

ORIGINAL ARTICLE

Impact of the European Clinical Trials Directive on prospective academic clinical trials associated with BMT

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The European Clinical Trials Directive (EU 2001; 2001/20/EC) was introduced to improve the efficiency of commercial and academic clinical trials. Concerns have been raised by interested organizations and institutions regarding the potential for negative impact of the Directive on non-commercial European clinical research. Interested researchers within the European Group for Blood and Marrow Transplantation (EBMT) were surveyed to determine whether researcher experiences confirmed this view. Following a pilot study, an internet-based questionnaire was distributed to individuals in key research positions in the European haemopoietic SCT community. Seventy-one usable questionnaires were returned from participants in different EU member states. The results indicate that the perceived impact of the European Clinical Trials Directive has been negative, at least in the research areas of interest to the EBMT.

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Introduction

The European Clinical Trials Directive (EU 2001; 2001/20/EC) was introduced on 1 May 2004 to simplify and harmonize the administrative procedures governing commercial and academic clinical trials. Concerns have been raised by interested organizations and institutions regarding the potential for negative impact of the Directive on non-commercial European clinical research.^{1–6} These have been supported by empirical investigation.⁷ The impact may not be negative in all EU member states for all types of

clinical trials.^{8,9} The predominant view is that the net impact of the Directive has been to increase the administrative burden associated with the competent authority and ethical clearances, in particular for multinational trials.¹⁰ The aim of the research presented here was to examine researcher concerns and perceptions regarding the impact of the Directive on academic clinical trials in the area of haematopoietic SCT.

Materials and methods

A pilot questionnaire (All questionnaires are available from the corresponding author upon request.) was designed and distributed electronically to active researchers within the European Group for Blood and Marrow Transplantation (EBMT). This aimed to explore researcher concerns about conducting clinical trials in the area of SCT, post-implementation of the European Clinical Trials Directive. Respondents were asked to provide information about their professional responsibilities associated with prospective clinical trials, including drug trials (job description, institution, country and experience with single-centre, multicentre national and multicentre international prospective clinical trials relating to SCT, and institutional activities related to different types of prospective clinical trials). Information was then provided regarding the date of implementation of the European Clinical Trials Directive in different EU member states. Respondents were asked whether they thought the numbers of academic and pharmaceutical clinical trials (single-centre, multicentre national and multicentre international) being conducted in their country and by their own institutions had been influenced by the implementation of the Directive. Respondents were also asked the reasons why they thought a decline in the numbers of trials had occurred where relevant.

Forty-one respondents returned the pilot questionnaire. The results indicated that the majority of respondents perceived the impact of the Directive to be negative (75%), although a minority reported that it had made no difference or had a positive effect on the implementation of prospective clinical trials. Nearly all respondents reported being involved, at a reasonably senior level, in academic

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clinical trials. The higher number of respondents from certain EU member states (for example, Germany) may have reflected the differential perception of problems and concerns in these states in particular (Table 1). The results of the pilot questionnaire were used to develop the main study questionnaire. The questionnaire used the results of the qualitative analysis of the pilot study results to formulate closed questions, focused on (1) researcher perceptions of the potential problems that have arisen following the implementation of the European Clinical Trials Directive (Table 2), and (2) their priorities for specific changes that could improve the implementation of clinical trials in areas of relevance to the EBMT (Table 3).

Cascade methodology was applied to ensure equal distribution of responses across EU member states. Respondents were recruited via the Chairs of the 11 EMBT Working Parties. This enabled the opinions of individuals in key research positions in the European haemopoietic SCT community to be surveyed.

