CLINT WP3 Final Report

The impact of the European Clinical Trials Directive (2001/20/EC) on initiation and implementation of prospective clinical trials in Stem cell transplantation

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Abstract

The current literature appears to indicate that the introduction of the Clinical Trials Directive 2001/20/EC has on balance had a negative impact on the implementation of prospective academic (non-commercial) clinical trials. This report examines the impact of changes in the ethical and regulatory regime...
resulting from the Directive. Data was gathered through questionnaire and workshop, from professionals involved in carrying out local, national and international prospective non-commercial clinical trials in the field of stem cell transplantation. The respondents appeared to predominantly perceive the impact of the implementation of the European Directive to be negative, although a minority perceived it had made no difference or even had a positive effect on the implementation of prospective clinical trials. The results indicate that, as might be predicted from anecdotal evidence and the scarce research into the impact of the European Clinical Trials Directive, the effects of the legislation on prospective clinical trials in the area of stem cell transplantation are not substantially different to other areas of clinical trials. Concerns relate primarily to the increased administrative burden associated with conducting trials, (including that associated with regulatory and ethical approvals, and insurance costs). In addition, respondents made specific recommendations regarding European level changes which might facilitate the future implementation of prospective clinical trials in the European context, including those relating to the harmonization and centralization of the approvals process, actions to reduce costs (for example, through reduction of insurance costs, or provision of state subsidisation for insurances), and a refocusing of activities on the medical relevance of research, rather than the legal implications. A second phase of this workpackage focussed on the impact of the Directive on informed consent and data protection issues, through a series of one-to-one interviews with senior practitioners in stem cell transplantation across Europe. The view of most interviewees was that the Directive had had little impact on these areas.
INTRODUCTION

Autologous and allogeneic stem cell transplantation (SCT) is the treatment of choice for many haematological diseases. Within healthcare provision, SCT represents one of the most costly medical interventions which is also associated with high levels of risk, (transplant-related mortalities of up to 50% are currently being observed. Ongoing research is resulting in the introduction of new drugs and technologies, which have the potential to improve patient outcome but also to increase costs. Critical evaluation of clinical outcomes is central to research in this area (for example, through the transmission of outcome data from individual centres to a central database held by the European Cooperative Group for Bone Marrow Transplantation (EBMT) for further analysis and reporting). The question arises as to whether the implementation of clinical trials, associated hypotheses testing and comparative analysis with other treatments has been negatively, or indeed positively, impacted by the European Clinical Trials Directive. The research reported here aims to investigate whether the European Clinical Trials Directive has had an impact (whether positive or negative) on academic
prospective clinical trials relevant to stem cell transplantation, and how this compares to the impact of the Directive on clinical trials in other areas of medical research. This report describes the implementation of the Clinical Trials Directive (2001/20/EC) its provisions, and some of the concerns raised by its implementation. It goes on to describe the methodology of Workpackage 3 of the CLINT project including questionnaires and workshop, the results, analysis and conclusions of the research together.

*The European Clinical Trials Directive.*

The EU Clinical Trials Directive (EU 2001; 2001/20/EC) was implemented on 1st May 2004 to simplify and harmonise the administrative procedures governing clinical trials by establishing a “clear, transparent process” for relevant authorities. An important element is the requirement that “Sponsors” of trials must design, conduct, record and report procedures according to internationally recognized principles of Good Clinical Practice (GCP). Specifically, a trial sponsor is the institution which takes legal responsibility for the trial and how it is carried out, including provision of effective insurance cover. A major result of the application of the Directive is the centralization of sponsorship to one single institution which facilitates both national and international clinical trials (across EU member states, and, in some instances, wider international clinical trials under circumstances where European centres are involved in the trial. Despite the intention of the Clinical Trials Directive to harmonise and integrate activities across European member states, the implementation of the Directive by individual EU member states has resulted in legislative differences between EU member states...
which may act to impede rather than facilitate pan-European harmonisation as well as presenting obstacles to the implementation of clinical trials themselves.

There is evidence (in part anecdotal) that the implementation of the European Clinical trials directive has had a mixed impact in terms of facilitation of prospective clinical trials in different areas of application. For example, concerns relate to the process of obtaining informed consent for patient participation in trials (for example, by proxy through a “professional legal representative” (Pincock, 2004), or to the increased level of paperwork and administration imposed on researchers following implementation of the Directive, and increased financial burden associated with insurance and with ethical and regulatory approvals (Hoey, 2007; Bosch, 2005). Whilst there appears to be some consensus that the impact has been largely negative, specific cases and concrete analysis are scarce in the relevant literature. Indeed, much of the accessible literature is in the form of commentary, opinion pieces and secondary reporting of unpublished research (Hoey, 2007; Bosch; 2005), although the focus of expert debate has been a predicted decline in academic clinical research (Morice, 2003).

Of considerable concern is the observation that, rather than facilitating the implementation of prospective clinical trials, a decline in the numbers of such trials being conducted is occurring (Hemminki and Kellokimpu-Lehtinen, 2006), although this may be EU member state specific, or related to particular clinical contexts. For example, Berendt et al (2008) report that the number of academic drug trials conducted in Denmark had been in decline since 1993,
for reasons which were not identified, and that this decline was not further impacted by the implementation of the European Clinical Trials Directive. In contrast, there is evidence to suggest that, in Austria, a 66% decrease in academic research occurred following the introduction of the Clinical Trials Directive, although trials sponsored by pharmaceutical companies remained unaffected (Singer, 2007). Indeed, there appear to be problems arising across different EU member states associated with different interpretations of the framework in national legislation of Member States, and, as a consequence, different implementation across Europe, which may pose particular problems regarding the implementation of multinational multicentre prospective clinical trials, a problem which would be compounded once trials are extended beyond the European context, for example to developing countries (EMEA, 2007).

In general, the literature appears to indicate that the impact has been negative. Hartman (2005) notes that as there is inadequate data relating to the types of problems encountered by academic researchers before the implementation of the European Clinical Trials Directive, comparison before and after the implementation will be difficult. Where data are available, the tendency for the Directive to have a negative impact is generally observable, although positive impacts are also identified (Hearn and Sullivan, 2007). For example, delays of between 6 to 12 months in setting up trials have been reported. Hartmann and Hartmann-Vareilles (2006) report that, in the area of oncology research, increased costs and burden of paperwork had acted as a
disincentive to researchers commencing new international trials. Whilst the results of this research have been widely quoted as evidence of the detrimental affect of the Directive, it is worth noting that some respondents reported that the new regulations were justified in terms of improving the quality of cancer clinical trials, and had increased the protection of patients entering trials. None-the-less, further research has highlighted the negative impacts of the Directive. For example, a clinical trial involving the chemotherapy drug doxorubicin has been reported to have suffered major setbacks and delays as a consequence of the implementation of the Directive (Keim, 2007).

The literature demonstrates a tendency to focus on financial, administrative and regulatory matters as barriers to implementation of prospective clinical trials following implementation of European Clinical Trials Directive 2001/20/EC. Additional difficulties may arise because of differences in legislation across member states. Ethical issues are frequently raised, and focus on the issue of how informed consent is obtained from patients entering into clinical trials. Specific problems and issues have also been identified in relation to protections for critically ill patients and emergency care research (Hartmann and Hartmann-Vareilles (2006)) as follows:

*The introduction of “sponsors” of clinical trials*

Problems identified include the practicalities of finding one sponsor for a multi-site (and often multi-national) academic clinical trial. Key concerns are the additional financial and administrative burdens that rest with a single sponsor. Issues relating to liability and to indemnity insurance are also relevant,
although this may vary according to the system applied to financing public health systems. Hartmann (2005) notes that member states with tax-financed public health systems, (for example, as is the case in the UK or Sweden), have found it easier to solve the liability problem associated with public sponsors. For example, in the UK, the Medicines and Healthcare Products Regulatory Agency (MHRA), Universities UK, and the Department of Health have carried out a regulatory impact assessment, which has enabled British charities and associations in the UK to sponsor pan-European multinational studies. However, problems relating to single institutional sponsorship may arise within those EU member states where different systems of financing apply.

Investigational Medicinal Product (IMP): supply and definition

Increased financial and administrative burdens apply in this context. In particular, the prospect of taking over the costs of prescribed medication. In only some European member states have mechanisms been put into place which allow for public cost takeover for tested drugs and co-medications (Hartmann 2005).

Reporting

There is a requirement within the Clinical Trials Directive for all suspected unexpected severe adverse reactions (SUSARs) associated with the investigational medicinal products (IMPs) to be reported to the competent authority, the ethics committee, and to all investigators within 15 days of knowledge of a non-fatal event. This has resulted in an increased
administrative burden associated with the multiple filing of reports, and increased burden in terms of processing them on the part of the relevant competent authorities to whom they are provided, which may result in important SUSARs being missed.

Ethics committees

The Directive introduced the requirement for ethical approval from one authority within in each EU member state. It is suggested that problems may arise over differences in procedures relating to ethical approval with multi-country trials. The administrative role of the ethics committee is deemed to be onerous, and some concerns relate to direct costs of submitting proposals, as well as the indirect additional administrative costs. Some EU member states have responded by introducing a waiver for fees in some form or another (EFGCP, 2007).

Indemnity requirements,

Insurance requirements differ across member states. Prior to introduction of the European Clinical Trials Directive, individual researchers would be covered under their institutional insurance schemes, the requirement for a single sponsor to be liable across the whole of the clinical trial means these insurances no longer apply. In addition as shown by CRASH2 in Germany, (CH Chung, A Freiberger, M Kalkum, SP Luntz, H Shakur and CM Seiler; Trials 2006, 7:22), differences in national requirements for clinical trial insurance may also present difficulties for single sponsors being able to utilise ‘world-wide’ insurance cover even for research carried out within Europe.
**Exceptions for non-commercial research**

Exceptionally, Sweden, Belgium, and Italy have introduced specific provisions for non-commercial clinical trials as part of their legal framework in order to maintain or augment the implementation of non-commercial clinical trials conducted within these EU member states. A new Directive (GCP-Directive 2005/28/EC \(^1\)), was due to be implemented through the EU by the end of January 2006. This new Directive will give member states more flexibility to legislate on non-commercial trials and was to include guidance on exceptions for non-commercial clinical trials. This Directive was adopted on 8 April 2005, with the aim of implementation by all EU member states by 29 January 2006. However at the time of writing the guidance on non-commercial trials is still awaited – although draft guidance on non-commercial clinical trials was issued for comment in June 2006.

**CLINT Workpackage 3**

The research reported here aims to investigate whether ethical and regulatory aspects of the European Clinical Trials directive have had an impact (whether positive or negative) on academic prospective clinical trials relevant to *stem cell transplantation*, in particular from the perspective of researcher barriers to conducting such trials. The research was in two parts. The first part focussed on the overall impact of the Directive on prospective academic clinical trials on *stem cell transplantation* while part 2 focussed on the impact of the Directive

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on issues relating to informed consent and data protection are also considered.

METHODS

Part 1
A questionnaire study was conducted in two phases. Those invited to participate in the first phase were all members of the European Group for Blood and Bone Marrow Transplantation (EBMT). Although initially envisaged to be a single stage study, the diversity of the responses in the first stage indicated that a range of concerns associated with the European Clinical Trials directive could be identified which were not predicted from the existing literature. Consequently it was decided to extend the study with a second stage using a more focussed questionnaire derived from the responses to the first stage. These open ended responses from the first stage were categorised and used to develop the second questionnaire, which was used in phase two of the study. Phase 2 participants were recruited from amongst stem cell transplantation practitioners from EBMT European working groups.

Part 2
A further study focussed on issues of informed consent and data protection and how these may have been affected by implementation of the Directive. This study was conducted through one-to-one telephone interviews with senior practitioners in stem cell transplantation across Europe.

Part 1: Phase 1.
The first questionnaire included various questions focused on understanding researcher concerns and perceptions associated with the initiation and implementation of prospective clinical trials, applied in the area of stem cell transplantation, following the European Clinical trials directive. The questionnaire is provided in ANNEX 1.

The questionnaire was developed to be completed electronically over the Internet using ‘Promise’ software developed by the CLINT WP4 and which is also used by EBMT for reporting on clinical trials. Respondents were contacted by email and provided with a password which could be used on the questionnaire Internet site to access the questionnaire itself.

