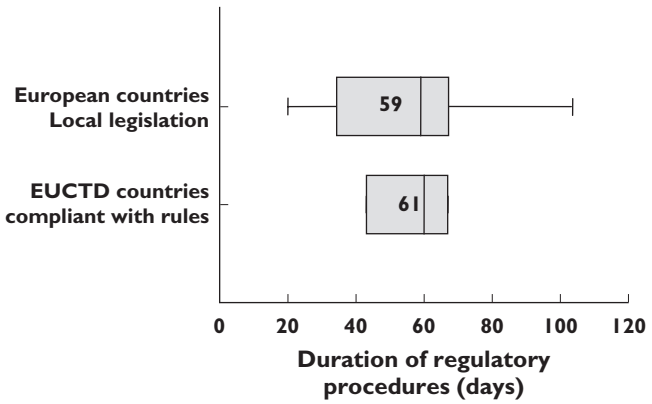

Figure 2

Duration of regulatory procedures (days) in EU countries following local legislation and European Union Clinical Trials Directive (EUCTD) countries compliant with rules. EUCTD countries compliant with EUCTD rules *vs.* countries following local legislation, $P = 0.117$

approval was smaller in EUCTD countries (range 43–67 days) compared with EU countries following local legislation (range 10–119 days).

Approval procedure was significantly longer in Europe (overall) compared with the USA (67 *vs.* 15 days, $P < 0.001$). Within the USA, sites following a central ethics procedure had a shorter duration compared with those following a local submission procedure (Figure 1, 9 days *vs.* 44 days, $P < 0.001$). The duration of approval procedure was longer in EUCTD sites compared with US sites following central ethics procedure (Figure 1; 75 *vs.* 9 days, $P < 0.001$). Median duration of approval procedures was similar in Europe compared with Australia (67 *vs.* 68 days, $P = 0.388$). Approval procedures were longer in EUCTD countries compared with Australia (Figure 1, 68 *vs.* 75 days, $P = 0.067$).

Discussion

Our data show that EUCTD-regulated countries (overall) take longer to approve a multicentre clinical trial compared with EU countries that follow national (local) legislation. This appeared mainly the result of the fact that EUTCD legislation was not followed properly. Yet even when EUCTD legislation was respected, the duration of regulatory approval procedures was only similar to that measured in countries following local legislation. The regulatory approval process is longer in Europe than in the USA, but is similar in Australia.

One would have expected that EUCTD countries would take a shorter time in the trial application process than local legislation EU countries. However, they took even longer. The failure to reduce the duration of regulatory approval procedures by EUCTD is primarily explained by sequential instead of simultaneous submission of trial application to regulatory authorities and involvement of local ethics committees in central ethics committees' procedures. According to the EUCTD, central ethics committees are responsible for reviewing the scientific and medical ethics issues associated with the research proposal, whereas local ethics committees should judge the competence of the local researcher and suitability of local facilities [4]. Our study reveals that local ethics committees repeated to a large extent the procedures (i.e. review of trial protocol and investigational manufacturing product dossier) of central ethics committees.

EUCTD countries complying with the procedures took the maximum allowed duration of assessment (61 days). This suggests that regulatory authorities will make use of the maximum allowed duration to give an opinion on trial application. EU sites following local legislation had the freedom to determine the duration of regulatory procedures, and some sites appeared to be very time-efficient, whereas others were very inefficient. If anything, the most one can say is that EUTCD will standardize the procedures and may eliminate the extremes (both of short and long duration).

Clearly, the USA has a shorter duration of regulatory approval procedures compared with Europe. In the USA, the legislation does not stipulate a certain deadline for the review procedure. Therefore, other factors may explain the shorter duration of the regulatory process. First, in the USA central ethics committees may have more experience with regulatory procedures, as legislation establishing central ethics committees has been effective since 1981 [5]. The role of local and central ethics committees is also very well defined. According to the National Research Act, each institution supported by federal funding has a local ethics committee (Investigational Research Board) in charge with trial approval assessment [6]. Central ethics committees are involved when institutions are performing FDA-regulated research and are too small to establish a local ethics committee. Second, US central ethics committees meet more

frequently than European committees, i.e. twice a week compared with once or twice a month.

A few studies have assessed the duration of regulatory procedures for trial initiation, but only before EUCTD implementation. One such study was performed in Spain and showed a duration of regulatory procedures of 72 days [7]. In our study, post EUCTD implementation, the Spanish regulatory authorities took 67 days to approve the trial application, a similar duration of procedures. Another study comprehensively reported trial initiation procedures, including regulatory procedures, staff training and drug distribution in 22 countries. The authors showed that, overall, the process of initiation took 10–12 months, almost double that anticipated. No separate data on duration of regulatory procedures were presented [8].

Except for duration of regulatory approval, an important factor influencing the competitive position of a country in clinical research is the number of patients recruited and retained in a trial. It was recently reported that the enrolment rate in a clinical trial is 50% (of those that received information for a clinical trial) in the USA and in Western Europe, whereas it is 80–90% in Eastern Europe [9]. Furthermore, 75% of patients were retained until completion of the trial in the USA and Western Europe, as opposed to 80–90% in Eastern Europe. Given these data, we believe that Eastern Europe in particular has a very competitive climate for performing clinical drug trials.

The European Commission is monitoring the effects of EUCTD implementation. The conclusion of a recent conference was that post EUCTD the trial application process is clearer and more standardized, although differences among countries on documentation requirements for ethical assessment still exist [10]. Our study has provided two important recommendations to improve current situation: first, more guidance on the role of local and central ethics committees, and second, enforcement of compliance with the 60-day timeline for review procedures.

Some issues need to be addressed when interpreting our findings. First, one should realize that the current study is based on a single multi-continental clinical trial and may not be representative of all clinical trials submitted to regulatory bodies after introduction of the EUCTD. Second, a limitation of our study may be its cross-sectional design. In longitudinal design, the duration of regulatory procedures (within each country) before and after EUCTD implementation could be evaluated. It is possible that some countries improved substantially after EUCTD implementation, but remain less efficient compared with countries following local legislation. Finally, this study evaluated EUCTD in early stages of implementation. It is possible that regulatory authorities in EUCTD-regulated countries gained more experience and have now become more efficient. Nevertheless, the current data give a good baseline impression and are a stimulus for Europe to keep on monitoring the trial initiation process from a regulatory perspective.

In conclusion, the European Clinical Trials Directive appears not to shorten the duration of regulatory procedures in Europe. Furthermore, Europe's competitive position in clinical research lags behind the USA. We have to prevent a shift of clinical trial activity to the USA and other parts of the world. This would certainly be the opposite effect of what the European Union intended with the introduction of the European Clinical Trial Directive.

Competing interests

None to declare.

The approval process took place within the multicentre study evaluating the effects of sulodexide in patients with diabetic nephropathy sponsored by Keryx Biopharmaceuticals. The funding body had no part in the initiation or execution of the current study. The funding body was not involved in data collection, data analysis, data interpretation or writing of the report.

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