Table 1 Response rates and distribution across EU member states

Country	Number of participants
Austria	2
Belgium	4
Denmark	1
Finland	2
France	9
Germany	12
Greece	1
Hungary	2
Italy	7
Netherlands	4
Norway	1
Poland	3
Spain	3
Sweden	6
Turkey	4
UK	9
No response	1

Table 2 Rating by the participants of the extent to which they agreed or disagreed with statements regarding the impact of the European Clinical Trials Directive, developed from the pilot study

Researcher agreement or disagreement with statements regarding the impact of the European Clinical Trials Directive	Mean rating (s.e.)	s.e.
Increased volume of paperwork	1.11 ^a	(0.04)
Increased demands for study conduct (such as monitoring or audit)	1.29 ^{ab}	(0.07)
Increased running costs associated with the trial	1.43 ^{ac}	(0.90)
Increased legal requirements in general	1.50 ^{bc}	(0.70)
Increased approval costs	1.55 ^{bc}	(0.20)
Increased costs of insurance/indemnity	1.63 ^{bc}	(0.10)
Delays in institutional approval (such as research and development or approval from the directorate)	1.65 ^{bc}	(0.11)
Increased liability	1.67 ^c	(0.10)
Increased number of regulatory authorities required to approve trial	1.68 ^c	(0.11)
Increased requirements for ethics approval	1.72 ^c	(0.12)
Committees requiring use of their own forms in addition to national or internationally agreed forms	1.94 ^c	(0.14)
Practical problems with official forms (e.g. form cannot be saved)	2.00 ^{cd}	(0.14)
Lack of harmonization between forms used by committees at national level	2.27 ^d	(0.16)
Lack of harmonization of forms used by different committees at local level	2.33 ^d	(0.16)

The statements are included in the above table. A lower average score indicates greater average respondent agreement with each statement. Superscript characters are used to indicate which means are significantly different from each other (as assessed by the Tukey *post-hoc* test for pairwise differences). Two means sharing a superscript character implies that they are not significantly different from each other. Otherwise they are.

Results

Seventy-one usable questionnaires were returned. As before, respondents provided information about their professional responsibilities. All respondents were senior researchers or principal investigators who were actively involved in clinical trials in the area of haemopoietic SCT and were located across different EU member states (Table 1). In all, 86% had been involved in multicentre national trials at a senior level. In line with the results of the pilot study, 70% of respondents indicated that they perceived the overall impact of the Directive to be negative, 20% positive, 3% reported no change and the remainder expressed no opinion. Respondents were asked whether they 'believed that time to Ethics Committee/Competent Authority approval is longer or shorter since the implementation of the Clinical Trials Directive', and, if they replied 'longer', to indicate whether this was attributable to increased pre-submission administration, increased post-submission committee delays or other factors. Generally respondents (63.4%) perceived that time to approval was longer. Of these, 93% attributed this to pre-submission administration delays and 69% to post-submission delays (some participants indicated both as relevant). Other delaying factors were indicated as important by 76% of this subsample.

In response to the question 'do you consider it more difficult for institutions in your country to become involved in academic prospective clinical trials since the implementation of the Clinical Trials Directive', 86% of the participants reported that it was more difficult to become involved in single-centre prospective clinical trials, 82% in multicentre clinical trials and 86% in international multi-centre clinical trials.

A series of statements regarding researcher perspectives on the impact of the European Clinical Trials Directive were developed from the pilot study. These statements are included as they appeared in the questionnaire in Table 2. Participants were asked to rate the extent to which

Table 3 Mean scores for priorities for changes in the European Clinical Trials Directive