Respondents were first asked to provide information about their professional responsibilities associated with prospective clinical trials related to stem cell transplantation (job description, institution, country and experience with single centre, multicentre national and multicentre international prospective clinical trials relating to stem cell transplantation, and institutional activities related to different types of prospective clinical trials in the relevant area). Information was then provided regarding the date of implementation of the European Clinical Trials directive in different EU member states. Respondents were then asked to indicate 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, both before and after implementation of the Clinical Trials Directive and whether the numbers of trials conducted had been influenced by the Directive. Information relevant to
the reasons for any potential decline in the numbers of trials was also collected. Both structured and open questions were included in this section, the closed questions being derived from the existing literature, and the open-ended questions soliciting additional information.

One factor of relevance may be the impact that the European Clinical Trials Directive has had on the time taken to complete the final process from approval of the final version of the protocol to the first entry of first patient (i.e. obtaining both ethical and regulatory approval). The next section of the questionnaire focused on time taken to first patient entry both before and after the implementation of the Directive, as well as the costs associated with ethical and regulatory approval. Finally respondents were asked whether they had recommendations regarding how to better facilitate prospective clinical trials in their own country.

**Analysis and Results**

**Respondents**

All potential respondents were affiliated to the EBMT. Although the entire membership was initially contacted, only a minority of these individuals were involved in the implementation of prospective clinical trials, restricting the number of potential responses. For some items (particularly those involving specific information which would need to be checked against factual sources, and which would be difficult to recall from memory) the number of respondents who answered was negligible, and these items are not further
discussed as their potential unreliability means that conclusions cannot be
drawn from the results. The analysis is therefore confined to descriptive
analysis, as this is most meaningful in the context of the study, whilst non-
parametric significance tests may have been appropriate to compare between
different EU member States, the low number of responses for most cells
would make such an analysis unreliable.

In total, 44 respondents responded to the request for questionnaire
completion. All respondents provided usable information. The national
breakdown of respondents is provided in Figure 1. Whilst not all EU member
states are represented, respondents were included who represented
reasonable geographical coverage of the EU member states influenced by the
European Clinical Trials Directive. The respondent’s roles in clinical trial
investigations are summarized in Figure 2. The majority of respondents in the
study held senior or lead roles in the investigations. Thus the respondents
should have a high level of involvement with the potential impact of the
European Clinical Trials Directive on prospective clinical trials.
Figure 1. The breakdown of respondents by primary place of work in different EU Member States. The respondent working in the Lebanon had previously been employed within Europe.

Figure 2. Roles of respondents in prospective clinical trials.
As can be seen from Figure 3 (below), the majority of respondents had been involved in both single and multicentre national prospective clinical trials, as well as international multicentre prospective clinical trials.

**Figure 3. Personal involvement of respondents in single and multicentre prospective clinical trials, and multi centre international clinical trials.**

Thus the respondent sample was appropriate to cover both the perspectives of different EU member states and type of prospective clinical trial, whether national single or multicentre, or international multicentre. Furthermore, participants had been involved in both academic and pharmaceutical trials (in most circumstances the former tended to dominate) across therapeutic, technical, supportive and post-transplant clinical areas.

**Figure 4. Personal involvement of respondents in academic and pharmaceutical prospective clinical trials in different clinical areas. It should be noted that seven**
participants reported involvement in both academic and pharmaceutical clinical trials, but did not state which type.

There was a tendency for respondents to perceive a reduction in numbers of prospective clinical trials in the respondents’ own institute and their own country, following implementation of the European Clinical Trials Directive (Figure 5). This really needs to be verified against the actual figures. However, not all respondents perceived that the impact of the European Clinical Trials directive was negative, although this view tended to dominate (Figure 6)

**Figure 5.** Number of participants perceiving a reduction in the number of prospective clinical trials being conducted post-European Clinical Trials directive in their own institutes and their own country.
Figure 6. Perceived impact of the European Clinical Trials Directive on number of prospective clinical trials being conducted in different EU member States.

The potential reasons for the increased difficulties in implementing prospective clinical trials are summarised in Figure 7, where responses are aggregated from the closed questions.

Figure 7. Perceived reasons for reduced numbers of prospective clinical trials (closed answer responses)
At the level of the individual’s own institution, increased demands relating to study conduct was judged to be the most problematic issue for many respondents, closely followed by the increased volume of paperwork required to meet statutory requirements (presumably the two are closely linked). Increased cost, (associated with running costs for the trial and approval costs) was also an important issue for many respondents. The increased number of regulatory authorities required to approve the trials was considered to be problematic, as were (to a slightly lesser extent), increased requirements for ethics approval and increased institutional liability should problems arise. The potential barriers perceived to apply to the implementation of prospective clinical trials at the national level were similar, although less frequently identified. Respondents could identify more issues related to their own institutions perhaps reflecting greater familiarity with their own personal experiences of implementing prospective clinical trials.

Finally, participants were asked to express their views regarding factors which might facilitate implementation of clinical trials post implementation of the European Clinical Trials Directive. An open response format was applied, and respondent answers were coded into super ordinate categories. The low number of responses to this question meant that the responses were statistically highly unrepresentative, and the broader themes identified are included in this report, to be utilized in the second questionnaire study. These are summarized in table 1.
TABLE 1
Recommendations regarding better facilitation of prospective clinical trials

Approval process
- Instigate and organise centralisation of documents needed for approval
- Reduction of the degree of monitoring required for investigator led trials.
- Harmonisation of legislation for EU-members
- Introduce a central ethics and regulatory body for all member states
- Reduction the number of Ethics committees needed for approval e.g. cantonal committees in Switzerland

Insurance
- Reduction of insurance fees (possibly through state subsidy)
- Reduction in the length of required institutional insurance (up to ten years e.g. in Italy)

Bureaucratic process
- Reduce administrative burden of implementing prospective clinical trials, in particular with respect to associated paperwork
- Increased focus on the scientific or clinical relevance of a study, less on legal implications

Funding
- Installation of proper public funding for trials
- More readily available support from the EU for translational type clinical research funding
- Provision of ethical and regulatory approval free of charge for academic institutions

DISCUSSION
Although the respondent sample was not large, the spread of responses across different EU member states was large enough to cover the range of responses from researchers actively involved in conducting prospective clinical trials in the area affected by the European Clinical Trials Directive.

Active researchers, primarily those involved in a senior role, who may be
expected to have a good insight into the impact of the European Clinical Trials directive into prospective clinical trials involving stem cell transplantation, also responded. Respondents also included those active in single and multi-centre national trials, and multicentre international trials, as well as pharmaceutical and academic trials applied to a variety of clinical areas. Thus it is reasonable to interpret the results as reflecting the types of problems encountered by active researchers in the area of prospective clinical trials associated with stem cell transplantation following implementation of the European Clinical Trials directive. The response rate also reflects the fact that EBMT membership are not all directly involved in prospective clinical trials, nor are at a sufficient level of seniority to feel confident in commenting on experienced and foreseen difficulties associated with establishing such clinical trials following implementation of the European Directive.

The respondents appeared to predominantly perceive the impact of the implementation of the European Directive to be negative, although a minority perceived it had made no difference or even had a positive effect on the implementation of prospective clinical trials. It is of course possible that those respondents who had more negative experiences of, and views about, the implementation of prospective clinical trials following the European directive were more likely to respond to the questionnaire. In addition, the higher number of respondents from certain EU member States (for example, Germany) may reflect differential perception of problems and concerns, possibly a consequence of the national implementation of the European Clinical Trials Directive having a greater impact on new clinical trials in some
EU member States compared to others. However, the sample does not allow for hypotheses testing in this respect.

The results indicate that, as might be predicted from anecdotal evidence and the scarce research into the impact of the European Clinical Trials Directive, the effects of the legislation on prospective clinical trials in the area of stem cell transplantation are not substantially different to other areas of clinical practice. Concerns relate primarily to the increased administrative burden associated with conducting trials, (including that associated with regulatory and ethical approvals, and insurance costs). In addition, respondents made specific recommendations regarding European level changes which might facilitate the future implementation of prospective clinical trials in the European context, including those relating to the harmonization and centralization of the approvals process, actions to reduce costs (for example, through reduction of insurance costs, or provision of state subsidisation for insurances), and a refocusing of activities on the medical relevance of research, rather than the legal implications. Unsurprisingly perhaps, respondents perceived a need for increased public funding for research in this area. Specific and pragmatic actions (for example, a “waiver” of fees for ethical and regulatory approvals for academic institutions involved in trials, presumably through state funding) were also identified by respondents.

Cross-validation of key results at the EBMT workshop, Florence, 2008

The above results were presented to an audience of interested researchers at the EBMT annual meeting held in Florence (2 April 2008). The report of this
meeting is provided separately (Annex 2). The results of the workshop group discussions indicated the emergence of a broad consensus with the results of the survey. Some additional and specific issues arose, very generally reflecting the results of the survey. For example, in the context of European centralisation of administrative procedures, the perceived need for electronic reporting of SUSARS via the internet to a single centralised European database, which can be accessed by all interested stakeholders, exemplified the lack of European harmonisation which exists at present. The submission of protocols to multiple ethics committees with different institutional remits exemplified the problems experienced with ethical and regulatory clearances. However, the workshop did not result in the identification of any additional broad issues which had resulted as a consequence of the European Clinical Trials Directive.

Limitations of the study

Some specific factors related to the potential consequences of the European Clinical Trials Directive, which can be measured, are omitted from this report. These are primarily related to specific information relating to the overall number of trials which have commenced post-directive in different member states. This information is being gathered in a separate activity within the Clint project, utilising the EBMT database. Similarly information about increased amounts of time between approval and inclusion of the first patient into the trial has been omitted, and this information is being gathered elsewhere in the project. Indeed, few respondents could answer questions which required looking up specific information, and appeared less confident about answering
questions applied at a national level, as compared to those reflecting their own institutional experiences. In addition, it was found that some potential respondents were unable to complete the questionnaire despite their willingness to do so because of software or computer related incompatibilities. None-the-less the first questionnaire provided considerable insights into perceived consequences of the European Clinical trials directive. The first questionnaire was therefore considered as a pilot for the development of a second questionnaire, where specific issues identified in the first questionnaire (in particular those originating in the qualitative sections of the first questionnaire), have been systematically investigated. Key EBMT stakeholders and researchers were targeted using cascade methodology. This ensured representation of the views of those most likely to be affected by the European Clinical Trials Directive in terms of implementation of prospective clinical trials related to stem cell transplantation.

**Part 1: Phase2**

The second questionnaire was developed from the qualitative outputs of the first questionnaire, including policy recommendations proposed by respondents to the first questionnaire. This part of the work has been submitted for peer-reviewed publication to the European journal *Bone Marrow Transplantation*. Detailed methodology, results and discussion on Phase 2 can be found in a copy of the submitted paper at Annex 3. The questionnaire used in Phase 2 can be found at Annex 4.
**Collaboration with Other Initiatives**

During the course of the project, other ongoing research activities touching on similar areas of research were identified. A number of these are of particular interest and relevance to the CLINT initiative. These are:

1. The FP6 (and now FP7) funded ECRIN project (European Clinical Research Infrastructures Network) which seek to integrate national clinical research facilities into an EU-wide network able to provide support to clinical research in any medical field and for any type of clinical research. Part of the remit of this initiative is to identify bottlenecks to multinational cooperation. In this context the researchers have had to address issues related to the implementation of the Directive.

2. The European Forum for Good Clinical Practice (EFGCP) work on mapping ethical review procedures for clinical research in 26 Countries across Europe. The initial results were published in 2007 (EFGCP. International Journal of Pharmaceutical Medicine 2007). EFGCP have indicated that they hope to update the information on a regular basis and revised data has already been provided for 2008.

3. ICREL, a one year project funded by FP7 and coordinated by EFGCP to measure and analyse the direct and indirect impact of Directive 2001/20/EC and related legislations in the EU on all categories of clinical research.
4. The European Organisation for Research and Treatment of Cancer (EORTC) has also carried out its own studies on the implementation of the Directive on cancer-related clinical trials. As these initiatives appear to have clear areas of overlap with the remit of the CLINT project, arrangements were made for a joint meeting with these research groups in order to share findings, discuss common problems and hopefully develop future collaborations. An initial meeting for sharing of results took place in October 2008. It being clear that there were several areas of common interest and overlap, a second meeting was arranged to take place at the EMBT Annual Conference in Goteborg in April 2009. The outcome of this meeting is described below.

Part 2: Informed Consent and Data Protection

This second part of the study looked beyond the impact of general ethical and legal aspects of the Clinical Trials Directive and to focus on the impact of differences in informed consent and data protection procedures across Europe on trans-national access to research data.

Currently, an informed consent template and information sheet template are sent to researchers by EBMT which is modified in each country according to the research project and local regulations and requirements.

Important questions relate to

- How informed consent is obtained
- How do ethics committees decide if this is acceptable?
• What is the process?
• How suitable are the EBMT informed consent form and information sheet templates for individual countries?

**Approach to Part 2**

The second questionnaire study completed in Part 1 of the CLINT project was targeted specifically at national members of EBMT with an active interest in clinical trials. For this second part of WP3 on informed consent and data protection many of the same people who responded to the second questionnaire of the first phase were approached. (Participants had been specifically asked in the earlier questionnaire to indicate whether they would be willing to be contacted again for a follow-up study). In Part 2 of the CLINT project, those individuals who responded positively to this question were requested to take part in a telephone interview. To avoid ‘questionnaire fatigue’, targeted one-to-one telephone interviews were used to explore the situation regarding informed consent and data protection for 20 respondents across as wide as possible a range of countries in Europe. Participants were asked for their consent for the interview to be recorded. All participants consented. Responses were referred to only by a code number. A copy of the interview script can be found at **Annex 5**.

**Analysis and Results**

The responses elicited mixed views from respondents on the impact of implementation of the Clinical Trials Directive on informed consent and data
protection issues. The majority view was that overall the Directive has had little impact on these particular aspects.

The most common concern appears to be of **increased administrative burden** (more forms to complete). German respondents in particular feel the Directive had greatly increased the level of documentation required.

“Informed consents are larger and more complicated and there are so many of them…Sometimes the patients/parents face 40 or 50 pages of different things and the overwhelming nature of that in the difficult circumstances of a child with cancer diagnosis, for example, is itself unethical.” (DE)

There was general agreement amongst respondents on the issues which should be covered and information that should be provided to study participants when obtaining informed consent.

There was however evidence of differences between countries in some areas. These include:

- Whether assessment of risk of adverse outcomes needs to be included in the information provided when obtaining the original consent
- Necessity of providing an assessment of the likelihood of a successful outcome
- The minimum time that should be allowed between providing information and obtaining consent
- Consent requirements for subsequent studies and if needed, when these should be obtained.
“If just want additional test or analysis you don’t need additional consent. Additional samples must obtain fresh consent” (BE)

“Depends if it’s clinical or biological……. What we usually do is to have an additional consent form for biological specimens at outset to say they may be used in future unspecified study/research purpose. This consent is additional and it is not associated with the clinical trial”. (FR)

The greatest difference between countries was found between those with a publicly funded health service and those that have health service funded through insurance. This also affects whether or not Ethics Committees need to see insurance certificate. The nature of the person or body initiating the clinical trial also affects insurance requirements.

“If investigator-initiated the University covers it and pays for the insurance….. But with societies/EBMT then it is (or has been) a problem. Most IRBs need the sponsor to provide the insurance.”

Information Sheets
Most respondents (85%) indicated that they would like to see an EBMT pro-forma information sheet developed. There was concern over the different requirements for information sheets both between different local research ethics committees within the same country and ethics committees in different countries.

“Some of what you write is quite subjective and a lot depends on the EC. Also …..tough comments come back from the EC and from the Patient Committee about an IC that are diametrically opposite each other. And then after the EC, the study goes for approval by the National Agency who could have different concerns again…..” (FR)

Data Protection:
There are some national differences between the type and extent of personal patient information required for ethical approval, including whether sex and age of patient need to be provided. In most cases personal data must be pseudo-anonymised and kept locked with restricted access. However,
responses indicated that some requirements such as Caldecott Guardians (UK) while in theory present to protect patient data may not in practice be very effective. There was also some concern that increasing digitalisation and transmission of patient information provides more opportunities for breaching of patient confidentiality.

“The legal requirement is not to identify a patient in studies.” (HU)

“it is necessary to have an independent monitor outside the institution conducting the trial to keep track of data protection issues.” (DE)

“In theory each Trust has a ‘Caldecott Guardian’ a nominated person responsible for the proper transfer of data.” (UK)

“Electric (sic) communications are a boon but they have also created all sorts of loopholes in patient confidentiality protection.” (UK)

“Yes it’s more difficult. You can’t share the data automatically. You have to have previous approval from your ethics committee and from the other centre’s ethics committee and state what data you are going to transfer and what study you are going to do with that data and what level of consent was available originally.” (ES)

Ethics Committee Requirements:

Respondents evidenced considerable concern over the level of variability of requirements by different ethics committees.

“not only is there a big difference from country to country but also within the same country…….”

“.even inside same country requirements vary from one Trust R&D dept. to another. Frustrating when one study approved somewhere in the UK then your own R& D doesn’t like it.” (UK)

Summary and conclusions:

There were some differences in responses even within same country. This may in part be due to lack of knowledge or even to differences in requirements of local research ethics committees. Responses also indicate a
lack of knowledge or uncertainty amongst researchers about some informed consent or data protection requirements. It is, however, clear that the greatest concern amongst researchers is that of the level of administrative burden imposed upon them, together with concerns over inconsistency of requirements between different ethics committees. The financial burden of insurance is also a significant problem. However overall, respondents indicated that the implementation of the Clinical Trials Directive had had little impact on informed consent and data protection issues. Most of the concerns that had been raised during the interviews were present before the implementation of the Directive which had so far resulted in little change either for better or for worse.

There were a number of issues that respondents thought important to be addressed, some at the level of the EU, national government or regulators and some more specifically which might be addressed by EBMT.

**Policy Change Proposals**

Participants were asked about actions that could be taken to facilitate issues of informed consent and data protection together with what changes they would like to see at a policy level. Suggestions for support and proposals for policy changes to the current situation included:

“A sample consent form and data protection information pamphlet for both patients and physician/research team is needed to facilitate improvement in participating countries will be needed. “(TR)

“Data transfer- EU standard for all.” (DE)
“All clinical researchers would like something homogenous for the whole of Europe….That would lead to authorization to automatically transfer data without having to make applications.” (ES)

“At least 90% of the paperwork involved with informed consent, ethics committees and all that is useless and doesn’t lead to increased protection for the patient.” (ES)

“We must not lose sight of the philosophy behind the informed consent, ie the fact that we want to protect the patient. Especially when you deal with pharmaceutical companies, it’s much more protection of the sponsor rather than protection of the patient which is why you have pages of detail” DE.

“The major reason people don’t contribute to EBMT trials is because it’s a lot of work and nobody is willing to pay for the person to do the paperwork….Recommends that centres that contribute to more than 1 EBMT trial, it should be a possibility that the EBMT could support the individual working with the data.” (AT)

“An issue for hematologists, is conflict with oncologists in the hospital trust, who have to get specific consent for administering chemotherapy…. it perhaps need to be explicit that by going into trial you are specifically consenting to chemotherapy.” (UK)

Recommendations to the EBMT

- Development of an EBMT pro forma information sheet for SCT clinical trials
- EBMT to develop national informed consent and data protection checklists for SCT clinical trials
- Identify ways of developing efficiencies to reduce current administrative burden.
- Lobby at national and EU level for greater simplification and harmonisation.
- Identify ways of addressing concerns over increased insurance costs.

Future Strategy
It has already been mentioned above that the CLINT project met in 2008 with other initiatives also addressing issues related to the implementation of the Clinical Trials Directive. A second meeting took place in April 2009. Representatives from ECRIN, EORTC and ICREL were invited to a CLINT workshop during the EBMT 35th Annual Congress in Gothenburg, Sweden. Each organisation presented it’s findings on how the Directive had impacted on prospective academic clinical trials. This was followed by a discussion on what recommendations should be made to the European Commission to influence the upcoming review of the Clinical Trials Directive which had been indicated would take place in 2010. The recommendations identified included:

- To require only one Clinical Trials Authorisation (CTA) irrespective of the numbers of participating nations, either by the development of a single CTA application across Europe or the mutual recognition of authorisations by Competent Authorities.

- To simplify and harmonise the procedures for clinical trial approval (e.g. the EudraCT forms as a single set of forms to be completed) and safety reporting (Eudravigilance and reporting rules).

- To define better and harmonise the roles of the ethics committees (achieve the so-called single-opinion) and of the competent authorities

- To adopt a risk-based approach: adaptation of the regulatory requirements considering the risk associated with the trial with regard to the safety reporting (e.g. limited safety reporting for commercially approved drugs), data monitoring, insurance, application dossiers,
substantial amendments, free-of-charge supply of drug (e.g. not in case of market approval).

• To allow co-sponsorship in the case of multinational trial with the aim of facilitating collaboration between research groups.

• To better define terms and concepts (IMP, interventional study, substantial amendment, etc.)

• To increase public financial support to investigator-led clinical trials.

• To extend access to EudraCT database

• To harmonise insurances requirements e.g. uniform costs per country, minimum and maximum indemnity payments, total duration of coverage, time to permit claims etc.

The meeting considered that these issues were of universal concern and it was important that they be developed and properly represented to the European Commission and other policy makers. This would require action beyond the end of both CLINT and ICREL. It was agreed that the four bodies represented, EBMT, EORTC, ECTIN and EFGCP would together develop a series of workshops over 2009/10 on key issues from those described above. This initiative is described in a Comment Piece submitted to the BMJ (see Annex 6). It was agreed that this initiative would be described as a Road Map Initiative for Clinical Research in Europe. A press release to this effect was released (Brussels 2 July 2009). This document is at Annex 7.
Overall Conclusion.

The results of WP3 have provided further evidence for the assertion that the Clinical trials Directive has overall had a negative impact on the conduct of prospective non-commercial clinical trials in stem cell transplantation. In addition, the CLINT collaboration with other initiatives looking at issues related to how the Directive impacts on clinical research, has confirmed that the results from WP3 are in close agreement with the findings from those other initiatives (ECRIN, EORTC, ICREL). Furthermore the ongoing collaboration between EBMT, ECRIN, EORTC and EFGCP in the Road Map Initiative for Clinical Research in Europe, demonstrates an excellent level of integration between different European initiatives, several of which are funded by the European Commission. There is every likelihood that this initiative will have a significant influence on the forthcoming review of the Clinical Trials Directive 2001/20/EC.
References


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Singer, E. (2007). Future of investigator initiated clinical trials in EU academia {abstract} Basic Clinical Pharmacological Toxicology, 101 (supplement 1:11)

ANNEXES

Annex 1: Questionnaire 1

Annex 2: Workshop summary report


Annex 4: Questionnaire 2

Annex 5: Part 2 – Interview Questions on informed consent and data protection

Annex 6: Goteborg meeting - Comment Piece

Annex 7: Road Map Initiative for Clinical Research in Europe
ANNEX 1
CLINT QUESTIONNAIRE
Regulatory and Ethical issues

Thank you for agreeing to participate in our study of the governance of clinical trials. To begin with we would like to ask you a few questions about yourself and your institution:

Job Description: [Free Text Reply]
Institution: [Free Text Reply]
Country: [Free Text Reply]
EBMT Centre Number (if known): [Free Text Reply]

We would now like to ask you some questions about your personal experience of prospective clinical trials related to stem cell transplantation. This may include but not limited to studies that are:

a. Therapeutic e.g. disease based,
b. Technical e.g. conditioning
c. Supportive e.g. GvHD, anti-infective or cytokines, and/or
d. Post-transplant care e.g. DLI

1. Have you personally been involved in the following clinical trials related to stem cell transplantation?

<table>
<thead>
<tr>
<th>Trial Type</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single centre prospective clinical trial</td>
<td>Yes [ ]</td>
<td>No [ ]</td>
</tr>
<tr>
<td>Multi-centre national prospective clinical trial</td>
<td>Yes [ ]</td>
<td>No [ ]</td>
</tr>
<tr>
<td>Multi-centre international prospective clinical trial</td>
<td>Yes [ ]</td>
<td>No [ ]</td>
</tr>
</tbody>
</table>

2. If appropriate, which of the following best describes your role in those trials you have been involved with? (please tick):

   Principal Investigator [ ]
   Co-Investigator [ ]
   Research Scientist [ ]
3. How would you categorise the studies you are/have been involved in, and what was the nature of the studies you are/have been involved in? (tick all that apply):

<table>
<thead>
<tr>
<th>Academic</th>
<th>Pharmaceutical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refers to clinical trials sponsored by a non-commercial group, such as EBMT, EORTC, national societies etc.</td>
<td></td>
</tr>
<tr>
<td>Refers to clinical trials sponsored by a commercial company</td>
<td></td>
</tr>
</tbody>
</table>

a. Therapeutic e.g. disease based: Academic [ ] , Pharmaceutical [ ]
b. Technical e.g. conditioning: Academic [ ] , Pharmaceutical [ ]
c. Supportive e.g. GvHD, anti-infective or cytokines: Academic [ ] , Pharmaceutical [ ]
d. Post-transplant care e.g. DLI: Academic [ ] , Pharmaceutical [ ]
e. Other: (Please describe):- [free text response]

We would now like to ask you some questions about your institution’s activity and experience of prospective clinical trials related to stem cell transplantation. This may include but not limited to studies that are:

a. Therapeutic e.g. disease based
b. Technical e.g. conditioning
c. Supportive e.g. GvHD, anti-infective or cytokines
d. Post-transplant care e.g. DLI

4. How many prospective clinical trials related to stem cell transplantation were started in your institution during 2004?