Type of change required post-implementation of the European Clinical Trials Directive	Mean rating	s.e.
Reduction in administrative burden	1.20 ^a	0.16
Harmonization of documents required for approval	1.35 ^{ab}	0.22
Increased public funding for prospective clinical trials	1.42 ^{abc}	0.18
More readily available support from the EU for translational clinical research	1.50 ^{abc}	0.19
Provision of ethical and regulatory approval free of charge for academic institutions	1.53 ^{bc}	0.20
Centralization of documents required for approval	1.55 ^{bcd}	0.17
National government or EU subsidization of insurance costs	1.60 ^{bcd}	0.21
Permitting co-sponsorship of academic prospective clinical trials	1.60 ^{bcd}	0.20
Improved definition of interventional versus non-interventional clinical trial	1.67 ^{bcd}	0.21
Clearer differentiation between 'commercial' and non-commercial clinical trial	1.72 ^{bcd}	0.22
Improved definition of substantial versus non-substantial protocol amendment	1.73 ^{cde}	0.22
Reduction in the degree of monitoring required for investigator-led trials	1.75 ^{cde}	0.23
Implementation of a true single opinion in a member state	1.82 ^{cde}	0.24
Improved definition of an interventional medicinal product (IMP)	1.85 ^{cde}	0.24
EU or nationally funded local training on administrative requirements of the directive	1.88 ^{cde}	0.24
Creation of a single Competent Authority for all EU member states	1.90 ^{cde}	0.24
Permitting industry to use data from 'non-commercial' clinical trials	2.35 ^m	0.30

Participants were asked to rate the extent to which they agreed or disagreed that changes associated with the implementation of the European Clinical trials directive should be prioritized. A lower average score indicates greater average respondent agreement that the change should be prioritized. Superscript characters are used to indicate which means are significantly different from each other (as assessed by Tukey's *post-hoc* test for pairwise differences). Two means share a superscript character implies that they are not significantly different from each other. Otherwise they are.

they agreed or disagreed with each statement (5-point rating scale, anchored by 1='agree strongly' and 2='disagree strongly', midpoint of 'neither agree nor disagree', and a 'no opinion' option). Application of a general linear model repeated-measures procedure tested for the main effects of trial type (single-centre, multicentre national and multicentre international), type of concern and potential interactions between these. For all types of trials, the average ratings were below the midpoint of the scale, indicating that participants tended to evaluate negatively the impact of the European Clinical Trials Directive across all of the items. Differences did not (quite) reach the significance for trial type ($F(2,41) = 3.7, P = 0.06$).

A significant effect attributable to type of concern was observed ($F(13,30) = 5.6, P < 0.001$). Significant pairwise differences (Tukey's *post-hoc* test) between different types of concern are summarized in Table 2. The greatest concern was associated with the increased *volume of paperwork, increased demands associated with running the trial (monitoring or audit, or legal requirements), or increased costs for insurance or ethical approval*. The significant interaction between type of concern and trial type ($F(26,17) = 2.39, P < 0.05$, Figure 1) indicated that greater concerns were expressed for multicentre international trials regarding *increased insurance costs, delays in institutional approval and increased liability*. Concerns about increased running costs and increased legal requirements were not so great. The lower levels of concern about the potential increase in regulatory approvals may reflect that, in most countries, there is already an obligation pre-Directive to gain approval.

Finally, respondents rated potential changes that might be implemented to facilitate national single-centre, national multicentre or international multicentre trials. The different items, derived from the pilot study, are reproduced in Table 3. As before, a general linear model repeated-

measures procedure was applied. A significant main effect attributable to type of change was observed ($F(16, 44) = 6.14, P < 0.001$). Significant differences are summarized in Table 3. Note that all of the mean scores had values less than the midpoint of the scale (3), indicating, on average, agreement with all the changes. *Reduction in administrative burden, harmonization of documents required for approval, and increased access to public funding for clinical trials and translational research* were priority changes for respondents.

Discussion

The results indicate that the perceived impact of the European Clinical Trials Directive has been negative, at least in the research areas of interest to EBMT. The results of the pilot and main studies suggest similar interpretation in this regard, despite the potential self-selection bias for respondents included in the pilot study. In terms of identifying potential changes that would remedy the situation, prioritization was given to the need to reduce the administrative burden associated with running academic clinical trials. As part of this, the need to harmonize documentation associated with the application process for trial approval and monitoring was identified. Increased insurance costs, delays in institutional approval and increased liability were particularly problematic for multicentre international trials. The creation of a single European Competent Authority was not rated as being as important as some of the other potential changes.