<table>
<thead>
<tr>
<th>Academic</th>
<th>Pharmaceutical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refers to clinical trials sponsored by a non-commercial group or charity, such as EBMT, EORTC, national societies etc.</td>
<td></td>
</tr>
<tr>
<td>Refers to clinical trials sponsored by a commercial company</td>
<td></td>
</tr>
</tbody>
</table>
**a) Single centre** prospective clinical trials:

- i) Academic: 0 [ ] 1-2 [ ] 3-5 [ ] >5[ ] [ ]
  - Don’t know
- ii) Pharmaceutical: 0 [ ] 1-2 [ ] 3-5 [ ] >5[ ] [ ]
  - Don’t know

**b) Multi-centre national** prospective clinical trials:

- i) Academic: 0 [ ] 1-2 [ ] 3-5 [ ] >5[ ] [ ]
  - Don’t know
- ii) Pharmaceutical: 0 [ ] 1-2 [ ] 3-5 [ ] >5[ ] [ ]
  - Don’t know

**c) Multi-centre international** prospective clinical trials:

- i) Academic: 0 [ ] 1-2 [ ] 3-5 [ ] >5[ ] [ ]
  - Don’t know
- ii) Pharmaceutical: 0 [ ] 1-2 [ ] 3-5 [ ] >5[ ] [ ]
  - Don’t know

5. How many prospective clinical trials related to stem cell transplantation were *started* in your institution *during 2005*?

**a) Single centre** prospective clinical trials:

- i) Academic: 0 [ ] 1-2 [ ] 3-5 [ ] >5[ ] [ ]
  - Don’t know
- ii) Pharmaceutical: 0 [ ] 1-2 [ ] 3-5 [ ] >5[ ] [ ]
  - Don’t know

**b) Multi-centre national** prospective clinical trials:

- i) Academic: 0 [ ] 1-2 [ ] 3-5 [ ] >5[ ] [ ]
  - Don’t know
- ii) Pharmaceutical: 0 [ ] 1-2 [ ] 3-5 [ ] >5[ ] [ ]
  - Don’t know

**c) Multi-centre international** prospective clinical trials:

- i) Academic: 0 [ ] 1-2 [ ] 3-5 [ ] >5[ ] [ ]
  - Don’t know
6. How many prospective clinical trials related to stem cell transplantation were started in your institution during 2006?

a) **Single centre** prospective clinical trials:

i) Academic: 0[ ] 1-2 [ ] 3-5 [ ] >5[ ] [ ]
Don’t know

ii) Pharmaceutical: 0[ ] 1-2 [ ] 3-5 [ ] >5[ ] [ ]
Don’t know

b) **Multi-centre national** prospective clinical trials:

i) Academic: 0[ ] 1-2 [ ] 3-5 [ ] >5[ ] [ ]
Don’t know

ii) Pharmaceutical: 0[ ] 1-2 [ ] 3-5 [ ] >5[ ] [ ]
Don’t know

c) **Multi-centre international** prospective clinical trials:

i) Academic: 0[ ] 1-2 [ ] 3-5 [ ] >5[ ] [ ]
Don’t know

ii) Pharmaceutical: 0[ ] 1-2 [ ] 3-5 [ ] >5[ ] [ ]
Don’t know

7. How many prospective clinical trials related to stem cell transplantation were started in your institution during 2007?

a) **Single centre** prospective clinical trials:

i) Academic: 0[ ] 1-2 [ ] 3-5 [ ] >5[ ] [ ]
Don’t know

ii) Pharmaceutical: 0[ ] 1-2 [ ] 3-5 [ ] >5[ ] [ ]
Don’t know

b) **Multi-centre national** prospective clinical trials:

i) Academic: 0[ ] 1-2 [ ] 3-5 [ ] >5[ ] [ ]
Don’t know

ii) Pharmaceutical: 0[ ] 1-2 [ ] 3-5 [ ] >5[ ] [ ]
Don’t know
c) Multi-centre international prospective clinical trials:

i) Academic:  
0[ ]  1-2 [ ]  3-5 [ ]  >5[ ]  [ ]  
Don’t know

ii) Pharmaceutical:  
0[ ]  1-2 [ ]  3-5 [ ]  >5[ ]  [ ]  
Don’t know

8. From the numbers indicated above, has your institution been involved in fewer Clinical Trials since the implementation of the Clinical Trials Directive?

Click here to see the date of implementation of the Clinical Trials Directive in different European Countries:

a) Yes [ ]  No [ ]

b) If yes, please tick any of the reasons below that apply.

   i) Increased volume of paperwork [ ]

   ii) Increased number of regulatory authorities approving trial [ ]

   iii) Increased requirements for ethics approval [ ]

   iv) Increased approval costs [ ]

   v) Increased running costs associated with trial [ ]

   vi) Increased demands for study conduct (such as monitoring or audit) [ ]

   vii Increased liability [ ]

   c) If there are other reasons please specify: [free text response]

9. In your opinion, are there now fewer Clinical Trials since the implementation of the Clinical Trials Directive in your country?

a) Yes [ ]  No [ ]  No Opinion [ ]
b) If yes, is this for the same reasons as indicated above at local level? Yes [ ] No [ ]

c) If for different reasons, please tick any of the reasons below that apply.

   i) Increased volume paperwork [ ]
   ii) Increased number regulatory authorities approving trial [ ]
   iii) Increased requirements for ethics approval [ ]
   iv) Increased approval costs [ ]
   v) Increased running costs of trial [ ]
   vi) Increased demands for study conduct [ ]
   vii) Increased liability [ ]

d) If there are other reasons please specify: [free text response]

We would like to establish whether the implementation of the Clinical Trials Directive has had a positive or negative impact on prospective clinical trials related to stem cell transplantation.

10. a) Overall, in your view has the implementation of the Clinical Trials Directive had a positive or negative impact on prospective clinical trials related to stem cell transplantation?

   Positive [ ] Negative [ ]

b) We would appreciate if you could indicate whether you personally agree or disagree with the following statements relating to the implementation of the Clinical Trials Directive (please tick applicable answer)

<table>
<thead>
<tr>
<th>Statement</th>
<th>I agree</th>
<th>I disagree</th>
<th>No opinion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved standardisation of review processes and documentation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved ethics review process</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>There is a single ethics committee opinion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Implementation of clear and consistent approval timelines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Directive triggered local investment in infrastructure and training</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased awareness by researchers and improved GCP compliance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Issue</td>
<td>Resolution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>There is now a clearer definition of a SUSAR (suspected unexpected severe adverse reaction)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safety reporting is now of better quality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The sharing of information between national competent authorities promotes safety for research participants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>It has now become more difficult to find a sponsor for clinical trials</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co-sponsorship of clinical trials should be permitted</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The definition of an “investigational medicinal product” versus “non-investigational medicinal product” is unclear</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The definition of “substantial” and “non-substantial” protocol amendment is not properly defined</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The definition of “interventional” versus “non-interventional” clinical trial is unclear</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The differentiation between “commercial” and “non-commercial” clinical trial is unclear</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>There is lack of harmonisation regarding information to be provided for regulatory submissions across Member States</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>There is lack of harmonisation regarding information to be provided for ethics submissions across Member States</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>There is lack of harmonisation regarding information to be provided for different local ethics submissions in the same country</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>There is lack of clarity between lead and local ethic committees about their review responsibilities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>There is lack of transparency associated “true” approval timelines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>There are unclear requirements concerning “approval” versus “notification” by competent authorities and/or ethic committees</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Data from “non-commercial” trials should be usable by the pharmaceutical industry for marketing purposes or to strengthen evidence</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

C) Please describe other examples you may have of instances where prospective clinical trials related to stem cell transplantation have been facilitated as a result of implementation of the EU Clinical Trials Directive.

[free text response]

D) Please describe other examples you may have of instances where problems have arisen in prospective clinical trials related to stem cell transplantation as a result of implementation of the EU Clinical Trials Directive.

[free text response]
We would now like to ask you some questions about your experience of the process for receiving ethical and regulatory approval for a project

11. If you can, please estimate below the average time it takes to complete the process from approval of the final version of a protocol to the entry of first patient for a prospective clinical trial related to stem cell transplantation (e.g. getting ethical and regulatory approval):

Click here to see the date of implementation of the Clinical Trials Directive in different European Countries:

a) Before the Clinical Trials Directive was implemented in your country
   i) single centre studies [numerical answer] months
   ii) multi-centre national studies [numerical answer] months
   iii) multi-centre international studies [numerical answer] months

b) After the Clinical Trials Directive was implemented in your country
   i) single centre studies [numerical answer] months
   ii) multi-centre national studies [numerical answer] months
   iii) multi-centre international studies [numerical answer] months

12. If you can, please estimate below the average time it takes to complete the process for gaining ethical approval at the local level for prospective clinical trial related to stem cell transplantation

a) Before the Clinical Trials Directive was implemented in your country
   i) single centre studies [numerical answer] months
   ii) multi-centre studies [numerical answer] months

b) After the Clinical Trials Directive was implemented in your country
i) single centre studies [numerical answer] months

ii) multi-centre studies [numerical answer] months

13. If you can, please provide some examples to show the time taken to complete the process from **approval of the final version of a protocol** to the **entry of first patient** for prospective clinical trial related to stem cell transplantation (e.g. getting ethical and regulatory approval).

**Please think of the last 3 studies you were involved in**

<table>
<thead>
<tr>
<th>Project title</th>
<th>Was this <em>pre or post</em> implementation of the Directive in your country?</th>
<th>Date Protocol Submitted</th>
<th>Date when Patient was recruited</th>
<th>Any specific problems encountered in the approval process?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>3.</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

14. We would now like to ask you some questions relating to the **documentation** required for the approval processes for **prospective** clinical trials related to stem cell transplantation. Please indicate in Table 1 below, Yes / No / Not Applicable in each case for the three different scenarios: For Table 2 please specify what the documentary requirements are.

**Table 1**

<table>
<thead>
<tr>
<th>Peer review</th>
<th>single centre studies</th>
<th>national multi-centre studies</th>
<th>international multi-centre studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval from local Ethics Committee</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Approval from national Ethics Committee</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Approval from Competent Authority / Medicines Agency / Ministry of Health (for drug trials)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Approval from Hospital Directorate or Research Department (R&amp;D)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Federal State / Bundesland approval</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Federal State / Bundesland notification only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Signed agreement between Sponsor and Principal Investigator</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Signed agreement between Sponsor and Hospital directorate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Signed agreement between Sponsor and City</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Funding body approval (e.g. MRC, INSERM, EBMT, EORTC,</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
15. In your country is there a difference in the nature of the approval process for Academic and Pharmaceutical trials?

   a) Yes [ ] No [ ]

   b) If yes, please describe: [free text response]

We would now like to ask some questions about the costs and funding opportunities associated with prospective clinical trials related to stem cell transplantation.

16. How is the healthcare system funded in your country?

   a. Fully funded through public taxation [ ]
   b. Partially funded through public taxation [ ]
   c. Totally funded through private insurance [ ]
   d. Partially funded through private insurance [ ]
   e. Other [ ]

   i) Please describe - [free text response]

17. What are the main sources of funding available for prospective clinical trials related to stem cell transplantation within your country?

   [free text response]
18. Have you ever participated in a prospective clinical trial funded by the European Union?
Yes [ ] No [ ]

19. In your opinion, what are the main barriers to obtaining funding for prospective clinical trials within your country?
[free text response]

20. This question is about the costs associated with obtaining approval for a single centre trial both before and after implementation of the Clinical Trials Directive? If there are or were costs please indicate and estimate these costs (also give applicable currency).

(a) Ethical Approval
i) | Yes | No | Approximate cost |
--- | --- | --- | ------------------ |
**Academically sponsored trials**
Pre-Directive costs
Post-Directive costs

**Pharmaceutical sponsored trials**
Pre-Directive costs
Post-Directive costs

ii) There are no costs associated with ethics approval [ ]

iii) Do the costs differ for multi-centre trials? Yes [ ] No [ ]

iv) If yes, please describe [free text response]

(b) Regulatory Approval
i) | Yes | No | Approximate cost |
--- | --- | --- | ------------------ |
**Academically sponsored trials**
Pre-Directive costs
Post-Directive costs

**Pharmaceutical sponsored trials**
Pre-Directive costs
Post-Directive costs
ii) There are no costs associated with regulatory approval [ ]

iii) Do the costs differ for multi-centre trials?

iv) If yes, please describe [free text response]

Finally, we would like to discuss how to better facilitate prospective clinical trials related to stem cell transplantation:

21. Do you have any recommendations how to better facilitate prospective clinical trials within your country?
   [free text response]

22. May we contact you for further information and discussion regarding your submitted questionnaire?

   a) Yes [ ] No [ ]

   b) If yes, please enter your name (Family name, given name): [free text response]

   c) If yes, please enter your email address: [free text response]

Thank you for your valued participation in this European Project
Annex 2

CLINT
Regulatory and Ethical Issues Workshop
2 April 2008

SUMMARY REPORT

On 2 April 2008, the CLINT Workpackage 3 held a Workshop at the end of the EBMT Annual Congress in Florence. This workshop was one of the workpackage 3 deliverables and its purpose was to share the results and analysis of the first CLINT questionnaire on ethical and regulatory issues emerging from the implementation of the European Clinical Trials Directive 2001/20/EC, to gather further data, comment on and contribute to the analysis and to identify potential policy options to address any issues of concern.

Some 40 people attended the Workshop which began with a presentation of the analysis of the results of the first questionnaire, highlighted respondents’ comments on how academic prospective clinical trials in stem cell transplantation might be better facilitated, and summarised preliminary observations and conclusions emerging from the questionnaire. These included the following:

Four breakout groups considered the following issues:

Group A: Safety
Group B: Definitions
Group C: Sponsorship
Group D: Harmonisation

A Rapporteur for each group then reported on their deliberations. This was followed up with plenary discussions and a summary.

**Group A’s views on safety** were mixed in response to the question ‘Does the group believe that implementation of the Directive had resulted in an overall improvement in patient safety?’

Those who responded positively said that there was now more Good Clinical Practice (GCP) training available for investigators at an institutional level. They also felt that now having one lead ethics committee (EC) that reviews the trial in detail improved patient safety. This was also perceived to have led to better communication between ECs than prior to implementation.

Those who responded negatively felt that too many Serious Adverse Events (SAEs) now get reported as SUSARs because of insecurity about SAE reporting. This results in over-reporting which produces too much paperwork with the result that important Suspected Unexpected Serious Adverse Reactions (SUSARs) may be overlooked because of the volume of material. They also believed that since implementation of the Directive less academic trials were being started and as a result fewer patients are able to participate in such clinical trials which may then have a negative impact on their safety.

The Group felt that the key changes needed were:
1. That SUSARs should only be reported to one central authority (European Medicines Agency (EMEA) was suggested) rather than to all Competent Authorities (CAs) or Ethics Committees (ECs). There was a strong feeling that most ECs are not equipped to dealing with the reported SAEs or SUSARS.

2. That ECs and Investigators should only receive an annual safety report, unless a SUSAR is relevant to the particular trial they are involved in.

3. That the process for reporting SUSARs should be simplified. In particular that it should be possible for them to be reported electronically or even over the telephone.

Overall the Group felt that safety reporting is now much more complicated and burdensome that before implementation of the Directive and many investigators/centres can no longer perform this task alone and need to hire a Contract Research Organisation (CRO). The increased cost means that some institutions are no longer able to participate in clinical trials.

**Group B’s views on definitions** was that implementation of the Directive had not resulted in any improvement in definitions. Some terms were considered to be particularly unclear and in urgent need of better definition. These included:

1. The distinction between ‘investigational product’ and ‘non-investigational product’
2. ‘Substantial’ and ‘non-substantial’ protocol amendments
3. The distinction between ‘interventional’ and ‘non-interventional’ clinical trial
4. The distinction between a ‘commercial’ and ‘non-commercial’ clinical trial

This group also commented that there needs to be more harmonisation in obtaining local approvals and in particular that clear timelines are needed especially for R&D approvals.

**Group C**, in considering sponsorship, felt that it was much more difficult to find a sponsor, particularly a single sponsor for multinational clinical trials. Consequently most considered that national or institutional co-sponsors should be permitted for such clinical trials with each country or institution being responsible for its own patients.

The group also felt that the EU should take more responsibility for ensuring harmonisation and operate more along the lines of the NIH which provides funding to deal with regulatory issues.

Insurance costs were seen to have increased significantly and the group felt that national governments should carry at least some of the burden of insurance where their citizens were patients in a clinical trial.

The group also pointed out that there was a particular problem in finding sponsors for paediatric clinical trials. One problem being that only licensed drugs could be used for clinical trials in paediatrics and this is not practical for children with cancer. There is a need in certain circumstances for the regulations to be changed to permit non-licensed and off-label drugs\(^2\) to be used.

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\(^2\) Off-label use is the practice of prescribing [http://en.wikipedia.org/wiki/Prescription_drug](http://en.wikipedia.org/wiki/Prescription_drug) drugs for a purpose outside the scope of the drug's approval.
**Group D** felt that the implementation of the Directive had done little to improve harmonisation. Both regulatory and ethics harmonisation was considered to be poor. The main obstacles to harmonisation were felt to be:

1. That the Directive left too much room for local interpretation which resulted in divergent regulation and definition.
2. More information and detailed help on harmonisation needed to be given to national authorities and more needed to be done to remove ‘backdoors’.
3. Information provided is often contradictory at EU level and even at national level.

The plenary session concluded that:

- More financial resources are needed to implement an academic prospective clinical trial in stem cell transplantation since the implementation of the EU clinical trials directive.
- Contrary to the view of Group D others in the workshop felt that there was some improvement in harmonization since implementation of the Directive as everyone at least has same definitions to some degree, even if interpretations differ.
- There appears to be better *intra*-national harmonisation in some countries.
- Co-sponsorship was a very important issue and should be permitted for academic prospective clinical trials.
- If each country decides on interpretation, and this goes to national law, systematic identification of what is wanted
- The Clinical Trials Directive is about quality control. However, in the area of Bone Marrow transplantation no distinction is made between therapy and drug studies and this is inappropriate.
- More types of clinical trials are now captured by the directive, many of which were much easier to implement previously.
- It could be beneficial to have some form of ‘European NIH’ so that only one institution needs to be involved as a competent authority in regulating clinical trials across Europe, but such a body would need to be very large.
- Any review and revision of 2001/20/EC needs to also take account of the views of other lobby and stakeholder groups as well as end user perspectives.
ANNEX 3

Impact of the European Clinical Trials Directive on prospective academic clinical trials associated with bone marrow transplantation

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Keywords; European Clinical Trials Directive; academic clinical trials; bone marrow transplantation; perceived impact.

Abstract
The European Clinical Trials Directive (EU 2001; 2001/20/EC) was introduced in order to improve the efficiency of both commercial and academic clinical trials. However, concerns have been raised by interested organisations and institutions regarding the potential for negative impact of the Directive on non-commercial European clinical research. A survey of interested researchers within the European Group for Blood and Bone Marrow Transplantation (EBMT) was conducted to determine whether researcher experiences confirmed this view. A pilot study was used to identify researcher concerns and beliefs about the impact of the directive on academic clinical research. This information was used to develop an internet based questionnaire, which was subsequently distributed to individuals in key research positions in the European haematopoietic stem cell transplantation community, with particular interests in academic prospective clinical trials. 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 a negative one, at least in the research areas of interest to EBMT. In particular, the results suggest that the Directive is perceived by researchers to have increased the administrative burden of researchers, and introduced additional barriers and bottlenecks into the research process. Policy changes are required, specifically aimed at facilitating academic clinical trials through promoting harmonisation, reducing administration and streamlining the regulatory and approval process, possibly though creation of a single European Competent Authority.
Acknowledgment. The research reported here was supported by the EU funded CLINT project, *(Facilitating International Prospective Clinical Trials in Stem Cell Transplantation) Proposal nº: 037662.* The views expressed are those of the authors.

Introduction
The European Clinical Trials Directive (EU 2001; 2001/20/EC) was introduced in order to improve the efficiency of both commercial and academic clinical trials, thus providing the basis for improved European competitiveness in research and industrial application. It was implemented on 1st May 2004 to simplify and harmonise the administrative procedures governing clinical trials, by establishing a “clear, transparent process” for relevant authorities and researchers. In particular, the Directive was directed towards ensuring best practice requirements in relevant procedures and ethical clearances applied at a pan-European level. Despite the intent of the Directive and consequent national legislation, concerns have been raised by interested organisations and institutions regarding the potential for negative impact of the Directive on non-commercial European clinical research (see, *inter alia*, Meunier 2003, Lacombe 2003, Moulton 2004), which has been supported by empirical investigation (Hartman and Hartman 2006). Whilst there is evidence to suggest that the impact is not necessarily negative in all EU member states for all types of clinical trials (for example, see Berendt et al, 2008), the predominant view suggests that the net impact of the implementation of the Directive has been to increase the administrative burden associated with the competent authority and ethical clearances, in particular for multinational trials (Frewer et al, submitted). The aim of the research presented here is to examine researcher concerns and perceptions regarding the impact of the Directive on academic clinical trials in the area of blood and bone marrow transplantation.

Methods
An initial pilot survey was conducted to identify clinician concerns associated with the implementation of the European Clinical Trials Directive. A pilot questionnaire was designed which was distributed to active researchers within the European Group for Blood and Bone Marrow Transplantation (EBMT). The questionnaire focused on understanding researcher concerns and perceptions associated with the initiation and implementation of prospective
clinical trials, applied in the area of stem cell transplantation, following the European Clinical trials directive. It was developed to be completed electronically over the Internet. Respondents were contacted by email and provided with a password which could be used on the questionnaire Internet site to access the questionnaire itself.

Initially 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 stem cell transplantation, and institutional activities related to different types of prospective clinical trials in the relevant area). Information was then provided regarding the date of implementation of the European Clinical Trials directive in different EU member states. Respondents were asked to indicate the numbers of academic and pharmaceutical clinical trials (single centre, multicentre national and multicentre international) being conducted per year in their country and by their own institutions, both before and after implementation of the Clinical Trials Directive, and whether they considered that the numbers of trials conducted had been influenced by the Directive. Information relevant to the reasons for any potential decline in the numbers of trials was also collected. Both closed and open questions were included in this section, the closed questions being derived from the existing literature, and the open-ended questions soliciting additional information.

For some questions (particularly those involving specific information which would need to be checked against factual sources, and which would be difficult to recall from memory) the number of respondents who answered was negligible, and these items are not further discussed as their potential unreliability means that conclusions cannot be drawn from the results. The analysis of the main study questionnaire therefore focused on the various issues reported as being perceived by participants to be relevant to the impact of the European clinical trials directive.

There were 41 respondents to this first study. The results indicated that the respondents appeared to predominantly perceive the impact of the implementation of the European Directive to be negative, although a minority reported that it had made no difference or even had a positive effect on the implementation of prospective clinical trials.
Whilst nearly all participants reported being involved, at a reasonably senior level, in academic clinical trials, some reporting biases may have distorted the results. In particular, participants who had more negative experiences of, and views about, initiating and conducting of prospective clinical trials following the European directive may have been more likely to respond to the questionnaire. The higher number of respondents from certain EU member States (for example, Germany) may have reflected differential perception of problems and concerns in these EU member states compared to others. It was therefore decided to use the results of the first questionnaire to develop a second questionnaire, where a cascade methodology was applied to ensure more equal distribution of responses across EU member states. In particular, the second questionnaire used the results of the qualitative responses in the first questionnaire to formulate closed questions in the second questionnaire. The focus of these new questions was on firstly, researcher perceptions of the potential problems which have arisen following the implementation of the European Clinical Trials Directive, and priorities for specific changes which could potentially improve the implementation of clinical trials in areas of relevance to EBMT in the future.