To conclude, the results support the impression provided by much of the literature that the European Clinical Trials Directive has increased the (perceived) administrative burden on researchers, and introduced additional barriers and bottlenecks into the research process. This may be

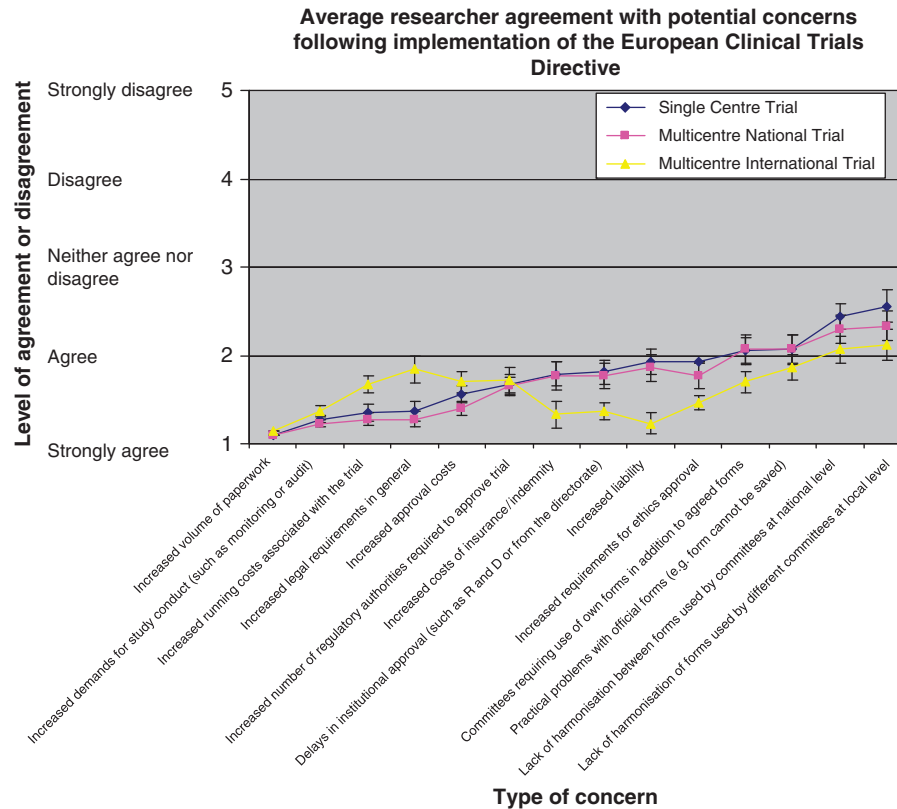


Figure 1 Differences in researcher concerns associated with the impact of the European Clinical Trials Directive on different types of clinical trial. The lower the mean rating, the greater the respondent agreement that the concern represented a problem regarding the implementation of clinical trials following the European Clinical Trials Directive.

attributable to the process by which each member state incorporated the Directive into national legislation, thereby introducing important differences in interpretation. Policy changes are required, specifically aimed at facilitating clinical trials by promoting harmonization, reducing administrative burdens, and streamlining the regulatory and approval process.

The CLINT project partners met to share the findings with ICREL (Impact on Clinical Research of European Legislation, a 1-year project funded by FP7 to measure change in the performance of clinical trials in Europe between 2003 and 2007), ECRIN (European Clinical Research Infrastructures Network) and ELN (The European Leukaemia Network). The meeting also took into account the findings of the European Science Foundation 'Forward Look'.¹¹ A series of stakeholder workshops (also involving EFGCP, the European Forum for Good Clinical Practice.) have explored issues relevant to clinical research in Europe, and will deliver recommendations through a final stakeholder conference in mid-2010, specifically a set of concrete and actionable recommendations relevant to the formal review of the Directive, which is scheduled in 2010.

Conflict of interest

The authors declare no conflict of interest.

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