Main study
The main study focused on the opinions of individuals in key research positions in the European haematopoietic stem cell transplantation community, with particular interests in academic prospective clinical trials. For this reason, participants were recruited via the European chairs of the EMBT Working Parties (11 Working Parties). Each chairperson was asked if they would be willing to respond themselves, as well as pass on the questionnaire to other members of their working party.

Results
Seventy one usable questionnaires were returned and included in the analysis. All participants were senior researchers or principal investigators actively involved in clinical trials in the area of haematopoietic stem cell transplantation. The respondents were located across different EU member states, (Table 1) with most respondents being based in Germany (17%), France (13%) and the UK (13%). The majority of respondents (86%) had been involved in multicentre national trials at a senior level (94% Senior or principal investigator) and were drawn from reasonably different EU member states or candidate countries. Seventy percent
of respondents indicated that the overall impact of the Directive was negative, 20% positive and 3% reported no change.

Participants were asked whether they believed that time to Ethics Committee/Competent Authority approval became longer or shorter following the implementation of the Clinical Trials Directive, and, if they replied ‘longer’ (i.e. indicating that the situation has become more negative) to indicate whether this was attributable to increased pre-submission administration, increased post-submission committee delays, or other factors. Generally participants (63.4%) perceived that time to approval was longer. Of respondents who perceived that delays were occurring, 93% attributed this to pre-submission administration delays and 69% to post-submission delays (note that some participants indicated both as relevant). Other delaying factors were indicated as important by 76% of this subsample. The limited number of qualitative responses provided by participants following a response which indicated increased delays to this item did not enable further investigation of what these issues might be.

Table 1 about here.

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>2</td>
</tr>
<tr>
<td>Belgium</td>
<td>4</td>
</tr>
<tr>
<td>Denmark</td>
<td>1</td>
</tr>
<tr>
<td>Finland</td>
<td>2</td>
</tr>
<tr>
<td>France</td>
<td>9</td>
</tr>
<tr>
<td>Germany</td>
<td>12</td>
</tr>
<tr>
<td>Greece</td>
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</tr>
<tr>
<td>Hungary</td>
<td>2</td>
</tr>
<tr>
<td>Italy</td>
<td>7</td>
</tr>
<tr>
<td>Netherlands</td>
<td>4</td>
</tr>
<tr>
<td>Norway</td>
<td>1</td>
</tr>
<tr>
<td>Poland</td>
<td>3</td>
</tr>
<tr>
<td>Spain</td>
<td>3</td>
</tr>
<tr>
<td>Sweden</td>
<td>6</td>
</tr>
<tr>
<td>Turkey</td>
<td>4</td>
</tr>
<tr>
<td>UK</td>
<td>9</td>
</tr>
<tr>
<td>No response</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 1. Response rates and distribution across EU member States. A total of 71 responses were received.

*Impact of the European Clinical Trials Directive on researcher involvement in, and experience of, academic clinical trials*
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 participants reported it was more difficult to become involved in single centre prospective clinical trials, 82% in multicentre clinical trials and 86% in international prospective clinical trials.

A series of questions regarding researcher perspectives on the impact of the European Clinical Trials Directive were developed from the pilot study. These questions are provided in Table 2. Participants were asked to rate the extent to which they agreed or disagreed with each statement (five point rating scale anchored by “agree strongly” and “disagree strongly”, with a midpoint of neither agree nor disagree, and a “no opinion” option. Application of a GLM repeated measures procedure tested for main effects of trial type (single centre, multicentre national and multicentre international), type of concern (see Table 2) and potential interactions between these. There was a trend towards differences being observed for trial type although this did not quite reach significance (F (2, 41) =3.7, p<0.06). Inspection of means indicated that this reflected slightly greater concern to be associated with multi-centre international trials (M 1.6, SE=0.08) compared to national multicentre trials (x=0.7, SE=0.08), which similarly were associated with more concern than national single centre trials (x=1.8, SE=0.08), lower scores indicating higher agreement with negative items. It should be noted that for all types of trials, the average ratings were below the midpoint of the scale, indicating that participants tended to negatively evaluate the impact of the European Clinical Trials Directive overall. A significant effect attributable to type of concern was observed (F(13, 30) =5.6, p<0.001). Significant pairwise differences between different types of concern are summarised in Table 2. All mean concern ratings were lower than the midpoint of the scale, indicating strong to neutral agreement with all types of concern. However, greatest concern was associated with the increased volume of paperwork, increased demands associated with running the trial itself, (monitoring or audit, or legal requirements), or increased costs for insurance or ethical approval. Issues associated with forms and information requirements were rated overall as less problematic. However, the significant interaction between type of concern and trial type (F=2.39, df 26, 17, p<0.05, Figure 1) indicated that concerns about forms were greater for international multicentre trials. Specifically, researchers taking part in
multicentre international clinical trials were least concerned about increased running costs or increased legal requirements, and less concerned about the increased volume of paperwork, increased approval costs, and (unexpectedly) the increased number of regulatory authorities involved compared to the other issues. The lower levels of concern about the potential increase in regulatory approvals, may reflect the fact that, in most, countries there is already an obligation pre-Directive to gain approval.

<table>
<thead>
<tr>
<th>TYPE OF CONCERN</th>
<th>MEAN RATING</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased volume of paperwork</td>
<td>1.11 a</td>
<td>0.04</td>
</tr>
<tr>
<td>Increased demands for study conduct (such as monitoring or audit)</td>
<td>1.29 a b</td>
<td>0.07</td>
</tr>
<tr>
<td>Increased running costs associated with the trial</td>
<td>1.43 a c</td>
<td>0.90</td>
</tr>
<tr>
<td>Increased legal requirements in general</td>
<td>1.50 a c</td>
<td>0.70</td>
</tr>
<tr>
<td>Increased approval costs</td>
<td>1.55 a c</td>
<td>0.20</td>
</tr>
<tr>
<td>Increased costs of insurance/indemnity</td>
<td>1.63 a c</td>
<td>0.10</td>
</tr>
<tr>
<td>Delays in institutional approval (such as research and development or approval from the directorate)</td>
<td>1.65 b c</td>
<td>0.11</td>
</tr>
<tr>
<td>Increased liability</td>
<td>1.67 c</td>
<td>0.10</td>
</tr>
<tr>
<td>Increased number of regulatory authorities required to approve trial</td>
<td>1.68 c</td>
<td>0.11</td>
</tr>
<tr>
<td>Increased requirements for ethics approval</td>
<td>1.72 c</td>
<td>0.12</td>
</tr>
<tr>
<td>Committees requiring use of their own forms in addition to national or internationally agreed forms</td>
<td>1.94 c</td>
<td>0.14</td>
</tr>
<tr>
<td>Practical problems with official forms (e.g. form cannot be saved)</td>
<td>2.00 c d</td>
<td>0.14</td>
</tr>
<tr>
<td>Lack of harmonisation between forms used by committees at national level</td>
<td>2.27 d</td>
<td>0.16</td>
</tr>
<tr>
<td>Lack of harmonisation of forms used by different committees at local level</td>
<td>2.33 d</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Table 2. Mean scores for concern ratings. Means with different superscripts are significantly different from each other (post hoc means comparisons, Tukey test, p<0.05). A lower score indicates higher agreement with the statement.

Prioritisation of changes to facilitate implementation of academic clinical trials in the future

The final part of the questionnaire asked participants to rate the potential changes which could be implemented to facilitate national single centre, national multicentre clinical trials, or international multicentre trials. The items were developed following qualitative analysis of the open ended responses to the question “What changes are needed to facilitate the implementation of clinical trials in Europe” in the pilot study. The different changes are summarised in Table 3. As before, a GLM repeated measures procedure was applied. A significant main effect attributable to type of change was observed (F916, 44) = 6.14, p<0.001. Significant differences are summarised in Table 3. All of the mean scores were less than the midpoint of the scale (3) indicating high levels of agreement for the issues identified.

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as priorities in the initial exploratory study. Prioritisation was assigned to changes relating to reduction in administrative burden, harmonisation of documents required for approval, and increased access to public funding for clinical trials and translational research (and, relatedly, to subsidisation of insurance costs, although this was not rated as such an important priority). The creation of a single Competent Authority for all EU member states was not scored by participants as being among the most important priorities. Permitting pharmaceutical industry partners to use data from “non-commercial” clinical trials was ranked as a relatively low priority by participants compared to the other potential changes.
Researcher concerns following the implementation of the European clinical trials directive

Figure 1. Differences in researcher concerns associated with the impact of the European Clinical Trials Directive by type of clinical trial (Single centre national, multi-centre national or multicentre international). A lower score indicates a higher level of agreement.
<table>
<thead>
<tr>
<th>TYPE OF CHANGE REQUIRED POST EUROPEAN CLINICAL TRIALS DIRECTIVE</th>
<th>MEAN RATING</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced administrative burden</td>
<td>1.20</td>
<td>0.16</td>
</tr>
<tr>
<td>Harmonisation of documents required for approval</td>
<td>1.35</td>
<td>0.22</td>
</tr>
<tr>
<td>Increased public funding for prospective clinical trials</td>
<td>1.42</td>
<td>0.18</td>
</tr>
<tr>
<td>More readily available support from the EU for translational clinical research</td>
<td>1.50</td>
<td>0.19</td>
</tr>
<tr>
<td>Provision of ethical and regulatory approval free of charge for academic institutions</td>
<td>1.53</td>
<td>0.20</td>
</tr>
<tr>
<td>Centralisation of documents required for approval</td>
<td>1.55</td>
<td>0.17</td>
</tr>
<tr>
<td>National government or EU subsidisation of insurance costs</td>
<td>1.60</td>
<td>0.21</td>
</tr>
<tr>
<td>Permitting co-sponsorship of academic prospective clinical trials</td>
<td>1.60</td>
<td>0.20</td>
</tr>
<tr>
<td>Improved definition of interventional versus non-interventional clinical trial</td>
<td>1.67</td>
<td>0.21</td>
</tr>
<tr>
<td>Clearer differentiation between “commercial” versus non-commercial clinical trial</td>
<td>1.72</td>
<td>0.22</td>
</tr>
<tr>
<td>Improved definition of substantial versus non-substantial protocol amendment</td>
<td>1.73</td>
<td>0.22</td>
</tr>
<tr>
<td>Reduction in the degree of monitoring required for investigator-led trials</td>
<td>1.75</td>
<td>0.23</td>
</tr>
<tr>
<td>Implementation of a true single opinion in a Member State</td>
<td>1.82</td>
<td>0.24</td>
</tr>
<tr>
<td>Improved definition of an interventional medicinal product (IMP)</td>
<td>1.85</td>
<td>0.24</td>
</tr>
<tr>
<td>EU or nationally funded local training on administrative requirements of the directive</td>
<td>1.88</td>
<td>0.24</td>
</tr>
<tr>
<td>Creation of a single Competent Authority for all EU member States</td>
<td>1.90</td>
<td>0.24</td>
</tr>
<tr>
<td>Permitting industry to use data from “non-commercial” clinical trials</td>
<td>2.35</td>
<td>0.30</td>
</tr>
</tbody>
</table>

Table 3 Mean scores for priorities for changes, post European Clinical Trials Directive (post hoc means comparisons, Tukey test, p<0.05)

**Discussion and conclusions**

The results of the study indicate that the perceived impact of the European Clinical Trials Directive has been a negative one, at least in the research areas of interest to EBMT. Whilst a response bias may have influenced the results of the exploratory study in-so-much as only researchers with a negative view responded, the use of cascade methodology to recruit participants in the second phase should have reduced this effect. The negative impact of the Directive appeared to be very similar for both single centre and multicentre trial types run at a national level (both). There was a trend for this negative impact to be greater for multi-centre international academic clinical trials. In terms of identifying potential changes which would remedy the situation, prioritisation was given to the need to reduce the administrative burden associated with running academic clinical trials, and (as part of this) the
need to harmonise documentation associated with the application process for trial approval and monitoring. While increased public funding for research was also identified by participants as a priority, this is unlikely to be solely a consequence of the Directive *per se*, but remains none-the-less a barrier to conducting research in this area. The creation of a single European Competent Authority was not rated as being as important as some of the other changes, but nevertheless rated an average score between "agree" and "strongly agree". Participants were less committed to secondary use by industry of data collected within an academic clinical trial.

To conclude, the results support the impression provided by much of the literature that, rather than improving the efficiency of European research in academic clinical trials and increasing its global competitiveness, the European Clinical Trials Directive has increased the (perceived) administrative burden of researchers, and introduced additional barriers and bottlenecks into the research process. Policy changes are required, specifically aimed at facilitating academic clinical trials through promoting harmonisation, reducing administration and streamlining the regulatory and approval process.

References


European Science Foundation (2008) FL 07-001 'Investigator-Driven Clinical Trials (Forward Look) [http://esf.org/emrc/idct](http://esf.org/emrc/idct) Accessed on 3 April 2009


ANNEX 4

Clint: Questionnaire M2

Thank you for agreeing to participate in our study about the governance of clinical trials related to stem cell transplantation.

To begin with we would like to ask you a few questions about yourself and your institution:

Job Description:

Institution:

Country:

EBMT Centre Number (if known):

We would now like to ask you some questions about your personal experience of prospective clinical trials related to stem cell transplantation. This may include but is not limited to studies that are:

- Therapeutic e.g. disease based,
- Technical e.g. conditioning
- Supportive e.g. GvHD, anti-infective or cytokines, and /or
- Post-transplant care e.g. DLI

1. Have you personally been involved in the following clinical trials related to stem cell transplantation?

   Single centre prospective clinical trial       Yes [ ]      No [ ]

   Multi-centre national prospective clinical trial Yes [ ]      No [ ]

   Multi-centre international prospective clinical trial Yes [ ]      No [ ]

2. If appropriate, which of the following best describes your role in those trials you have been involved with? (please select one):

   Principal Investigator [ ]
   Co-Investigator [ ]
   Research Scientist [ ]
3. **Overall, in your view, has the implementation of the Clinical Trials Directive had a positive or negative impact on prospective clinical trials related to stem cell transplantation?**

   Positive [ ]  Negative [ ]  No change [ ]  No Opinion [ ]

4. **Do you believe that time to Ethics Committee/Competent Authority approval is: longer or shorter since the implementation of the Clinical Trials Directive?**

   Longer [ ]  Shorter [ ]  No change [ ]  No Opinion [ ]

   If longer, do you believe this is due mainly to:

   a) Pre-submission administration [ ]
   b) Post-submission committee delays [ ]
   c) Both a) and b) [ ]
   d) Other [ ]

   (Please describe)

   e) No Opinion [ ]

5. **Do you consider it is more difficult for institutions in your country to become involved in academic prospective clinical trials since the implementation of the Clinical Trials Directive?**

   a. **For single centre clinical trials:**

      Yes [ ]  No [ ]  No change [ ]  No opinion [ ]

      If ‘yes’ indicate any of the reasons below which you think are relevant:
i. Increased volume of paperwork

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Neither</th>
<th>Disagree</th>
<th>Strongly disagree</th>
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<tr>
<td>[ ]</td>
<td>[ ]</td>
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</table>

ii. Practical problems with official forms (e.g. form cannot be saved)

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Neither</th>
<th>Disagree</th>
<th>Strongly disagree</th>
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<tr>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
</tbody>
</table>

iii. Lack of harmonisation of forms used by different committees at local level

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Neither</th>
<th>Disagree</th>
<th>Strongly disagree</th>
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<tr>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
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<td>[ ]</td>
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</table>

iv. Lack of harmonisation between forms used by committees at national level

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Neither</th>
<th>Disagree</th>
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</thead>
<tbody>
<tr>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
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<td>[ ]</td>
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</table>

v. Committees requiring use of their own forms in addition to national or internationally agreed forms

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Neither</th>
<th>Disagree</th>
<th>Strongly disagree</th>
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vi. Increased number of regulatory authorities required to approve trial

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vii. Increased requirements for ethics approval

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viii. Increased approval costs

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ix. Delays in Institutional approval (such as Research and Development or approval from the Directorate)

Strongly Agree  Agree  Neither  Disagree  Strongly disagree
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x. Increased running costs associated with trial

Strongly Agree  Agree  Neither  Disagree  Strongly disagree
[ ]  [ ]  [ ]  [ ]  [ ]

xi. Increased demands for study conduct (such as monitoring or audit)

Strongly Agree  Agree  Neither  Disagree  Strongly disagree
[ ]  [ ]  [ ]  [ ]  [ ]

xii. Increased liability

Strongly Agree  Agree  Neither  Disagree  Strongly disagree
[ ]  [ ]  [ ]  [ ]  [ ]

xiii. Increased legal requirements in general

Strongly Agree  Agree  Neither  Disagree  Strongly disagree
[ ]  [ ]  [ ]  [ ]  [ ]

xiv. Increased costs of insurance / indemnity

Strongly Agree  Agree  Neither  Disagree  Strongly disagree
[ ]  [ ]  [ ]  [ ]  [ ]

b. For national multicentre clinical trials:

Yes [ ]  No [ ]  No change [ ]  No opinion [ ]

If yes indicate any of the reasons below which you think are relevant:

i. Increased volume of paperwork

Strongly Agree  Agree  Neither  Disagree  Strongly disagree
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### ii. Practical problems with official forms (e.g. form cannot be saved)

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### iii. Lack of harmonisation of forms used by different committees at local level

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### iv. Lack of harmonisation between forms used by committees at national level

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### v. Committees requiring use of their own forms in addition to national or internationally agreed forms

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### vi. Increased number of regulatory authorities required to approve trial

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### vii. Increased requirements for ethics approval

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### viii. Increased approval costs

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**x. Increased running costs associated with trial**

| Strongly Agree | Agree | Neither | Disagree | Strongly disagree |
| [ ] | [ ] | [ ] | [ ] | [ ] |

**xi. Increased demands for study conduct (such as monitoring or audit)**

| Strongly Agree | Agree | Neither | Disagree | Strongly disagree |
| [ ] | [ ] | [ ] | [ ] | [ ] |

**xii. Increased liability**

| Strongly Agree | Agree | Neither | Disagree | Strongly disagree |
| [ ] | [ ] | [ ] | [ ] | [ ] |

**xiii. Increased legal requirements in general**

| Strongly Agree | Agree | Neither | Disagree | Strongly disagree |
| [ ] | [ ] | [ ] | [ ] | [ ] |

**xiv. Increased costs of insurance / indemnity**

| Strongly Agree | Agree | Neither | Disagree | Strongly disagree |
| [ ] | [ ] | [ ] | [ ] | [ ] |

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c. **For international multicentre clinical trials:**

Yes [ ]        No [ ]        No change [ ]        No opinion [ ]

If yes indicate any of the reasons below which you think are relevant:

**i. Increased volume of paperwork**

| Strongly Agree | Agree | Neither | Disagree | Strongly disagree |
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**ii. Practical problems with official forms (e.g. form cannot be saved)**
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### iii. Lack of harmonisation of forms used by different committees at local level

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### iv. Lack of harmonisation between forms used by committees at national level

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### v. Lack of harmonisation between forms used by committees in different countries

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### vii. Increased number of regulatory authorities required to approve trial

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### ix. Increased approval costs

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xi. Increased running costs associated with trial

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xii. Increased demands for study conduct (such as monitoring or audit)

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xiii. Increased liability

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xiv. Increased legal requirements in general

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xv. Increased costs of insurance / indemnity

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6. Please indicate the extent to which you agree or disagree that each of the following changes would result in better facilitation of academic prospective clinical trials in the future.

a. National government or EU subsidisation of insurance costs

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b. Reduced administrative burden

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<td>c. EU or nationally funded local training on administrative requirements of the Directive</td>
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| d. More readily available support from the EU for translational clinical research |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Strongly Agree                  | Agree           | Neither         | Disagree        | Strongly disagree |
| [ ]                             | [ ]             | [ ]             | [ ]             | [ ]             |

| e. Increased public funding for prospective clinical trials |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Strongly Agree                  | Agree           | Neither         | Disagree        | Strongly disagree |
| [ ]                             | [ ]             | [ ]             | [ ]             | [ ]             |

| f. Provision of ethical and regulatory approval free of charge for academic institutions |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Strongly Agree                  | Agree           | Neither         | Disagree        | Strongly disagree |
| [ ]                             | [ ]             | [ ]             | [ ]             | [ ]             |

| g. Permitting co-sponsorship of academic prospective clinical trials. |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Strongly Agree                  | Agree           | Neither         | Disagree        | Strongly disagree |
| [ ]                             | [ ]             | [ ]             | [ ]             | [ ]             |

| h. Centralisation of documents needed for approval |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Strongly Agree                  | Agree           | Neither         | Disagree        | Strongly disagree |
| [ ]                             | [ ]             | [ ]             | [ ]             | [ ]             |

| i. Harmonisation of documents required for approval |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Strongly Agree                  | Agree           | Neither         | Disagree        | Strongly disagree |
| [ ]                             | [ ]             | [ ]             | [ ]             | [ ]             |

| j. Reduction in the degree of monitoring required for investigator-led trials |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Strongly Agree                  | Agree           | Neither         | Disagree        | Strongly disagree |
| [ ]                             | [ ]             | [ ]             | [ ]             | [ ]             |

| k. Implementation of a true single opinion in a Member State |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Strongly Agree                  | Agree           | Neither         | Disagree        | Strongly disagree |
| [ ]                             | [ ]             | [ ]             | [ ]             | [ ]             |
I. Creation of a single Competent Authority for all EU Member States.

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m. Improved definition of an interventional medicinal product (IMP)

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n. Improved definition of substantial versus non-substantial protocol amendment

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o. Improved definition of interventional versus non-interventional CT

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p. Clearer differentiation between ‘commercial’ versus ‘non-commercial’ CT

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q. Permitting industry to use data from ‘non-commercial’ clinical trials

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r. Other (please specify up to 3 other proposed changes)

i.
ii.
iii.

Q7: May we contact you for further information and discussion regarding your submitted questionnaire?

If ‘yes’ please enter your name (family name, given name) and your email address.

Name:

Email:
Please email the completed Word version of the questionnaire to:

david.coles@wur.nl

Thank you very much for taking the time to assist our research.

David Coles
ANNEX 5

Questions for Telephone Interviews on Informed Consent and Data Protection

Part A: Informed Consent

Information that needs to be provided to patients for an information sheet to be acceptable to a local research ethics committee (LREC) in your country.

1. Which of the following are requirements. If not requirements which of the information is still normally provided in the information sheet.

   a. Purpose of the study
   b. Desired outcome
   c. Number of people who have received the treatment to date
   d. Serious or unpleasant side effects reported to date.
   e. Frequency with which side effects occur.
   f. How long does the study last?
   g. Details on medical procedures
      i. Information on painful or unpleasant tests and/or procedures (what level of information is provided?)
      ii. Information on any dangerous procedures (what level of information is provided? Does it have to be written or can it be oral?)
      iii. Possible adverse outcomes
      iv. Assessment of level of risk of adverse outcomes
      v. Assessment of likelihood of successful outcome
   h. Any restrictions on participants’ activities (e.g. diet, taking other medications, reproductive activity etc.)
   i. Informed consent obtained through personal interview (rather than patient simply being left to read the information sheet).
2. Is there a minimum time that a patient must have to make a decision about treatment?

3. Should technical terms be explained by the clinician or by provision of a glossary?

4. For multinational clinical trials, are you aware of any cultural differences in research ethics committee requirements for how researchers approach sensitive issues such as pregnancy, infertility etc.?

5. Translator requirements.
   a. Do you need a translator if the patient does not speak the language, or will a written translation of the information sheet suffice?
   b. If a translator is required must it be a professional translator or will a friend/family member be acceptable.

6. For multi-centre or multinational trials:
   a. Is back-translation needed to compare original and revised information sheets?
   b. To what extent does this present a problem, in terms of cost and burden, for non-commercial clinical trials?

7. Consent for minors.
   a. What is the age of competency for informed consent in your country?
   b. Who can provide informed consent for minors or other groups unable to consent?

8. Are there any special provisions required for obtaining consent from other vulnerable groups (e.g. pregnant women, the elderly)?


Ethics Committees frequently adopt different approaches to patients consenting for additional studies and additional or secondary analysis of data.
a. What is the procedure for getting consent for a subsequent study using the same data?

b. Should the subsequent studies be specified beforehand in order to get consent?

c. Is the term “for this and subsequent studies” acceptable in a consent form or is a fresh consent required for every subsequent study or use of data?

d. With respect to subsequent use of data for patients who have died since the data were collected – who is able to provide consent?
   i. Physician
   ii. Parents
   iii. Children
   iv. Other relatives,
   v. An independent authority

10. Which of the following details of research team (and other interested parties) have to be provided in information sheet?

   a. Name of Principal Investigator
   b. Names of other researchers
   c. Does other information on researchers need to be provided?
   d. Name of both physician and clinical researcher (if different) that patient will see and frequency of contact.
   e. Contact details in case of difficulties
   f. Name of study sponsor
   g. Name of Institutional Review Board (IRB)
   h. Contact details of IRB (in case patient wants an independent response to questions or concerns).

11. Insurance Issues

   Insurance provision requirements often vary between national systems which are (for example) NHS based, private health care based, insurance cover
based, mixed system. E.g. In many cases, a patient’s own insurance covers them as a result of anything adverse that happens as a result of the trial. In other countries this may not be the case.

a. What level of insurance has to be provided in your country?

b. Is it necessary to hand out the full (e.g. EBMT) insurance policy document to patients? or:
   i. Will a summary of the essential provisions of the policy suffice?
   ii. Would it be sufficient if the full policy were to be available on request at the trial site or on a website?

c. Does the ethics committee need to see the full insurance policy?

d. Should the patient be able to access the insurance directly, rather than via the physician?

12. Are there any other specific requirements for information sheets and informed consent in your country that have not been mentioned in these questions?

13. Would an EBMT pro-forma information sheet be facilitate the design and implementation of multinational SCT clinical trials?

Part B: Data Protection

1. Which of the following data on patients and the clinical trial are requirements for ethical and regulatory approval.

   a. Patient Details:
      i. Initials of patient
      ii. Sex
      iii. Data of birth
      iv. Treating hospital
      v. Rare disease

   b. Any other information on patient that is required?

   c. Condition being treated or studied
2. In some cases, LRECs do not want information about date of birth to be recorded. Is this an issue in your country?

3. If so, if date of birth cannot be used, can year of birth (to give age) be used instead?

4. What are the requirements for ensuring security of personal data?

5. How is security of personal data ensured for rare conditions?

   For example, even if anonymised it may be possible to identify a patient with a comparatively rare disease if information about treatments and responses to treatments is stored. The more data collected then the easier it becomes to identify individual patients.
   a. Are there any specific data protection requirements in your country in order to prevent identification of individuals in such cases?

6. What are your country’s ethics committee requirements for cross-border transfer of data in multinational clinical trials?


   Does the way in which your country has interpreted the Clinical Trials Directive 2001/20/EC and the Data Protection Directive 95/46/EC present any difficulties for:
   a. Obtaining informed consent
   b. Use or cross-border transfer of data in multinational academic clinical trials?

8. In multinational clinical trials have you any experience of other countries’ data protection requirements presenting any difficulties for the design of informed consent forms and accompanying information sheets including information provided and the questions that can be asked?

   a. If so what are the difficulties?

Part C: Policy issues
One task of the CLINT project is to make policy recommendations regarding facilitating clinical trials.

Finally, do you have any specific policy recommendations you would like to make in relation to informed consent or data protection issues affecting national or multinational prospective academic clinical trials?
It is a lamentable fact that even initiatives born from the best of intentions can fail to meet their objectives. There is no doubt that the goals of the European Clinical Trials Directive (EU 2001/20/EC), i.e. to improve the safety and efficiency of both commercial and investigator-led clinical trials and to provide the basis for improved European competitiveness in this area, were laudable. Unfortunately from the early days of consultation and legislative preparation several clinical research organisations highlighted the potential for adverse effects on translational research in Europe (Meunier 2003, Lacombe 2003, Moulton 2004). Today, five years from implementation, there is hard evidence to suggest that the Directive has actually had a negative impact on investigator-led studies.

The directive was designed to optimise patient safety, to make the process of trial implementation more efficient, to ensure best practice in ethical review and regulatory procedures, and to harmonise these procedures across Europe. In fact the implementation of the Directive by individual EU member states has resulted in legislative differences between the different nations that have acted to impede rather than facilitate pan-European harmonisation and have presented obstacles to the conduct of clinical trials themselves (for examples, see Hartman and Hartman, 2006). Although there are examples of improved practice in some areas of Europe (Berendt et al) the general consensus, and perhaps more importantly the general perception, is that the regulatory requirements are highly demanding and expensive irrespective of the level of risk; that trial implementation is slower and that investigator led-studies
are decreasing in number and/or complexity. All these effects are compounded in the context of multi-national studies where the challenge of identifying, addressing and complying with each nation’s theoretically similar but in practice distinctly different regulatory and ethical requirements, has proved stultifying (Bosch, 2005; Elwyn et al. 2005, Hemminikiand and Kellokumpku-Lehtinen, 2006; Keim, 2007, Hearn et al. 2007, van Vyve 2008, Hackshaw et al. 2008, ICREL Report, in press).

The EU has responded to the concerns by funding a number of initiatives designed to identify the impact (positive or negative) of the Clinical Trials Directive and to date nine European organisations have participated in four such collaboratives (Table 1). In addition the European Science Foundation (ESF) representing the European Medical Research Councils (EMRC) has recently completed a Forward Look for Investigator-Directed Clinical Trials (ESF 2009). All of these projects have identified problems with the Clinical Trials Directive as it is currently interpreted in the member states and have reported or will complete their reports prior to the review of the directive due in October 2010. The European Leukemia Net (ELN) was funded with the major aim to initiate international European trials in leukemias and faced firsthand the enormous problems for academic sponsors. The ESF have made 25 wide–ranging recommendations in order to improve the conduct of translational medicine in Europe, that include not only revision of the regulatory issues but also highlight the need for training and education and adequate funding for approved studies. The four collaboratives, whose focus was rather more restricted to the regulatory issues, together with the EORTC, have identified concerns that not only overlap with each other but also mirror many of the recommendations of the ESF. CLINT, ECRIN, ELN, EORTC and ICREL have now shared their experiences and have identified a number of possible solutions to the most critical obstacles to clinical trials in Europe:
• To require only one Clinical Trials Authorisation (CTA) irrespective of the numbers of participating nations, either by the development of a single CTA application across Europe or the mutual recognition of authorisations by Competent Authorities.

• To simplify and harmonise the procedures for clinical trial approval (e.g. the EudraCT forms as a single set of forms to be completed) and safety reporting (Eudravigilance and reporting rules).

• To define better and harmonise the roles of the ethics committees (achieve the so-called single-opinion) and of the competent authorities

• To adopt a risk-based approach: adaptation of the regulatory requirements considering the risk associated with the trial with regard to the safety reporting (e.g. limited safety reporting for commercially approved drugs), data monitoring, insurance, application dossiers, substantial amendments, free-of-charge supply of drug (e.g. not in case of market approval).

• To allow co-sponsorship in the case of multinational trial with the aim of facilitating collaboration between research groups.

• To better define terms and concepts (IMP, interventional study, substantial amendment, etc.)

• To increase public financial support to investigator-led clinical trials.

• To extend access to EudraCT database

• To harmonise insurances requirements e.g. uniform costs per country, minimum and maximum indemnity payments, total duration of coverage, time to permit claims etc
So, the problems are recognised and potential solutions may be available. Because the Directive will undergo formal review in 2010, we have an opportunity to develop practical and concrete proposals for consideration within the EU. Over the coming months CLINT, ECRIN, EORTC and ICREL will each host one or more workshops designed to provide input into a concept for modification that will promote clinical research in Europe. The critical factor in the success of this initiative will be to engage all the key stakeholders (commercial and non-commercial sponsors, investigators from all areas of medicine, ethics committee members, competent authorities, funding bodies and patients). The academic voice was unusually silent during the development of the Directive, now is the time to be heard. We invite all interested parties to engage with and support us in these activities, as irrespective of our origins we have a common goal to optimise patient care, provide prompt access to new treatments and improve the health of our citizens. Details of the workshops will appear on the websites of the above-named groups – come and be counted!

References


Table 1

<table>
<thead>
<tr>
<th>Collaboration</th>
<th>Objective</th>
<th>Participating organisations</th>
</tr>
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<tbody>
<tr>
<td>CLINT</td>
<td>Facilitating international CLINical Trials in stem cell transplantation: an initiative of the European Group for Blood and Marrow Transplantation (EBMT)</td>
<td>EBMT University of Central Lancashire Imperial College Center for Blood and Marrow Transplant Research (CIBMTR)</td>
</tr>
<tr>
<td>ECRIN</td>
<td>European Clinical Research Infrastructure Network</td>
<td></td>
</tr>
<tr>
<td>ELN</td>
<td>European Leukaemia Network, focussed on initiation of international investigator-led trials from successful national leukemia study groups</td>
<td>More than 400 university based haematology departments across Europe Co-ordinated by the University of Mannheim and represented by the University of Frankfurt (European Leukemia Information Center)</td>
</tr>
<tr>
<td>ICREL</td>
<td>Impact on Clinical Research of European Legislation focused on the effect of the clinical trials directive</td>
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ANNEX 7

Road Map Initiative for Clinical Research in Europe
The First in a series of 5 Workshops

Brussels, 2 July 2009 – In view of the European Commission’s plans to review the Clinical Trials Directive (DIR 2001/20/EC) in 2010, academic institutions/investigators, sponsors, ethics committees, competent authorities and patients representatives are joining forces on 7 July in a first of a series of five workshops with the aim of arriving at a united position – a component missing during the original development of the Directive. The ultimate objective of this workshop being a more efficient CTA process that stimulates rather than stifles research and innovation.

The Road Map Initiative’s partners came together during a CLINT Project workshop at the EBMT 35th Annual Congress in Gothenburg this year, where consensus was reached on the need to promote a single CTA process with clear definitions of the respective roles of the competent authority (e.g. assessment of the IMPD, the Investigational Medicinal Product Dossier, at the EU level) and the ethics committees (e.g. protection of participants at the national level). The objective of next week’s workshop is to discuss how the CTA process could become more efficient without increasing the risk for trial participants. A single CTA for multi-national clinical trials would reduce the complexity of the process and the resources required to run them, however, any such development would have to satisfy the diverse needs of the stakeholders involved. Tuesday’s workshop aims to provide a forum for all key players to air their views and articulate their needs which will feed into a future recommendation to the Commission.

The primary aims of Directive 2001/20/EC were not only to protect patients and improve standards but also to encourage competition and to harmonize administrative procedures. However, it introduced the concept of a Clinical Trial Authorisation (CTA) by a competent authority and a favourable opinion from a lead or central research ethics committee as a prerequisite for the performance of a clinical trial. In multi-national clinical trials this authorisation process has to be followed in each country where the clinical trial is supposed to be performed. The content of the CTA application dossier is defined by each Member State in a different way, and the review processes result in different additional requirements, which results in a longer trial preparation period for multi-national trials and increased administrative cost.

The results of ICREL (Impact on Clinical Research of European Legislation), a one year project funded by FP7, to produce hard data to measure change in the performance of clinical trials in Europe between 2003 and 2007, pointed out the following:

- An increase of the study preparation time
- A shift from academic research to commercial trials
- An increase in costs, administrative burden and timeframes without clearly improving the involvement and safety of patients in clinical trials.

The CTA workshop is just the first of 5 workshops which will be organised by the initiative’s partners over the next 9 months in order to explore with all the relevant stakeholders a number of possible solutions to improve clinical research in Europe:

- To require only one Clinical Trials Authorisation (CTA) irrespective of the numbers of participating nations, either by the development of a single CTA application across Europe or the mutual recognition of authorisations by Competent Authorities.
- To simplify and harmonise the procedures for clinical trial approval (e.g. the EudraCT forms as a single set of forms to be completed) and safety reporting (Eudravigilance and reporting rules).
- To define better and harmonise the roles of the ethics committees (achieve the so-called single-opinion) and of the competent authorities.
- To adopt a risk-based approach: adaptation of the regulatory requirements considering the risk associated with the trial with regard to the safety reporting (e.g. limited safety reporting for commercially approved drugs), data monitoring, insurance, application dossiers, substantial amendments, free-of-charge supply of drug (e.g. not in case of market approval).
- To allow co-sponsorship in the case of multinational trial with the aim of facilitating collaboration between research groups.
- To better define terms and concepts (IMP, interventional study, substantial amendment, etc.)
- To increase public financial support to investigator-led clinical trials.
- To harmonise insurances requirements e.g. uniform costs per country, minimum and maximum.
- Indemnity payments, total duration of coverage, time to permit claims etc.

The series of workshops will culminate in a stakeholder Conference in April 2010 to which representatives of, DG Enterprise, DG Research and DG SANCO will be invited to participate.